Literature

1. **Pre-extensively drug-resistant tuberculosis among multidrug-resistant tuberculosis patients in Ethiopia: a laboratory-based surveillance study.**

IJID Reg. 2022;5:39-43. doi: 10.1016/j.ijregi.2022.08.012. eCollection 2022 Dec.

Diriba G(1), Alemu A(1), Tola HH(2), Yenew B(1), Amare M(1), Eshetu K(3), Sinshaw W(1), Abebaw Y(1), Meaza A(1), Seid G(1), Moga S(1), Zerihun B(1), Getu M(1), Dagne B(1), Mollalign H(1), Tadesse M(1), Buta B(1), Wordofa N(1), Alemu E(1), Erresso A(1), Hailu M(1), Tefera Z(1), Wondimu A(1), Belhu T(1), Gamtesa DF(1), Getahun M(1), Kebede A(4), Abdela S(1).

BACKGROUND: The rise of drug-resistant tuberculosis (DR-TB) has presented a substantial challenge to the national tuberculosis (TB) control program. Understanding the epidemiology of pre-extensively drug-resistant tuberculosis (pre-XDR-TB) could help clinicians to adapt MDR-TB treatment regimens at an earlier stage. This study aimed to assess second-line anti-TB drug resistance among MDR-TB patients in Ethiopia using routine laboratory-based data.
METHODS: Laboratory-based cross-sectional data were collected from the national TB reference laboratory and seven regional tuberculosis culture laboratories in Ethiopia from July 2019 to March 2022. The required data, such as drug-susceptibility testing (DST) results and sociodemographics, were collected on a structured checklist from laboratory registration books and electronic databases. Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 23. Descriptive statistics were performed to show the distribution and magnitude of drug resistance.
RESULTS: Second-line drugs (SLDs) susceptibility testing was performed for 644 MDR isolates, of which 19 (3%) were found to be pre-XDR-TB cases. Of the total MDR-TB isolates, 19 (3%) were resistant to at least one fluoroquinolone drug, while 11 (1.7%) were resistant to at least one injectable second-line drug. Of the 644 MDR-TB isolates, 1.9% (5/261) pre-XDR were from new MDR-TB cases, while 3.7% (14/383) were from previously treated MDR-TB patients. The most frequently identified mutations, based on MTBDRsl results, were in codon A90V of the gyrA gene (77.3%) and A1401G of the rrs gene (45.5%).
CONCLUSION: The overall prevalence of pre-XDR-TB in Ethiopia is considerable. The majority of SLD resistance mutations were in the gyrA gene at position A90V. Modern, rapid DST is necessary to enable identification of pre-XDR-TB and XDR-TB in supporting proper regimen administration for patients.

DOI: 10.1016/j.ijregi.2022.08.012

PMCID: PMC9513164
PMID: 36176268

2. **Drug resistant tuberculosis: Implications for transmission, diagnosis, and disease management.**

Front Cell Infect Microbiol. 2022 Sep 23;12:943545. doi: 10.3389/fcimb.2022.943545. eCollection 2022.

Liebenberg D(1), Gordhan BG(1), Kana BD(1).

Drug resistant tuberculosis contributes significantly to the global burden of antimicrobial resistance, often consuming a large proportion of the healthcare budget and associated resources in many endemic countries. The rapid emergence of resistance to newer tuberculosis therapies signals the need to ensure appropriate antibiotic stewardship, together with a concerted drive to develop new regimens that are active against currently circulating drug resistant strains. Herein, we highlight that the current burden of drug resistant tuberculosis is driven by a combination of ongoing transmission and the intra-patient evolution of resistance through several mechanisms. Global control of tuberculosis will require interventions that effectively address these and related aspects. Interrupting tuberculosis transmission is dependent on the availability of novel rapid diagnostics which provide accurate results, as near-patient as is possible, together with appropriate linkage to care. Contact tracing, longitudinal follow-up for symptoms and active mapping of social contacts are essential elements to curb further community-wide spread of drug resistant strains. Appropriate prophylaxis for contacts of drug resistant index cases is imperative to limit disease progression and subsequent transmission. Preventing the evolution of drug resistant strains will require the development of shorter regimens that rapidly eliminate all populations of mycobacteria, whilst concurrently limiting bacterial metabolic processes that drive drug tolerance, mutagenesis and the ultimate emergence of resistance. Drug discovery programs that specifically target bacterial genetic determinants associated with these processes will be paramount to tuberculosis eradication. In addition, the development of appropriate clinical endpoints that quantify drug tolerant organisms in sputum, such as differentially culturable/detectable tubercle bacteria is necessary to accurately assess the potential of new therapies to effectively shorten treatment duration. When combined, this holistic approach to addressing the critical problems associated with drug resistance will support delivery of quality care to patients suffering from tuberculosis and bolster efforts to eradicate this disease.

DOI: 10.3389/fcimb.2022.943545
PMCID: PMC9538507
PMID: 36211964 [Indexed for MEDLINE]

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

3. **The Changing Paradigm of Drug-Resistant Tuberculosis Treatment: Successes, Pitfalls, and Future Perspectives.**

Clin Microbiol Rev. 2022 Oct 6:e0018019. doi: 10.1128/cmr.00180-19. Online ahead of print.

Dookie N(#)(1), Ngema SL(#)(1), Perumal R(1)(2), Naicker N(1)(2), Padayatchi N(1)(2), Naidoo K(1)(2).

Drug-resistant tuberculosis (DR-TB) remains a global crisis due to the increasing incidence of drug-resistant forms of the disease, gaps in detection and prevention, models of care, and limited treatment options. The DR-TB treatment landscape has evolved over the last 10 years. Recent developments include the remarkable activity demonstrated by the newly approved anti-TB drugs bedaquiline and pretomanid against Mycobacterium tuberculosis. Hence, treatment of DR-TB has drastically evolved with the introduction of the short-course regimen for multidrug-resistant TB (MDR-TB), transitioning to injection-free regimens and the approval of the 6-month short regimens for rifampin-resistant TB and MDR-TB. Moreover, numerous clinical trials are under way with the aim to reduce pill burden and shorten the DR-TB treatment duration. While there have been apparent successes in the field, some challenges remain. These include the ongoing inclusion of high-dose isoniazid in DR-TB regimens despite a lack of evidence for its efficacy and the inclusion of ethambutol and pyrazinamide in the standard short regimen despite known high levels of background resistance to both drugs. Furthermore, antimicrobial heteroresistance, extensive cavitary disease and intracavitary gradients, the emergence of bedaquiline resistance, and the lack of biomarkers to monitor DR-TB treatment response remain serious challenges to the sustained successes. In this review, we outline the impact of the new drugs and regimens on patient treatment outcomes, explore evidence underpinning current practices on regimen selection and duration, reflect on the disappointments and pitfalls in the field, and highlight key areas that require continued efforts toward improving treatment approaches and rapid biomarkers for monitoring treatment response.

DOI: 10.1128/cmr.00180-19
PMID: 36200885

4. **Mutation detection and minimum inhibitory concentration determination against linezolid and clofazimine in confirmed XDR-TB clinical isolates.**

BMC Microbiol. 2022 Oct 3;22(1):236. doi: 10.1186/s12866-022-02622-x.

Singh K(1), Sharma S(1), Banerjee T(1), Gupta A(2), Anupurba S(3).

BACKGROUND: The emergence of multidrug-resistant tuberculosis (MDR-TB) has complicated the situation due to the decline in potency of second-line anti-tubercular drugs. This limits the treatment option for extensively drug-resistant tuberculosis (XDR-TB). The aim of this study was to determine and compare the minimum inhibitory concentration (MIC) by agar dilution and resazurin microtiter assay (REMA) along with the detection of mutations against linezolid and clofazimine in confirmed XDR-TB clinical isolates.
RESULTS: A total of 169 isolates were found positive for Mycobacterium tuberculosis complex (MTBC). The MIC was determined by agar dilution and REMA methods. The isolates which showed non-susceptibility were further subjected to mutation detection by targeting rplC gene (linezolid) and Rv0678 gene (clofazimine). The MIC for linezolid ranged from 0.125 µg/ml to > 2 µg/ml and for clofazimine from 0.25 µg/ml to > 4 µg/ml. The MIC50 and MIC90 for linezolid were 0.5 µg/ml and 1 µg/ml respectively while for clofazimine both were 1 µg/ml. The essential and categorical agreement for linezolid was 97.63% and 95.26% and for clofazimine, both were 100%. The sequencing result of the rplC gene revealed a point mutation at position 460 bp, where thymine (T) was substituted for cytosine (C) while seven mutations were noted between 46 to 220 bp in Rv0678 gene.
CONCLUSION: REMA method has been found to be more suitable in comparison to the agar dilution method due to lesser turnaround time. Mutations in rplC and Rv0678 genes were reasons for drug resistance against linezolid and clofazimine respectively.

DOI: 10.1186/s12866-022-02622-x
PMCID: PMC9531458
PMID: 36192704 [Indexed for MEDLINE]

Conflict of interest statement: The author(s) declare that they have no competing interests.

5. **A five-year review of prevalence and treatment outcomes of pre-extensively drug-resistant plus additional drug-resistant tuberculosis in the Henan Provincial Tuberculosis Clinical Medicine Research Center.**

J Glob Antimicrob Resist. 2022 Oct 6:S2213-7165(22)00226-0. doi: 10.1016/j.jgar.2022.09.010. Online ahead of print.

Li Z(1), Liu F(2), Chen H(3), Han Y(3), You Y(2), Xie Y(2), Zhao Y(3), Tan J(3), Guo X(3), Cheng Y(3), Wang Y(3), Li J(3), Cheng M(3), Xia S(3), Niu X(3), Wei L(3), Wang W(4).

OBJECTIVES: This study investigated the prevalence and significant clinical outcomes of pre-extensively drug-resistant plus additional drug-resistant tuberculosis (pre-XDR-plus) in Henan Provincial Chest Hospital between 2017 and 2021.
METHODS: We analyzed and summarized the drug sensitivity test (DST) results of clinical Mycobacterium tuberculosis (MTB) strains in TB patients seeking care in the Tuberculosis Clinical Medical Research Center of Henan Province between 2017 and 2021. Medical records of pre-extensively drug-resistant plus additional drug-resistant TB patients were statistically analyzed, including demographic characteristics, regimens, and outcomes.
RESULTS: Of the 3689 Mycobacterium tuberculosis strains, 639 (17.32%), 353 (9.56%), and 109 (2.95%), multidrug-resistant tuberculosis (MDR-TB), pre-extensively drug-resistant tuberculosis (pre-XDR), and pre-extensively drug-resistant plus additional drug-resistant tuberculosis (pre-XDR-plus), respectively. The proportion of MDR decreased from 19.1% in 2017 to 17.5% in 2021 (Chi-square = 0.686, P=0.407), the proportion of pre-XDR from 11.4% in 2017 to 9.0% in 2021 (Chi-square = 2.39, P= 0.122), and pre-XDR-plus from 4.7% in 2017 to 1.8% in 2020, with the declining trend was significant (Chi-square=9.348, P=0.002). The most commonly used anti-TB drugs were pyrazinamide (PZA,37/46, 80.43%) and cycloserine (CS, 32/46, 69.57%), followed by linezolid (LZD, 25/46, 54.35%), protionamide (TH, 25/46, 54.35%), and para-aminosalicylic acid (PAS, 23/46, 50.00%). Patients receiving the LZD regimen were 5 times more likely to have a favorable outcome than those not receiving LZD (OR=6.421, 95% CI 2.101-19.625, P=0.001). Patients receiving a regimen containing CS were 4 times more likely to have a favorable outcome compared to those not taking CS (OR=5.444, 95% CI 1.650-17.926, P=0.005).
CONCLUSIONS: Our data suggest that the population of pre-XDR-plus had significantly decreased over the past five years in the Henan Provincial Chest Hospital. The COVID-19and flood disaster affect TB patients' selection of medical services. In addition, the pre-XDR-plus patients whose regimens contain LZD or CS were more likely to have favorable outcomes.

DOI: 10.1016/j.jgar.2022.09.010
PMID: 36210030

6. **Multidrug-Resistant Tuberculosis Outbreak among Immigrants in Tokyo, Japan, 2019-2021.**

Jpn J Infect Dis. 2022 Sep 22;75(5):527-529. doi: 10.7883/yoken.JJID.2021.643. Epub 2022 Mar 31.

Kobayashi Y(1), Tateishi A(1), Hiroi Y(1), Minakuchi T(1), Mukouyama H(2), Ota M(3), Nagata Y(3), Hirao S(3), Yoshiyama T(4), Keicho N(4).

In mid-September 2019, a teenage Chinese male student and part-time waiter in Tokyo was diagnosed with multidrug-resistant (MDR) sputum smear-positive pulmonary tuberculosis (TB). This study describes the outbreak investigation of his friends and colleagues at the restaurant. We investigated 6 friends and 15 colleagues; 5 friends and 13 colleagues underwent interferon-γ release assay (IGRA). Of these, 3 friends (60.0%) and 4 colleagues (30.8%) were IGRA-positive. Each of the friends and colleagues was found to have MDR-TB (20% and 7.7%, respectively). Challenges during the investigation were the unavailability of regimens for latent TB infection (LTBI) for contacts with MDR-TB, budgetary constraints concerning implementing computed tomography (CT) scans for the contacts, frequent address changes of foreign-born patients and contacts, investigation during the coronavirus disease pandemic, and variations of alphabetical expression of the names of the patients and contacts, particularly for those from China. It is recommended that the national government officially adopt prophylaxis regimens for LTBI with MDR-TB, address the budgetary constraints regarding CT scans, and deploy liaison officers for coordinating investigations involving many foreign-born patients and contacts scattered in multiple municipalities. The names of foreign-born persons could more accurately be identified using both the alphabet and Chinese characters.

DOI: 10.7883/yoken.JJID.2021.643
PMID: 35354703 [Indexed for MEDLINE]

7. **Fluoroquinolone heteroresistance, antimicrobial tolerance, and lethality enhancement.**

Front Cell Infect Microbiol. 2022 Sep 29;12:938032. doi: 10.3389/fcimb.2022.938032. eCollection 2022.

Singh A(1)(2), Zhao X(3)(4), Drlica K(3).

With tuberculosis, the emergence of fluoroquinolone resistance erodes the ability of treatment to interrupt the progression of MDR-TB to XDR-TB. One way to reduce the emergence of resistance is to identify heteroresistant infections in which subpopulations of resistant mutants are likely to expand and make the infections fully resistant: treatment modification can be instituted to suppress mutant enrichment. Rapid DNA-based detection methods exploit the finding that fluoroquinolone-resistant substitutions occur largely in a few codons of DNA gyrase. A second approach for restricting the emergence of resistance involves understanding fluoroquinolone lethality through studies of antimicrobial tolerance, a condition in which bacteria fail to be killed even though their growth is blocked by lethal agents. Studies with Escherichia coli guide work with Mycobacterium tuberculosis. Lethal action, which is mechanistically distinct from blocking growth, is associated with a surge in respiration and reactive oxygen species (ROS). Mutations in carbohydrate metabolism that attenuate ROS accumulation create pan-tolerance to antimicrobials, disinfectants, and environmental stressors. These observations indicate the existence of a general death pathway with respect to stressors. M. tuberculosis displays a variation on the death pathway idea, as stress-induced ROS is generated by NADH-mediated reductive stress rather than by respiration. A third approach, which emerges from lethality studies, uses a small molecule, N-acetyl cysteine, to artificially increase respiration and additional ROS accumulation. That enhances moxifloxacin lethality with M. tuberculosis in culture, during infection of cultured macrophages, and with infection of mice. Addition of ROS stimulators to fluoroquinolone treatment of tuberculosis constitutes a new direction for suppressing the transition of MDR-TB to XDR-TB.

DOI: 10.3389/fcimb.2022.938032
PMCID: PMC9559723
PMID: 36250047 [Indexed for MEDLINE]

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

8. **Community- vs. hospital-based management of multidrug-resistant TB in Pakistan.**

Int J Tuberc Lung Dis. 2022 Oct 1;26(10):929-933. doi: 10.5588/ijtld.21.0695.

Fatima R(1), Yaqoob A(2), Qadeer E(3), Khan MA(4), Ghafoor A(5), Jamil B(1), Haq MU(6), Ahmed N(7), Baig S(7), Rehman A(8), Abbasi Q(9), Khan AW(5), Ikram A(10), Hicks JP(11), Walley J(11).

BACKGROUND Multidrug-resistant TB (MDR-TB) treatment takes 18-24 months and is complex, costly and isolating. We provide trial evidence on the WHO Pakistan recommendation for community-based care rather than hospital-based care.METHODS Two-arm, parallel-group, superiority trial was conducted in three programmatic management of drug-resistant TB hospitals in Punjab and Sindh Provinces, Pakistan. We enrolled 425 patients with MDR-TB aged >15 years through block randomisation in community-based care (1-week hospitalisation) or hospital-based care (2 months hospitalisation). Primary outcome was treatment success.RESULTS Among 425 patients with MDR-TB, 217 were allocated to community-based care and 208 to hospital-based care. Baseline characteristics were similar between the community and hospitalised arms, as well as in selected sites. Treatment success was 74.2% (161/217) under community-based care and 67.8% (141/208) under hospital-based care, giving a covariate-adjusted risk difference (community vs. hospital model) of 0.06 (95% CI -0.02 to 0.15; P = 0.144).CONCLUSIONS We found no clear evidence that community-based care was more or less effective than hospital-based care model. Given the other substantial advantages of community-based care over hospital based (e.g., more patient-friendly and accessible, with lower treatment costs), this supports the adoption of the community-based care model, as recommended by the WHO.

DOI: 10.5588/ijtld.21.0695
PMID: 36163662 [Indexed for MEDLINE]

9. **Pyrazinamide resistance in rifampicin discordant tuberculosis.**

PLoS One. 2022 Sep 21;17(9):e0274688. doi: 10.1371/journal.pone.0274688. eCollection 2022.

Mvelase NR(1)(2), Singh R(1)(2), Swe Swe-Han K(1)(2), Mlisana KP(1)(2)(3).

INTRODUCTION: Mycobacterium tuberculosis strains with phenotypically susceptible rpoB mutations (rifampicin discordant) have emerged following implementation of rapid molecular drug resistance testing for tuberculosis. Whilst rifampicin resistance is known to be associated with resistance to other rifamycins (rifapentine and rifabutin) as well as isoniazid and pyrazinamide, rifampicin discordant strains have shown high rates of susceptibility to isoniazid and rifabutin. However, pyrazinamide susceptibly testing results have not been reported.
MATERIALS AND METHODS: We evaluated pyrazinamide resistance in 80 rifampicin

discordant and 25 rifampicin and isoniazid susceptible isolates from KwaZulu-Natal in South Africa using Mycobacteria Growth Indicator Tube method and sequencing of the pncA. We also compared susceptibility of pyrazinamide with that of isoniazid.
RESULTS: Pyrazinamide resistance was found in 6/80 (7.5%) rifampicin discordant isolates. All pyrazinamide resistant isolates were also resistant to isoniazid and pyrazinamide resistance was found to be associated with isoniazid resistance. No pyrazinamide resistance was found among the isoniazid susceptible isolates.
CONCLUSION: Given the low prevalence of pyrazinamide resistance in rifampicin discordant TB, this anti-TB drug still has a significant role in the treatment of these patients. Performing pyrazinamide susceptibility testing remains a challenge, our findings show that isoniazid susceptible isolates are unlikely to be resistant to pyrazinamide among the discordant TB isolates.

DOI: 10.1371/journal.pone.0274688
PMCID: PMC9491533
PMID: 36129921 [Indexed for MEDLINE]

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

10. **First insights into the phylogenetic diversity of Mycobacterium tuberculosis in Kuwait and evaluation of REBA MTB-MDR assay for rapid detection of MDR-TB.**

PLoS One. 2022 Oct 20;17(10):e0276487. doi: 10.1371/journal.pone.0276487. eCollection 2022.

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

Early detection of Mycobacterium tuberculosis (Mtb) in clinical specimens, its susceptibility to anti-TB drugs and disruption of infection transmission to new hosts are essential components for global tuberculosis (TB) control efforts. This study investigated major Mtb genotypes circulating in Kuwait and evaluated the performance of REBA MTB-MDR (REBA) test in comparison to GenoType MTBDRplus (gMTBDR+) assay for rapid detection of resistance of Mtb to isoniazid and rifampicin (MDR-TB). M. tuberculosis isolates (n = 256) originating predominantly from expatriate patients during a 6-month period were tested by spoligotyping and a dendrogram was created by UPGMA using MIRU-VNTRplus software. Phenotypic drug susceptibility testing (DST) was performed by MGIT 960 system. Genotypic DST for isoniazid and rifampicin was done by REBA and gMTBDR+ assays. Spoligotyping assigned 188 (73.4%) isolates to specific spoligotype international type (SIT) while 68 isolates exhibited orphan patterns. All major

M. tuberculosis lineages were detected and EAI, CAS and Beijing families were predominant. Phylogenetic tree showed 131 patterns with 105 isolates exhibiting a unique pattern while 151 isolates clustered in 26 patterns. Fifteen isolates were resistant to one/more drugs. REBA and gMTBDR+ detected isoniazid resistance in 11/12 and 10/12 and rifampicin resistance in 4/5 and 4/5 resistant isolates, respectively. The diversity of SIT patterns are highly suggestive of infection of most expatriate patients with unique Mtb strains, likely acquired in their native countries before their arrival in Kuwait. Both, REBA and gMTBDR+ assays performed similarly for detection of resistance of Mtb to isoniazid and rifampicin for rapid detection of MDR-TB.

DOI: 10.1371/journal.pone.0276487
PMID: 36264939

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

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

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

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

DOI: 10.1016/j.ssmqr.2022.100042
PMCID: PMC8896740
PMID: 35252955

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

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

Antimicrob Agents Chemother. 2022 Oct 18;66(10):e0081122. doi: 10.1128/aac.00811-22. Epub 2022 Sep 15.

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

Bedaquiline has been widely used as a part of combination dosage regimens for

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

DOI: 10.1128/aac.00811-22
PMCID: PMC9578397
PMID: 36106884 [Indexed for MEDLINE]

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

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

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

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

Twenty-three new riminophenazine and pyrido[3,2-b]quinoxaline derivatives were prepared and examined for their antimycobacterial activities against Mycobacterium marinum and Mycobacterium tuberculosis H37Rv, taking clofazimine (1) as the lead. Structure-activity relationship (SAR) analysis revealed that the introduction of a heterocycle or diethylamine substituted benzene moiety on the N-5 atom might be beneficial for activity. The most potent compound 7m also

displayed enhanced activity against wild-type as well as multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB clinical isolates, with the MICs ranging from 0.08 to 1.25 μg/mL, especially effective toward strain M20A507, resistant to 1. Further mechanism study indicated that its anti-TB activity was independent of cell membrane disruption, but related to NDH-2 reduction and the resulting high ROS production. Our study provides instructive guidance for the further development of clofazimine derivatives into promising antimicrobial agents against MDR and XDR TB.

DOI: 10.1016/j.bioorg.2022.105929
PMID: 35701239 [Indexed for MEDLINE]

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

14. **Jantarabenjakul W(1)(2), Supradish Na Ayudhya P(3), Suntarattiwong P(3), Thepnarong N(2), Rotcheewaphan S(4), Udomsantisuk N(4), Moonwong J(2), Kosulvit P(3), Tawan M(2), Sudjaritruk T(5)(6), Puthanakit T(1)(2).**

IJID Reg. 2022 Sep 18;5:79-85. doi: 10.1016/j.ijregi.2022.09.005. eCollection 2022 Dec.

Temporal trend of drug-resistant tuberculosis among Thai children during 2006-2021.

BACKGROUND: The prevalence of drug-resistant tuberculosis (DR-TB) in adults has stabilized in the past decade. Our study aimed to describe the prevalence of DR-TB in Thai children between 2006 and 2021.
MATERIALS AND METHODS: Children younger than 15 years old who had culture-confirmed Mycobacterium tuberculosis complex (MTB), positive PCR-MTB, or positive Xpert MTB/RIF were included in this cohort. Drug susceptibility testing (DST) was performed using phenotypic and/or genotypic methods. The prevalence of DR-TB was compared using the chi-square test.
RESULTS: Among 163 confirmed TB cases (44% as pulmonary TB, 27% as extrapulmonary TB, and 29% with both), the median age (IQR) was 12.2 (7.3-14.2) years. DST was performed in 139 cases (85%), revealing prevalences of all DR-TB, isoniazid-resistant TB (Hr-TB), and rifampicin monoresistant/multidrug-resistant TB (Rr/MDR-TB) of 21.6% (95% CI 14.7-28.4), 10.8% (95% CI 5.6-16.0%), and 2.9% (95% CI 0.1-5.7%), respectively. The DR-TB rates did not differ significantly

between 2006-2013, 2014-2018, and 2019-2021 ($p > 0.05$). Two pre-extensively DR-TB (pre-XDR) cases with fluoroquinolone resistance were detected after 2014.
CONCLUSION: The prevalence of DR-TB in Thai children was stable. However, one-tenth of DR-TB cases confirmed with DST were Hr-TB, which required adjustment of the treatment regimen. The pre-XDR cases should be closely monitored.

DOI: 10.1016/j.ijregi.2022.09.005
PMCID: PMC9550601
PMID: 36238580

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.

15. **The second national anti-tuberculosis drug resistance survey in Tanzania, 2017-2018.**

Trop Med Int Health. 2022 Oct;27(10):891-901. doi: 10.1111/tmi.13814. Epub 2022 Sep 11.

Mutayoba BK(1)(2), Ershova J(3), Lyamuya E(4), Hoelscher M(2), Heinrich N(2), Kilale AM(5), Range NS(5), Ngowi BJ(6), Ntinginya NE(7), Mfaume SM(5), Nkiligi E(8), Doulla B(9), Lyimo J(8), Kisonga R(10), Kingalu A(8), Lema Y(5), Kondo Z(8), Pletschette M(2).

OBJECTIVE: To determine the levels and patterns of resistance to first- and second-line anti-tuberculosis (TB) drugs among new and previously treated sputum smear positive pulmonary TB (PTB) patients.
METHODS: We conducted a nationally representative cross-sectional facility-based survey in June 2017-July 2018 involving 45 clusters selected based on probability proportional to size. The survey aimed to determine the prevalence of anti-TB drug resistance and associated risk factors among smear positive PTB patients in Tanzania. Sputum samples were examined using smear microscopy, Xpert MTB/RIF, culture and drug susceptibility testing (DST). Logistic regression was used to account for missing data and sampling design effects on the estimates and their standard errors.
RESULTS: We enrolled 1557 TB patients, including 1408 (90.4%) newly diagnosed and 149 (9.6%) previously treated patients. The prevalence of multidrug-resistant TB (MDR-TB) was 0.85% [95% confidence interval (CI): 0.4-1.3] among new cases and 4.6% (95% CI: 1.1-8.2) among previously treated

cases. The prevalence of Mycobacterium tuberculosis strains resistant to any of the four first-line anti-TB drugs (isoniazid, rifampicin, streptomycin and ethambutol) was 1.7% among new TB patients and 6.5% among those previously treated. Drug resistance to all first-line drugs was similar (0.1%) in new and previously treated patients. None of the isolates displayed poly-resistance or extensively drug-resistant TB (XDR-TB). The only risk factor for MDR-TB was history of previous TB treatment (odds ratio = 5.7, 95% CI: 1.9-17.2).
CONCLUSION: The burden of MDR-TB in the country was relatively low with no evidence of XDR-TB. Given the overall small number of MDR-TB cases in this survey, it will be beneficial focusing efforts on intensified case detection including universal DST.

DOI: 10.1111/tmi.13814
PMID: 36089572 [Indexed for MEDLINE]

16. **FAST tuberculosis transmission control strategy speeds the start of tuberculosis treatment at a general hospital in Lima, Peru.**

Infect Control Hosp Epidemiol. 2022 Oct;43(10):1459-1465. doi: 10.1017/ice.2021.422. Epub 2021 Oct 6.

Tierney DB(1)(2), Orvis E(3), Nathavitharana RR(2)(4), Hurwitz S(1)(2), Tintaya K(5), Vargas D(6), Segura P(6), de la Gala S(5), Lecca L(5), Mitnick CD(#)(1)(7), Nardell EA(#)(1)(2).

OBJECTIVE: To evaluate the effect of the FAST (Find cases Actively, Separate safely, Treat effectively) strategy on time to tuberculosis diagnosis and treatment for patients at a general hospital in a tuberculosis-endemic setting.
DESIGN: Prospective cohort study with historical controls.
PARTICIPANTS: Patients diagnosed with pulmonary tuberculosis during hospitalization at Hospital Nacional Hipolito Unanue in Lima, Peru.
METHODS: The FAST strategy was implemented from July 24, 2016, to December 31, 2019. We compared the proportion of patients with drug susceptibility testing and tuberculosis treatment during FAST to the 6-month period prior to FAST. Times to diagnosis and tuberculosis treatment were also compared using Kaplan-Meier plots and Cox regressions.
RESULTS: We analyzed 75 patients diagnosed with pulmonary tuberculosis through FAST. The historical cohort comprised 76 patients. More FAST patients underwent drug susceptibility testing (98.7% vs 57.8%; OR, 53.8; P < .001), which led to the diagnosis of drug-resistant tuberculosis in 18 (24.3%) of 74 of the

prospective cohort and 4 (9%) of 44 of the historical cohort (OR, 3.2; P = .03). Overall, 55 FAST patients (73.3%) started tuberculosis treatment during hospitalization compared to 39 (51.3%) controls (OR, 2.44; P = .012). FAST reduced the time from hospital admission to the start of TB treatment (HR, 2.11; 95% CI, 1.39-3.21; P < .001).
CONCLUSIONS: Using the FAST strategy improved the diagnosis of drug-resistant tuberculosis and the likelihood and speed of starting treatment among patients with pulmonary tuberculosis at a general hospital in a tuberculosis-endemic setting. In these settings, the FAST strategy should be considered to reduce tuberculosis transmission while simultaneously improving the quality of care.

DOI: 10.1017/ice.2021.422
PMCID: PMC8983787
PMID: 34612182

Conflict of interest statement: Conflicts of interest. All authors report no conflicts of interest relevant to this article.

17. **[Consensus on linezolid in the treatment of tuberculosis(2022 update)].**

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Oct 12;45(10):988-995. doi: 10.3760/cma.j.cn112147-20220320-00220.

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

Chinese Society for Tuberculosis, Chinese Medical Association.

Linezolid is the core drug for the treatment of multidrug-resistant tuberculosis. In 2018, Chinese Society for Tuberculosis, Chinese Medical Association(CSTB) issued a "consensus on linezolid in the treatment of tuberculosis". With the wider use of it in clinic, the improved understanding and the progress in research, CSTB organized experts to update this consensus and formed "consensus on linezolid in the treatment of tuberculosis(2022 update)", with a view to play a guiding role for clinicians. The consensus included the molecular structure and mechanism of action, pharmacodynamics, pharmacokinetics, clinical application, indications, contraindications and relative contraindications, dosage, usage and formulation of chemotherapy regimen, adverse reactions and clinical application. In this edition, we updated the drug resistance mechanism of linezolid, and the medical evidence was rated and recommended according to the grading of recommendations assessment, development and evaluation (GRADE) method.

18. **Caregiver willingness to give TPT to children living with drug-resistant TB**

patients.

Int J Tuberc Lung Dis. 2022 Oct 1;26(10):949-955. doi: 10.5588/ijtld.21.0760.

Rouzier V(1), Murrill M(2), Kim S(3), Naini L(4), Shenje J(5), Mitchell E(6), Raesi M(7), Lourens M(8), Mendoza A(9), Conradie F(10), Suryavanshi N(11), Hughes M(12), Shah S(13), Churchyard G(14), Swindells S(15), Hesseling A(16), Gupta A(1).

BACKGROUND Pediatric household contacts (HHCs) of patients with multidrug-resistant TB (MDR-TB) are at high risk of infection and active disease. Evidence of caregiver willingness to give MDR-TB preventive therapy (TPT) to children is limited.METHODS This was a cross-sectional study of HHCs of patients with MDR-TB to assess caregiver willingness to give TPT to children aged <13 years.RESULTS Of 743 adult and adolescent HHCs, 299 reported caring for children aged <13 years of age. The median caregiver age was 35 years (IQR 27-48); 75% were women. Among caregivers, 89% were willing to give children MDR TPT. In unadjusted analyses, increased willingness was associated with TB-related knowledge (OR 5.1, 95% CI 2.3-11.3), belief that one can die of MDR-TB (OR 5.2, 95% CI 1.2-23.4), concern for MDR-TB transmission to child (OR 4.5, 95% CI 1.6-12.4), confidence in properly taking TPT (OR 4.5, 95% CI 1.6-12.6), comfort telling family about TPT (OR 5.5, 95% CI 2.1-14.3), and willingness to take TPT oneself (OR 35.1, 95% CI 11.0-112.8).CONCLUSIONS A high percentage of caregivers living with MDR- or rifampicin-resistant TB patients were willing to give children a hypothetical MDR TPT. These results provide important evidence for the potential uptake of effective MDR TPT when implemented.

DOI: 10.5588/ijtld.21.0760
PMCID: PMC9524515
PMID: 36163664 [Indexed for MEDLINE]

19. **Health Risks During Ukrainian Humanitarian Crisis.**

Risk Manag Healthc Policy. 2022 Sep 22;15:1775-1781. doi: 10.2147/RMHP.S375021. eCollection 2022.

Cojocaru E(1), Cojocaru C(2), Cojocaru E(#)(3), Oancea CI(#)(4).

BACKGROUND: The unprecedented exodus in the history of the European Union of more than 6 million Ukrainian refugees (May 13, 2022) is a cause for concern and could lead to a new difficult situation in terms of infectious disease control. Following the SARS-CoV-2 pandemic, Europe is facing a new challenge that could

lead to a new wave of COVID-19 and an increase in the number of cases of tuberculosis or eradicated diseases, such as polio.
AIM: The purpose of this analysis was to provide an overview of lung diseases and health risks that could be encountered in refugees from Ukraine and translated to European Union`countries.
METHODS: A systematic review was conducted in PubMed, World Health Organization, the UN Refugee Agency and the government's websites. Selected publications investigated the health problems arising from Ukrainian population migration from conflict areas and their impact on the public health system in the adoptive countries. The main potentially contagious diseases in Ukraine have also been reviewed.
RESULTS: The population of Ukraine has serious public health problems such as SARS-CoV-2 infection, multidrug-resistant tuberculosis, high levels of drug resistance and difficulties with an effective vaccination program, so there are significant risks of developing epidemics in transit or host countries. The current crisis has major peculiarities because the migrants were not concentrated in the camps but there was a dispersion of them on large territories of European countries.
CONCLUSION: In order to meet the health needs of refugees, it is necessary to adapt health systems culturally and linguistically, to train health workers on the particularities of existing diseases in the countries of refugee origin, and to facilitate collection of medical data on migrants' health.

DOI: 10.2147/RMHP.S375021
PMCID: PMC9512537
PMID: 36171868

Conflict of interest statement: The authors report no conflicts of interest in this work.

20. **Household contact management for rifampicin-resistant tuberculosis.**

Lancet Glob Health. 2022 Oct;10(10):e1387. doi: 10.1016/S2214-109X(22)00362-X.

Reuter A(1), Apolisi I(1), Daniels J(1), Furin J(2), Cox H(3).

Comment on
Lancet Glob Health. 2022 Jul;10(7):e1034-e1044.

DOI: 10.1016/S2214-109X(22)00362-X
PMID: 36113520 [Indexed for MEDLINE]

Conflict of interest statement: JF has received a grant from the Stop TB Partnership to support the roll out of child-friendly formulations of second-line medications. All other authors declare no competing interests.

21. **RNase HI Depletion Strongly Potentiates Cell Killing by Rifampicin in Mycobacteria.**

Antimicrob Agents Chemother. 2022 Oct 18;66(10):e0209121. doi: 10.1128/aac.02091-21. Epub 2022 Sep 26.

Al-Zubaidi A(1)(2), Cheung CY(3), Cook GM(2)(3), Taiaroa G(4), Mizrahi V(5)(6)(7)(8), Lott JS(1)(2), Dawes SS(1)(2).

Multidrug-resistant (MDR) tuberculosis (TB) is defined by the resistance of Mycobacterium tuberculosis, the causative organism, to the first-line antibiotics rifampicin and isoniazid. Mitigating or reversing resistance to these drugs offers a means of preserving and extending their use in TB treatment. R-loops are RNA/DNA hybrids that are formed in the genome during transcription, and they can be lethal to the cell if not resolved. RNase HI is an enzyme that removes R-loops, and this activity is essential in M. tuberculosis: knockouts of rnhC, the gene encoding RNase HI, are nonviable. This essentiality makes it a candidate target for the development of new antibiotics. In the model organism Mycolicibacterium smegmatis, RNase HI activity is provided by two enzymes, RnhA and RnhC. We show that the partial depletion of RNase HI activity in M. smegmatis, by knocking out either of the genes encoding RnhA or RnhC, led to the accumulation of R-loops. The sensitivity of the knockout strains to the antibiotics moxifloxacin, streptomycin, and rifampicin was increased, the latter by a striking near 100-fold. We also show that R-loop accumulation accompanies partial transcriptional inhibition, suggesting a mechanistic basis for the synergy between RNase HI depletion and rifampicin. A model of how transcriptional inhibition can potentiate R-loop accumulation is presented. Finally, we identified four small molecules that inhibit recombinant RnhC activity and that also potentiated rifampicin activity in whole-cell assays against M. tuberculosis, supporting an on-target mode of action and providing the first step in developing a new class of antimycobacterial drug.

DOI: 10.1128/aac.02091-21
PMCID: PMC9578417
PMID: 36154174 [Indexed for MEDLINE]

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

22. **Characteristics of Drug-sensitive and Drug-resistant Tuberculosis Cases among Adults at Tuberculosis Referral Hospitals in Indonesia.**

Am J Trop Med Hyg. 2022 Oct 17:tpmd220142. doi: 10.4269/ajtmh.22-0142. Online ahead of print.

Burhan E(1), Karyana M(2), Karuniawati A(3), Kusmiati T(4), Wibisono BH(5), Handayani D(1), Riyanto BS(6), Sajinadiyasa IGK(7), Sinaga BYM(8), Djaharuddin I(9), Indah Sugiyono R(10), Susanto NH(10), Diana A(10)(11), Kosasih H(10), Lokida D(12); Siswanto(2), Neal A(13), Lau CY(14), Siddiqui S(13).

As Indonesia's rifampin resistance testing rates are lower than global testing rates per the 2020 WHO global tuberculosis (TB) report, prevalence of multidrug-resistant TB may be underestimated. Our study aimed to evaluate prevalence and patterns of TB drug resistance (DR) within Indonesia. We conducted a cross-sectional analysis of baseline data collected from 2017-2018 as part of a cohort study of adults with presumed pulmonary TB at 7 DR-TB referral hospitals in Indonesia. Bacteriological examinations (acid-fast bacilli, GeneXpert, sputum culture) and drug-susceptibility testing were performed following the guidelines of the National TB Program. Of 447 participants with complete bacteriological examinations, 312 (69.8%) had positive sputum cultures for Mycobacterium tuberculosis. The proportion of MDR and pre-extensively drug-resistant was higher in previously treated compared with newly diagnosed participants (52.5% [73/139] versus 15% [26/173]). Compared with drug-sensitive case, drug-resistant TB was associated with cavities. Given the difference between rates of DR in TB referral hospitals from our study compared with the WHO survey in 2019 that showed 17.7% and 3.3% DR among previously treated and newly diagnosed participants globally, further characterization of Indonesia's TB epidemiology in the general population is needed. Strategies, including public policies to optimize case finding, strengthen capacity for resistance testing, and prevent loss to follow-up will be critical to reduce the burden of TB in Indonesia.

DOI: 10.4269/ajtmh.22-0142
PMID: 36252800

23. **[Post-tuberculosis lung disease: a neglected disease].**

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Oct 12;45(10):955-959. doi: 10.3760/cma.j.cn112147-20220208-00099.

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

Ma Y(1), Ye XP(1), Fu XY(1), Wu GH(1).

Globally, the number of patients with post-tuberculosis lung disease (PTLD) is huge, with high morbidity and mortality. PTLD is defined as chronic respiratory abnormality that affects large and small airways (bronchiectasis and obstructive lung disease), lung parenchyma, pulmonary vasculature, and pleura and may be complicated, with or without symptoms, attributable at least in part to previous pulmonary tuberculosis. The aforementioned chronic respiratory abnormality may be complicated due to coinfection such as fungi and nontuberculosis mycobacteria. Risk factors for PTLD include multiple episodes of tuberculosis, drug-resistant tuberculosis, delays in diagnosis, smoking, and possible diabetes. Empirical expert opinion advocates preventive anti-tuberculosis treatment for high-risk groups of tuberculosis, early diagnosis and treatment of tuberculosis, surgical treatment for specific groups, pulmonary rehabilitation for patients after tuberculosis treatment, early identification and treatment of co-infection. It is effective to prevent the occurrence of PTLD, improve the treatment effect, and prevent the deterioration of the disease. As a high TB burden country, PTLD has been seriously neglected in China. Internationally, there is currently a lack of epidemiological survey data on post-TB pulmonary disease, and there are few studies on its clinical characteristics, risk factors, prevention, and treatment. With an emerging literature on PTLD, collaborative research is urgently needed to inform our understanding of the natural history, prevention, and treatment of PTLD, and to allow for the development of much needed evidence-based guidelines.

DOI: 10.3760/cma.j.cn112147-20220208-00099
PMID: 36207951 [Indexed for MEDLINE]

24. **An optimized method for purifying, detecting and quantifying Mycobacterium tuberculosis RNA from sputum for monitoring treatment response in TB patients.**

Sci Rep. 2022 Oct 17;12(1):17382. doi: 10.1038/s41598-022-19985-w.

Zainabadi K(1), Lee MH(2), Walsh KF(2)(3), Vilbrun SC(4), Mathurin LD(4), Ocheretina O(2), Pape JW(2)(4), Fitzgerald DW(5).

Diagnostics that more accurately detect and quantify viable Mycobacterium tuberculosis (Mtb) in the sputum of patients undergoing therapy are needed. Current culture- and molecular-based tests have shown limited efficacy for monitoring treatment response in TB patients, either due to the presence of viable sub-populations of Mtb which fail to grow under standard culture

conditions (termed differentially detectable/culturable Mtb, DD Mtb) or the prolonged half-life of Mtb DNA in sputum. Here, we report an optimized RNA-based method for detecting and quantifying viable Mtb from patient sputum during the course of therapy. We first empirically derived a novel RNA extraction protocol from sputum that improves recovery of Mtb RNA while almost completely eliminating contamination from Mtb DNA and host nucleic acids. Next, we identified five Mtb 16S rRNA primer sets with varying limits of detection that were capable of distinguishing between live versus dead H37Rv Mtb. This combined protocol was then tested on sputa from a longitudinal cohort of patients receiving therapy for drug sensitive (DS) or drug resistant (DR) TB with first-line or second-line regimens, respectively. Results were compared with that of culture, including CFU, BACTEC MGIT, and a limiting dilution assay capable of detecting DD Mtb. The five 16S rRNA primer sets positively identified nearly all (range 94-100%) culture positive sputa, and a portion (19-37%) of culture negative sputa. In comparison, ten highly expressed Mtb mRNAs showed positivity in 72-86% of culture positive sputa, and in 0-13% of culture negative sputa. Two of the five 16S rRNA primer sets were able to positively identify 100% of culture positive sputa, and when tested on culture negative sputa from the DS cohort at 2 months post-initiation of therapy, identified 40% of samples as positive; a percentage that is in line with expected treatment failure rates when first-line therapy is discontinued early. These two primer sets also detected 16S rRNA in 13-20% of sputa at 6 months post-initiation of therapy in the DR cohort. Cycle threshold values for 16S rRNA showed a strong correlation with Mtb numbers as determined by culture ($R > 0.87$), including as Mtb numbers declined during the course of treatment with first-line and second-line regimens. The optimized molecular assay outlined here may have utility for monitoring treatment response in TB patients.

DOI: 10.1038/s41598-022-19985-w
PMCID: PMC9574834
PMID: 36253384 [Indexed for MEDLINE]

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

25. **Safety of Treatment Regimens Containing Bedaquiline and Delamanid in the endTB Cohort.**

Clin Infect Dis. 2022 Sep 29;75(6):1006-1013. doi: 10.1093/cid/ciac019.

Hewison C(1), Khan U(2), Bastard M(3), Lachenal N(4), Coutisson S(4), Osso E(5), Ahmed S(6), Khan P(2), Franke MF(5), Rich ML(5)(7), Varaine F(1), Melikyan N(3),

Seung KJ(5)(7), Adenov M(8), Adnan S(9), Danielyan N(10), Islam S(11), Janmohamed A(6), Karakozian H(12), Kamene Kimenye M(13), Kirakosyan O(14), Kholikulov B(15), Krisnanda A(16), Kumsa A(17), Leblanc G(18), Lecca L(19), Nkuebe M(20), Mamsa S(9), Padayachee S(21), Thit P(22), Mitnick CD(5)(7), Huerga H(3).

Comment in
doi: 10.1093/cid/ciac347.

BACKGROUND: Safety of treatment for multidrug-resistant tuberculosis (MDR/RR-TB) can be an obstacle to treatment completion. Evaluate safety of longer MDR/RR-TB regimens containing bedaquiline and/or delamanid.
METHODS: Multicentre (16 countries), prospective, observational study reporting incidence and frequency of clinically relevant adverse events of special interest (AESIs) among patients who received MDR/RR-TB treatment containing bedaquiline and/or delamanid. The AESIs were defined a priori as important events caused by bedaquiline, delamanid, linezolid, injectables, and other commonly used drugs. Occurrence of these events was also reported by exposure to the likely causative agent.
RESULTS: Among 2296 patients, the most common clinically relevant AESIs were peripheral neuropathy (26.4%), electrolyte depletion (26.0%), and hearing loss (13.2%) with an incidence per 1000 person months of treatment, 1000 person-months of treatment 21.5 (95% confidence interval [CI]: 19.8-23.2), 20.7 (95% CI: 19.1-22.4), and 9.7 (95% CI: 8.6-10.8), respectively. QT interval was prolonged in 2.7% or 1.8 (95% CI: 1.4-2.3)/1000 person-months of treatment. Patients receiving injectables (N = 925) and linezolid (N = 1826) were most likely to experience events during exposure. Hearing loss, acute renal failure, or electrolyte depletion occurred in 36.8% or 72.8 (95% CI: 66.0-80.0) times/1000 person-months of injectable drug exposure. Peripheral neuropathy, optic neuritis, and/or myelosuppression occurred in 27.8% or 22.8 (95% CI: 20.9-24.8) times/1000 patient-months of linezolid exposure.
CONCLUSIONS: AEs often related to linezolid and injectable drugs were more common than those frequently attributed to bedaquiline and delamanid. MDR-TB treatment monitoring and drug durations should reflect expected safety profiles of drug combinations.
CLINICAL TRIALS REGISTRATION: NCT02754765.

DOI: 10.1093/cid/ciac019
PMCID: PMC9522425
PMID: 35028659 [Indexed for MEDLINE]

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-tuberculosis (TB) drugs (one payment was made to Partners In Health as honorarium for this work). M. R. declared 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 S. P. reports being a subinvestigator on the Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL) trial, sponsored by Médecins Sans Frontières, as an employee of the Tuberculosis & HIV Investigative Network. 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.

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

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

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

Multidrug-resistant tuberculosis (MDR-TB) is a refractory disease with high mortality rate due to no or few choices of antibiotics. Adjunctive immunotherapy may help improve treatment outcome of MDR-TB. Our decade-long studies demonstrated that phosphoantigen-specific Vγ2Vδ2 T cells play protective roles in immunity against TB. Here, we hypothesized that enhancing protective Vγ2Vδ2 T-effector cells could improve treatment outcome of MDR-TB. To address this, we employed clinically approved drugs Zoledronate (ZOL) and IL-2 to induce anti-TB Vγ2Vδ2 T-effector cells as adjunctive immunotherapy against MDR-TB infection of macaques. We found that adjunctive ZOL/IL-2 administrations during TB drugs treatment of MDR-TB-infected macaques significantly expanded Vγ2Vδ2 T cells and enhanced/sustained Vγ2Vδ2 T-effector subpopulation producing anti-TB cytokines until week 21. ZOL/IL-2 administrations, while expanding Vγ2Vδ2 T cells, significantly increased/sustained numbers of circulating CD4+ Th1 and CD8+ Th1-like effector populations, with some γδ T- or αβ T-effector populations trafficking to airway at week 3 until week 19 or 21 after MDR-TB infection. Adjunctive ZOL/IL-2 administrations after MDR-TB infection led to lower bacterial burdens in lungs than TB drugs alone, IL-2 alone or saline controls, and resulted in milder MDR-TB pathology/lesions. Thus, adjunctive

Zoledronate + IL-2 administrations can enhance anti-TB Vγ2Vδ2 T- and αβ T-effector populations, and improve treatment outcome of MDR-TB.

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

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

27. **High mortality among patients hospitalized for drug-resistant tuberculosis with acquired second-line drug resistance and high HIV prevalence.**

HIV Med. 2022 Nov;23(10):1085-1097. doi: 10.1111/hiv.13318. Epub 2022 May 24.

Anderson K(1)(2), Pietersen E(1), Shepherd BE(3), Bian A(3), Dheda K(1)(4)(5), Warren R(6), Sterling TR(7)(8), van der Heijden YF(7)(8)(9).

OBJECTIVES: We compared mortality between HIV-positive and HIV-negative South African adults with drug-resistant tuberculosis (DR-TB) and high incidence of acquired second-line drug resistance.
METHODS: We performed a retrospective review of DR-TB patients with serial second-line TB drug susceptibility tests (2008-2015) who were hospitalized at a specialized TB hospital. We used Kaplan-Meier analysis and Cox models to examine associations with mortality.
RESULTS: Of 245 patients, the median age was 33 years, 54% were male and 40% were HIV-positive, 96% of whom had ever received antiretroviral therapy (ART). At initial drug resistance detection, 99% of patients had resistance to at least rifampicin and isoniazid, and 18% had second-line drug resistance (fluoroquinolones and/or injectable drugs). At later testing, 88% of patients had acquired additional second-line drug resistance. Patient-initiated treatment interruptions (> 2 months) occurred in 47%. Mortality was 79%. Those with HIV had a shorter time to death (p = 0.02; log-rank): median survival time from DR-TB treatment initiation was 2.44 years [95% confidence interval (CI): 2.09-3.15] versus 3.99 years (95% CI: 3.12-4.75) for HIV-negative patients. HIV-positive patients who received ART within 6 months before DR-TB treatment had a higher mortality hazard than HIV-negative patients [adjusted hazard ratio (aHR) ratio = 1.82, 95% CI: 1.21-2.74]. By contrast, HIV-positive patients who did not receive ART within 6 months before DR-TB treatment did not have a significantly higher mortality hazard than HIV-negative patients (aHR = 1.09; 95% CI: 0.72-1.65), although those on ART had lower median CD4 counts than those not on ART (157 vs. 281 cells/μL, respectively; p = 0.02).
CONCLUSIONS: A very high incidence of acquired second-line drug resistance and

high overall mortality were observed, reinforcing the need to reduce the risk of acquired resistance and for more effective treatment.

DOI: 10.1111/hiv.13318
PMID: 35608016 [Indexed for MEDLINE]

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

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

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

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

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

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

29. **Nosiheptide Harbors Potent In Vitro and Intracellular Inhbitory Activities against Mycobacterium tuberculosis.**

Microbiol Spectr. 2022 Oct 12:e0144422. doi: 10.1128/spectrum.01444-22. Online ahead of print.

Yu X(1), Zhu R(1), Geng Z(2), Kong Y(1), Wang F(1), Dong L(1), Zhao L(1), Xue Y(1), Ma X(3), Huang H(1).

Multidrug-resistant tuberculosis (MDR-TB) is often associated with poor clinical outcomes. In this study, we evaluated the potential of nosiheptide (NOS) as a new drug candidate for treating Mycobacterium tuberculosis infections, including MDR-TB. The antimicrobial susceptibility testing was performed to determine the MICs of NOS against 18 reference strains of slowly growing mycobacteria (SGM) and 128 clinical isolates of M. tuberculosis. The postantibiotic effects (PAE) and interaction with other antituberculosis drugs of NOS were also evaluated using M. tuberculosis H37Rv. Fifteen out of the 18 tested reference strains of SGM had MICs far below 1 μg/mL. From the 128 M. tuberculosis clinical isolates, the MIC50 and MIC90 were 0.25 μg/mL and 1 μg/mL, respectively; the tentative epidemiological cutoff (ECOFF) was defined at 1 μg/mL. Furthermore, a Lys89Thr mutation was found in one M. tuberculosis isolate with a MIC of NOS >8 μg/mL. After 24 h of incubation, NOS at 1 μg/mL inhibited 25.79 ± 1.22% of intracellular bacterial growth, which was comparable with the inhibitory rate of 25.71 ± 3.67% achieved by rifampin at 2 μg/mL. Compared to rifampicin and isoniazid (INH), NOS had a much longer PAE, i.e., a value of about 16 days. In addition, a partial synergy between NOS and INH was observed. NOS has potent inhibitory activities against M. tuberculosis in vitro as well as in macrophages. Furthermore, the long PAE and partial synergistic effect with INH, in addition to the added safety of long-term use as a feed additive in husbandry, provide support for NOS being a promising drug candidate for tuberculosis treatment. IMPORTANCE This study is aimed at chemotherapy for MDR-TB, mainly to explore the anti-TB activity of the existing chemotherapeutic reagent. We found that NOS has potent inhibitory activities against M. tuberculosis in vitro regardless of the drug-resistant profile. Furthermore, NOS also showed the long PAE and partial synergistic effect with INH and is nontoxic, providing support for its promise as a drug candidate for drug-resistant tuberculosis treatment.

DOI: 10.1128/spectrum.01444-22
PMID: 36222690

30. **FDA-Approved Amoxapine Effectively Promotes Macrophage Control of Mycobacteria by Inducing Autophagy.**

Microbiol Spectr. 2022 Sep 21:e0250922. doi: 10.1128/spectrum.02509-22. Online ahead of print.

Wang J(1), Sha J(1), Strong E(1), Chopra AK(1), Lee S(1).

Antibiotic resistance poses a significant hurdle in combating global public health crises, prompting the development of novel therapeutics. Strategies to enhance the intracellular killing of mycobacteria by targeting host defense mechanisms offer numerous beneficial effects, which include reducing cytotoxicity caused by current lengthy anti-tubercular treatment regimens and slowing or circumventing the development of multidrug-resistant strains. The intracellular pathogen Mycobacterium tuberculosis infects macrophages and exploits host machinery to survive and multiply. Using a cell-based screen of FDA-approved drugs, we identified an antidepressant, Amoxapine, capable of inhibiting macrophage cytotoxicity during mycobacterial infection. Notably, this reduced cytotoxicity was related to the enhanced intracellular killing of Mycobacterium bovis BCG and M. tuberculosis within human and murine macrophages. Interestingly, we discovered that postinfection treatment with Amoxapine inhibited mTOR (mammalian target of rapamycin) activation, resulting in the induction of autophagy without affecting autophagic flux in macrophages. Also, inhibition of autophagy by chemical inhibitor 3-MA or knockdown of an essential component of the autophagic pathway, ATG16L1, significantly diminished Amoxapine's intracellular killing effects against mycobacteria in the host cells. Finally, we demonstrated that Amoxapine treatment enhanced host defense against M. tuberculosis in mice. In conclusion, our study identified Amoxapine as a novel host-directed drug that enhances the intracellular killing of mycobacteria by induction of autophagy, with concomitant protection of macrophages against death. IMPORTANCE The emergence and spread of multidrug-resistant (MDR) and extensive drug-resistant (XDR) TB urges the development of new therapeutics. One promising approach to combat drug resistance is targeting host factors necessary for the bacteria to survive or replicate while simultaneously minimizing the dosage of traditional agents. Moreover, repurposing FDA-approved drugs presents an attractive avenue for reducing the cost and time associated with new drug development. Using a cell-based screen of FDA-approved host-directed therapies (HDTs), we showed that Amoxapine inhibits macrophage cytotoxicity during mycobacterial infection and enhances the intracellular killing of mycobacteria within macrophages by activating the autophagy pathway, both in vitro and in vivo. These findings confirm targeted autophagy as an effective strategy for developing new HDT

against mycobacteria.

DOI: 10.1128/spectrum.02509-22
PMID: 36129262

31. **Distribution and Pattern of Anti-Tubercular Drug Resistance in Patients with Pulmonary Tuberculosis in Mymensingh Region of Bangladesh.**

Mymensingh Med J. 2022 Oct;31(4):1102-1107.

Hasan MS(1), Hossain MA, Paul SK, Nasreen SA, Ahmed S, Haque N, Hasan M, Khan MK, Das BR, Biswas JP, Islam A.

Globally, the emergence of multidrug-resistant strains of Mycobacterium tuberculosis is an increasing problem that adversely affects patient care and public health. This cross sectional descriptive study was carried out in the Department of Microbiology, Mymensingh Medical College from January 2010 to December 2010 to isolate M. tuberculosis from smear-positive sputum samples by Lowenstein-Jensen (L-J) media and investigate the drug resistance pattern. Among 101 smear-positive cases 80(79.20%) yielded growth of Mycobacteria, 5(4.95%) were contaminated and 16(15.84%) showed no growth. Among 80 isolates 76(95.0%) were M. tuberculosis and the remaining 4(5.0%) were Non-tuberculous Mycobacteria (NTM). Out of 76 M. tuberculosis 27(35.52%) were resistant to at least one drug, 4(5.26%) to Isoniazid (INH), 1(1.32%) to Rifampicin (RMP), 8(10.53%) to Streptomycin (SM) and 0(0.0%) to Ethambutol (EMB) and multi-drug resistant tuberculosis (MDR-TB) was 9(11.84%). The present study creates the impression that fairly high rate of anti-tuberculosis drug resistance among the tuberculosis cases and also high MDR-TB (Resistant to both Rifampicin and Isoniazide). The emergence of MDR-TB poses significant trouble to TB control activities throughout the world. The complexity of MDR-TB operation makes it essential to produce new skills to design, plan, application and monitor interventions for the management of MDR-TB. More surveillance and immediate remedial interventions should be performed to combat the trouble of MDR-TB to the general population.

PMID: 36189558 [Indexed for MEDLINE]

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

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

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

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

33. **Sequencing Mycobacteria and Algorithm-determined Resistant Tuberculosis Treatment (SMARTT): a study protocol for a phase IV pragmatic randomized controlled patient management strategy trial.**

Trials. 2022 Oct 8;23(1):864. doi: 10.1186/s13063-022-06793-w.

Van Rie A(1), De Vos E(2), Costa E(3), Verboven L(2), Ndebele F(4), Heupink TH(2), Abrams S(2); SMARTT team, Fanampe B(5), Van der Spoel Van Dyk A(6), Charalambous S(4), Churchyard G(4), Warren R(3).

Collaborators: Maraba N, Makkan H, Beattie T, Sibeko ZR, Bohlela S, Segwaba P, Ogunbayo EA, Mhlambi N, Wells F, Rigouts L, Maartens G, Conradie F, Black J, Potgieter S.

BACKGROUND: Rifampicin-resistant tuberculosis (RR-TB) remains an important global health problem. Ideally, the complete drug-resistance profile guides individualized treatment for all RR-TB patients, but this is only practised in high-income countries. Implementation of whole genome sequencing (WGS) technologies into routine care in low and middle-income countries has not become a reality due to the expected implementation challenges, including translating WGS results into individualized treatment regimen composition.
METHODS: This trial is a pragmatic, single-blinded, randomized controlled medical device trial of a WGS-guided automated treatment recommendation strategy for individualized treatment of RR-TB. Subjects are 18 years or older and diagnosed with pulmonary RR-TB in four of the five health districts of the Free State province in South Africa. Participants are randomized in a 1:1 ratio to either the intervention (a WGS-guided automated treatment recommendation strategy for individualized treatment of RR-TB) or control (RR-TB treatment according to the national South African guidelines). The primary effectiveness outcome is the bacteriological response to treatment measured as the rate of change in time to liquid culture positivity during the first 6 months of treatment. Secondary effectiveness outcomes include cure rate, relapse rate (recurrence of RR-TB disease) and TB free survival rate in the first 12 months following RR-TB treatment completion. Additional secondary outcomes of interest include safety, the feasibility of province-wide implementation of the strategy into routine care, and health economic assessment from a patient and health systems perspective.

DISCUSSION: This trial will provide important real-life evidence regarding the feasibility, safety, cost, and effectiveness of a WGS-guided automated treatment recommendation strategy for individualized treatment of RR-TB. Given the pragmatic nature, the trial will assist policymakers in the decision-making regarding the integration of next-generation sequencing technologies into routine RR-TB care in high TB burden settings.
TRIAL REGISTRATION: ClinicalTrials.gov NCT05017324. Registered on August 23, 2021.

DOI: 10.1186/s13063-022-06793-w
PMCID: PMC9548157
PMID: 36209235 [Indexed for MEDLINE]

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

34. **Mutations Associated with Pyrazinamide Resistance in Mycobacterium tuberculosis: A Review and Update.**

Curr Microbiol. 2022 Oct 8;79(11):348. doi: 10.1007/s00284-022-03032-y.

Rajendran A(1), Palaniyandi K(2).

Pyrazinamide (PZA) has remained a keystone of tuberculosis (TB) therapy, and it possesses high imperative sterilizing action that can facilitate reduction in the present chemotherapy regimen. The combination of PZA works both with first- and second-line TB drugs, notably fluoroquinolones, clofazimine, bedaquiline, delamanid and pretomanid. Pyrazinamide inhibits various targets that are involved in different cellular processes like energy production (pncA), trans-translation (rpsA) and pantothenate/coenzyme A (panD) which are required for persistence of the pathogen. It is well known that pncA gene encoding pyrazinamidase is involved in the transition of PZA into the active form of pyrazinoic acid, which implies that mutation in the pncA gene can develop PZA resistance in Mycobacterium tuberculosis (M. tuberculosis) strain leading to a major clinical and public health concern. Therefore, it is very crucial to understand its resistance mechanism and to detect it precisely to help in the management of the disease. Scope of this review is to have a deep understanding of molecular mechanism of PZA resistance with its multiple targets which would help study the association of mutations and its resistance in M. tuberculosis. This will in turn help learn about the resistance of PZA and develop more accurate molecular diagnostic tool for drug-resistant TB in future TB therapy.

DOI: 10.1007/s00284-022-03032-y
PMID: 36209317 [Indexed for MEDLINE]

35. **The Relevance of Host Gut Microbiome Signature Alterations on de novo Fatty Acids Synthesis in Patients with Multi-Drug Resistant Tuberculosis.**

Infect Drug Resist. 2022 Sep 21;15:5589-5600. doi: 10.2147/IDR.S372122. eCollection 2022.

Shi J(#)(1), Gao G(#)(2), Yu Z(#)(3), Wu K(4), Huang Y(5), Wu LP(6), Wu Z(1), Ye X(1), Qiu C(1), Jiang X(1).

BACKGROUND: Tuberculosis (TB) is still the single pathogen infectious disease with the largest number of deaths worldwide. The relationship that intestinal microbiota disorder and de novo fatty acid synthesis metabolism have with disease progression in multi-drug resistant TB (MDR-TB) has not yet been fully studied.
OBJECTIVE: To investigate the effects of long periods of MDR-TB, pre-extensively drug-resistant TB (pre-XDR-TB), or rifampicin-resistant TB (RR-TB) on gut microbiome dysbiosis and advanced disease.
METHODS: The sample was chosen between March 2019 and September 2019 in Wenzhou Central Hospital and comprised 11 patients with pre-XDR-TB, 23 patients with RR-TB, and 28 patients with MDR-TB. Healthy individuals were chosen as the control group (CK group). An overnight fast blood sample was drawn via venipuncture into tubes without anticoagulant. For analysis, 300 mg of faeces from patients from the same group was mixed and analysed using DNA extraction, NGS sequencing, and bioinformatics. A QIAamp Fecal DNA Mini Kit was used to isolate the DNA. The extracted DNA was stored at -20°C.
RESULTS: Advanced TB was concurrent with an elevated level of the proportions of acetyl-CoA carboxylase (ACC1) to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and fatty acid synthase (FASN) to GAPDH in de novo fatty acids synthesis, and Eubacterium, Faecalibacterium, Roseburia, and Ruminococcus were increased significantly in RR-TB patients compared to healthy individuals, whereas their abundance in the pre-XDR-TB and MDR-TB groups showed little change in comparison with the control group. Proteobacteria levels were greatly increased in the RR-TB and MDR-TB patient groups but not in the patients with pre-XDR-TB or the healthy subjects. The pre-XDR-TB group exhibited alterations of the intestinal microbiome: coliform flora showed the highest abundance of Verrucomicrobiales, Enterobacteriales, Bifidobacteriales and Lactobacillales. De

novo fatty acids synthesis was enhanced in patients and was associated with the gut microbiome dysbiosis induced by the antimicrobials, with Bacteroidetes, Bacteroidales, and Bacteroidaceae displaying the most important correlations on a phylum, order, and family level, respectively.
CONCLUSION: The progression to advanced TB was observed to be a result of the interaction between multiple interrelated pathways, with gut-lung crosstalk potentially playing a role in patients with drug-resistant TB.

DOI: 10.2147/IDR.S372122
PMCID: PMC9509681
PMID: 36168638

Conflict of interest statement: None of the authors reported a conflict of interest related to the study.

36. **Recent Transmission and Prevalent Characterization of the Beijing Family Mycobacterium tuberculosis in Jiangxi, China.**

Pol J Microbiol. 2022 Sep 24;71(3):371-380. doi: 10.33073/pjm-2022-033. eCollection 2022 Sep 1.

Luo D(1), Yu S(1), Huang Y(2), Zhan J(1), Chen Q(1), Yan L(3), Chen K(1).

The Beijing genotype is the most common type of tuberculosis in Jiangxi Province, China. The association of population characteristics and their prevalence in the development of recent transmission is still unclear. 1,433 isolates were subjected to drug-resistant tests and MIRU-VNTR analysis. We compared differences in demographic characteristics and drug resistance patterns between the Beijing and non-Beijing family strains. We also explored the association of the clustering rate with the Beijing genotype of Mycobacterium tuberculosis. The Beijing genotype was dominant (78.16%). The results of MIRU-VNTR showed that 775 of 1,433 strains have unique patterns, and the remaining gather into 103 clusters. A recent transmission rate was 31.54% (452/1,433). The Beijing genotype strains were more likely to spread among the recurrent population (p = 0.004), people less than 50 years of age (p = 0.02 or 0.003), and the personnel in the northern regions (p = 0.03). Drug resistance patterns did not show significant differences between Beijing and non-Beijing genotype isolates. Furthermore, we found that HIV-positive cases had a lower clustering rate (p = 0.001). Our results indicated that the recurrent population and people under 50 years of age were more likely to be infected with the Beijing genotype of M. tuberculosis. The strains from the Beijing family were

easier to cluster compared to strains isolated from the non-Beijing family. Social activity and AIDS substantially impacted the clustering rate of the Beijing genotype of M. tuberculosis. Multidrug resistant M. tuberculosis affected Beijing genotype transmission.

DOI: 10.33073/pjm-2022-033
PMID: 36185019 [Indexed for MEDLINE]

37. **The economic burden of TB faced by patients and affected families in Papua New Guinea.**

Int J Tuberc Lung Dis. 2022 Oct 1;26(10):934-941. doi: 10.5588/ijtld.21.0664.

Aia P(1), Viney K(2), Kal M(1), Kisomb J(1), Yasi R(1), Wangchuk LZ(3), Islam T(4), Jadambaa N(5), Rehan R(5), Nishikori N(6), Labelle S(6), Ershova J(7).

BACKGROUND The costs associated with TB disease can be catastrophic for patients, affecting health and socioeconomic outcomes. Papua New Guinea (PNG) is a high TB burden country and the costs associated with TB are unknown.METHODS We undertook a national survey of TB patients to determine the magnitude of costs associated with TB in PNG, the proportion of households with catastrophic costs and cost drivers. We used a cluster sampling approach and recruited TB patients from health facilities. Descriptive statistics were used to analyse the costs and cost drivers and multivariate logistic regression to determine factors associated with catastrophic costs.RESULTS We interviewed 1,000 TB patients; 19 (1.9%) of them had multidrug-resistant TB (MDR-TB). Costs due to TB were attributable to income loss (64.4%), non-medical (29.9%) and medical (5.7%) expenses. Catastrophic costs were experienced by 33.9% (95% CI 31.0-36.9) of households and were associated with MDR-TB (aOR 4.47, 95% CI 1.21-16.50), hospitalization (aOR 3.94, 95% CI 2.69-5.77), being in the poorest (aOR 3.52, 95% CI 2.43-5.10) or middle wealth tertiles (aOR 1.51, 95% CI 1.03-2.21) or being employed (aOR 2.02, 95% CI 1.43-2.89).CONCLUSION The costs due to TB disease were catastrophic for one third of TB-affected households in PNG. Current support measures could be continued, while new cost mitigation interventions may be considered where needed.

DOI: 10.5588/ijtld.21.0664
PMID: 36163675 [Indexed for MEDLINE]

38. **Patient and health-care provider experience of a person-centred,**

multidisciplinary, psychosocial support and harm reduction programme for patients with harmful use of alcohol and drug-resistant tuberculosis in Minsk, Belarus.

BMC Health Serv Res. 2022 Sep 30;22(1):1217. doi: 10.1186/s12913-022-08525-x.

Harrison RE(1), Shyleika V(1), Falkenstein C(1), Garsevanidze E(1), Vishnevskaya O(1), Lonnroth K(2), Sayakci Ö(1), Sinha A(3), Sitali N(4), Skrahina A(5), Stringer B(3), Tan C(6), Mar HT(1), Venis S(3), Vetushko D(5), Viney K(2)(7), Vishneuski R(1), Carrion Martin AI(8).

BACKGROUND: Tuberculosis (TB) often concentrates in groups of people with complex health and social issues, including alcohol use disorders (AUD). Risk of TB, and poor TB treatment outcomes, are substantially elevated in people who have AUD. Médecins sans Frontières and the Belarus Ministry of Health have worked to improve treatment adherence in patients with multi-drug or rifampicin resistant (MDR/RR)-TB and harmful use of alcohol. In 2016, a person-centred, multidisciplinary, psychosocial support and harm reduction programme delivered by TB doctors, counsellors, psychiatrists, health-educators, and social workers was initiated. In 2020, we described patient and provider experiences within the programme as part of a wider evaluation.
METHODS: We recruited 12 patients and 20 health-care workers, using purposive sampling, for in-depth individual interviews and focus group discussions. We used a participant-led, flexible, exploratory approach, enabling participants and the interviewer to shape topics of conversation. Qualitative data were coded manually and analysed thematically. As part of the analysis process, identified themes were shared with health-care worker participants to enable their reflections to be incorporated into the findings.
RESULTS: Key themes related to the patients' and practitioners experience of having and treating MDRTB with associated complex health and social issues were: fragility and despair and guidance, trust and health. Prejudice and marginalisation were global to both themes. Counsellors and other health workers built a trusting relationship with patients, enabling guidance through a multi-disciplinary approach, which supported patients to achieve their vision of health. This guidance was achieved by a team of social workers, counsellors, doctors and health-educators who provided professional and individualised help for patients' illnesses, personal or interpersonal problems, administrative tasks, and job searches.
CONCLUSIONS: Patients with MDR/RR-TB and harmful use of alcohol faced complex issues during treatment. Our findings describe how person-centred, multi-disciplinary, psychosocial support helped patients in this setting to cope with these challenges and complete the treatment programme. We recommend that these findings are used to: i) inform programmatic changes to further boost the person-centred care nature of this program; and ii) advocate for this type of

person-centred care approach to be rolled out across Belarus, and in contexts that face similar challenges.

DOI: 10.1186/s12913-022-08525-x
PMCID: PMC9523183
PMID: 36180873 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

39. **Safety and Effectiveness Outcomes From a 14-Country Cohort of Patients With Multi-Drug Resistant Tuberculosis Treated Concomitantly With Bedaquiline, Delamanid, and Other Second-Line Drugs.**

Clin Infect Dis. 2022 Oct 12;75(8):1307-1314. doi: 10.1093/cid/ciac176.

Huerga H(1), Khan U(2), Bastard M(1), Mitnick CD(3)(4)(5), Lachenal N(6), Khan PY(2)(7), Seung KJ(3)(4)(5), Melikyan N(1), Ahmed S(8), Rich ML(3)(4)(5), Varaine F(9), Osso E(3)(6), Rashitov M(10), Salahuddin N(11), Salia G(12), Sánchez E(13), Serobyan A(14), Rafi Siddiqui M(15), Grium Tefera D(16), Vetushko D(17), Yeghiazaryan L(18), Holtzman D(19), Islam S(11), Kumsa A(20), Jacques Leblanc G(21), Leonovich O(22), Mamsa S(11), Manzur-Ul-Alam M(23), Myint Z(24), Padayachee S(25), Franke MF(3), Hewison C(9).

BACKGROUND: Concomitant use of bedaquiline (Bdq) and delamanid (Dlm) for multi-drug/rifampicin resistant tuberculosis (MDR/RR-TB) has raised concerns about a potentially poor risk-benefit ratio. Yet this combination is an important alternative for patients infected with strains of TB with complex drug resistance profiles or who cannot tolerate other therapies. We assessed safety and treatment outcomes of MDR/RR-TB patients receiving concomitant Bdq and Dlm, along with other second-line anti-TB drugs.
METHODS: We conducted a multi-centric, prospective observational cohort study across 14 countries among patients receiving concomitant Bdq-Dlm treatment. Patients were recruited between April 2015 and September 2018 and were followed until the end of treatment. All serious adverse events and adverse events of special interest (AESI), leading to a treatment change, or judged significant by a clinician, were systematically monitored and documented.
RESULTS: Overall, 472 patients received Bdq and Dlm concomitantly. A large majority also received linezolid (89.6%) and clofazimine (84.5%). Nearly all (90.3%) had extensive disease; most (74.2%) had resistance to fluoroquinolones. The most common AESI were peripheral neuropathy (134, 28.4%) and electrolyte depletion (94, 19.9%). Acute kidney injury and myelosuppression were seen in 40

(8.5%) and 24 (5.1%) of patients, respectively. QT prolongation occurred in 7 patients (1.5%). Overall, 78.0% (358/458) had successful treatment outcomes, 8.9% died, and 7.2% experienced treatment failure.
CONCLUSIONS: Concomitant use of Bdq and Dlm, along with linezolid and clofazimine, is safe and effective for MDR/RR-TB patients with extensive disease. Using these drugs concomitantly is a good therapeutic option for patients with resistance to many anti-TB drugs.

DOI: 10.1093/cid/ciac176
PMCID: PMC9555840
PMID: 35243494 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. Bedaquiline donations made from Janssen to the Global Drug Facility were used for patients in the endTB observational study. Donations of delamanid from Otsuka were used for initial patients enrolled in the endTB Observational Study. The companies from which drug donations were received did not have any role on the study design, data analyses, data interpretation or manuscript writing. All other authors report no potential conflicts. 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.

40. **Quantifying Mycobacterium tuberculosis transmission dynamics across global settings: a systematic analysis.**

Am J Epidemiol. 2022 Oct 13:kwac181. doi: 10.1093/aje/kwac181. Online ahead of print.

Smith J(1)(2), Cohen T(3), Dowdy D(4), Shrestha S(4), Gandhi NR(1), Hill AN(5).

The degree to which individual heterogeneity in the production of secondary cases ("superspreading") affects tuberculosis (TB) transmission has not been systematically studied. We searched for population-based or surveillance studies in which whole genome sequencing was used to estimate TB transmission and the size distributions of putative TB transmission clusters were enumerated. We fit cluster size distribution data to a negative binomial branching process model to jointly infer the transmission parameters R (the reproductive number) and dispersion parameter, k, which quantifies the propensity of superspreading in a population (generally, lower values of k (<1.0) suggest increased heterogeneity). Of 4,796 citations identified in our initial search, nine

studies met inclusion criteria ($n=5$ all TB; $n=4$ drug resistant TB) from eight global settings. Estimated R values (range: 0.10, 0.73) were below 1.0, consistent with declining epidemics in the included settings; estimated k values were well below 1.0 (range: 0.02, 0.48), indicating the presence of substantial individual-level heterogeneity in transmission across all settings. We estimated that a minority of cases (range 2-31%) drive the majority (80%) of ongoing transmission at the population level. Identifying sources of heterogeneity and accounting for them in TB control may have a considerable impact on mitigating TB transmission.

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DOI: 10.1093/aje/kwac181
PMID: 36227246

41. **Host cell transcriptomic response to the multidrug-resistant Mycobacterium tuberculosis clonal outbreak Beijing strain reveals its pathogenic features.**

Virulence. 2022 Dec;13(1):1810-1826. doi: 10.1080/21505594.2022.2135268.

Prombutara P(1)(2)(3), Adriansyah Putra Siregar T(3)(4), Laopanupong T(3), Kanjanasirirat P(5), Khumpanied T(5), Borwornpinyo S(5)(6), Rai A(7), Chaiprasert A(8)(9), Palittapongarnpim P(3)(10)(11), Ponpuak M(3)(10).

The upsurge of multidrug-resistant infections has rendered tuberculosis the principal cause of death among infectious diseases. A clonal outbreak multidrug-resistant triggering strain of Mycobacterium tuberculosis was identified in Kanchanaburi Province, labelled "MKR superspreader," which was found to subsequently spread to other regions, as revealed by prior epidemiological reports in Thailand. Herein, we showed that the MKR displayed a higher growth rate upon infection into host macrophages in comparison with the H37Rv reference strain. To further elucidate MKR's biology, we utilized RNA-Seq and differential gene expression analyses to identify host factors involved in the intracellular viability of the MKR. A set of host genes function in the cellular response to lipid pathway was found to be uniquely up-regulated in host macrophages infected with the MKR, but not those infected with H37Rv. Within this set of genes, the IL-36 cytokines which regulate host cell cholesterol metabolism and resistance against mycobacteria attracted our interest, as our previous study revealed that the MKR elevated genes associated with cholesterol breakdown during its growth inside host macrophages. Indeed, when comparing macrophages infected with the MKR to H37Rv-infected cells, our RNA-Seq data showed that the expression ratio of IL-36RN, the negative regulator of the IL-36

pathway, to that of IL-36G was greater in macrophages infected with the MKR. Furthermore, the MKR's intracellular survival and increased intracellular cholesterol level in the MKR-infected macrophages were diminished with decreased IL-36RN expression. Overall, our results indicated that IL-36RN could serve as a new target against this emerging multidrug-resistant M. tuberculosis strain.

DOI: 10.1080/21505594.2022.2135268
PMCID: PMC9578452
PMID: 36242542 [Indexed for MEDLINE]

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

42. **Identification of Arginine Phosphorylation in Mycolicibacterium smegmatis.**

Microbiol Spectr. 2022 Oct 10:e0204222. doi: 10.1128/spectrum.02042-22. Online ahead of print.

Ogbonna EC(1), Anderson HR(2), Schmitz KR(1)(2).

Tuberculosis is a leading cause of worldwide infectious mortality. The prevalence of multidrug-resistant Mycobacterium tuberculosis infections drives an urgent need to exploit new drug targets. One such target is the ATP-dependent protease ClpC1P1P2, which is strictly essential for viability. However, few proteolytic substrates of mycobacterial ClpC1P1P2 have been identified to date. Recent studies in Bacillus subtilis have shown that the orthologous ClpCP protease recognizes proteolytic substrates bearing posttranslational arginine phosphorylation. While several lines of evidence suggest that ClpC1P1P2 is similarly capable of recognizing phosphoarginine-bearing proteins, the existence of phosphoarginine modifications in mycobacteria has remained in question. Here, we confirm the presence of posttranslational phosphoarginine modifications in Mycolicibacterium smegmatis, a nonpathogenic surrogate of M. tuberculosis. Using a phosphopeptide enrichment workflow coupled with shotgun phosphoproteomics, we identified arginine phosphosites on several functionally diverse targets within the M. smegmatis proteome. Interestingly, phosphoarginine modifications are not upregulated by heat stress, suggesting divergent roles in mycobacteria and Bacillus. Our findings provide new evidence supporting the existence of phosphoarginine-mediated proteolysis by ClpC1P1P2 in mycobacteria and other actinobacterial species. IMPORTANCE Mycobacteria that cause tuberculosis infections employ proteolytic pathways that modulate cellular behavior by destroying specific proteins in a highly regulated manner. Some proteolytic enzymes have emerged as novel antibacterial targets against drug-resistant tuberculosis infections. However, we have only a limited understanding of how

these enzymes function in the cell and how they select proteins for destruction. Some proteolytic enzymes are capable of recognizing proteins that carry an unusual chemical modification, arginine phosphorylation. Here, we confirm the existence of arginine phosphorylation in mycobacterial proteins. Our work expands our understanding of a promising drug target in an important global pathogen.

DOI: 10.1128/spectrum.02042-22
PMID: 36214676

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

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

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

ABSTRACTTuberculosis (TB) is more prevalent in rural than urban areas in China, and delineating TB transmission patterns in rural populations could improve TB control. We conducted a prospective population-based study of culture-positive pulmonary TB patients diagnosed between July 1, 2009 and December 31, 2020 in two rural counties in China. Genomic clusters were defined with a threshold distance of 12-single-nucleotide-polymorphisms, based on whole-genome sequencing. Risk factors for clustering were identified by logistic regression. Transmission links were sought through epidemiological investigation of genomic-clustered patients. Of 1517 and 751 culture-positive pulmonary TB patients in Wusheng and Wuchang counties, respectively, 1289 and 699 strains were sequenced. Overall, 624 (31.4%, 624/1988) patients were grouped into 225 genomic clusters. Epidemiological links were confirmed in 41.8% (196/469) of clustered isolates, including family (32.7%, 64/196) and social contacts (67.3%, 132/196). Social contacts were generally with relatives, within the community or in shared aggregated settings outside the community, but the proportion of clustered contacts in each category differed between the two sites. The time interval between diagnosis of student cases and contacts was significantly shorter than family and social contacts, probably due to enhanced student contact screening. Transmission of multidrug-resistant (MDR) strains was likely responsible for 81.4% (83/102) of MDR-TB cases, with minimal acquisition of additional resistance mutations. A large proportion of TB transmission in rural China occurred among social contacts, suggesting that active screening and aggressive contact tracing could benefit TB control, but contact screening

should be tailored to local patterns of social interactions.

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

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

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

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

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

New chemical scaffolds with novel mechanism of action are urgently needed for the treatment of drug resistant tuberculosis. The oxidative phosphorylation pathway of Mycobacterium tuberculosis consists of multiple clinically validated drug targets. This pathway can function through any one of the two terminal oxidases-the proton pumping cytochrome bc1-aa3 supercomplex, or the less energy efficient but high affinity cytochrome bd oxidase. Inhibiting the bc1 complex alone has been found bacteriostatic and not bactericidal. On the other hand, inhibition of both these oxidases turns lethal to the pathogen. In the present study, we used a bc1 complex mutant of M. tuberculosis to screen (Quinazoline 4-yloxy)acetamide and (4-oxoquinazoline-3(4H)-yl)acetamide derivatives against the alternate oxidase, i.e., cytochrome bd oxidase. Two molecules, S-021-0601 and S-021-0607 were found to inhibit the mutant with MICs 8 and 16 μM respectively, compared to MICs of 128 and 256 μM against the wild type M. tuberculosis. In the wild type, one of the compounds showed synergism with Q203, an inhibitor of bc1 complex, in inhibiting growth under aerobic conditions. Both compounds showed synergism with Q203 in depleting bacterial ATP and inhibiting oxygen consumption. Both the compounds at 32 μM (one-fourth or one-eighth of their MICs for wild type) were bactericidal to wild type bacteria under hypoxic condition, causing ∼1.9 log10 reduction in viable counts which increased to ∼4-log10 when combined with Q203.

DOI: 10.1016/j.ejmech.2022.114639

PMID: 35973312 [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.

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

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

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

Author information:
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BACKGROUND: People living with human immunodeficiency virus (HIV) are more likely to develop tuberculosis (TB), and their co-infection (HIV-TB) increases the risk of death. We aimed to describe the global trends, regional differences and age distribution of HIV-TB.
METHODS: Annual new cases, age-standardized incidence rates (ASRs) and age-specific incidence rates with 95% uncertainty intervals (UIs) of HIV-infected drug-susceptible tuberculosis (HIV-DS-TB), HIV-infected multidrug-resistant tuberculosis without extensive drug resistance (HIV-MDR-TB) and HIV-infected extensively drug-resistant tuberculosis (HIV-XDR-TB) during 1990-2019 were collected from the Global Burden of Disease Study 2019. To reveal the trends of HIV-TB by region and age, the percentage change of new cases and estimated annual percentage change (EAPC) of ASRs were calculated.
RESULTS: The ASR of HIV-XDR-TB increased significantly by an average of 14.77% (95% CI: 11.05%-18.62%) per year during 1990-2019 worldwide, while the ASRs of HIV-DS-TB and HIV-MDR-TB decreased after 2005. HIV-XDR-TB was a great threat to Eastern Europe for the largest number of new cases (792, 95% UI: 487-1167) and the highest ASR (0.34 per 100,000 population, 95% UI: 0.21-0.50). In addition, Oceania had the largest rise in ASRs of HIV-MDR-TB (EAPC = 22.56, 95% CI: 18.62-26.64) and HIV-XDR-TB (EAPC = 32.95, 95% CI: 27.90-38.20) during 1990-2019. Recently, age-specific incidence rates of HIV-XDR-TB increased in all age groups, especially in the 50-69 age groups among high, low-middle and low Socio-Demographic Index regions. Additionally, the proportion of patients aged <15 years was nearly 10% of new cases in sub-Saharan Africa in 2019, which was

higher than in other regions.
CONCLUSIONS: HIV-infected drug-resistant TB is common in Oceania and Eastern Europe. Moreover, HIV-XDR-TB among elderly people became increasingly prevalent. In the future, the collaboration of management for HIV and TB should be intensified in Oceania and Eastern Europe, and more concerns need to be paid in elderly people.

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

46. **Proteomic analysis of sequential isolates of multidrug-resistant Mycobacterium tuberculosis during treatment failure.**

J Infect. 2022 Nov;85(5):e137-e139. doi: 10.1016/j.jinf.2022.08.010. Epub 2022 Aug 17.

Lee DG(1), Kim HJ(2), Park MJ(3), Hong JH(2), Ryoo S(4).

DOI: 10.1016/j.jinf.2022.08.010
PMID: 35987390 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest None.

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

J Biomol Struct Dyn. 2022 Nov;40(18):8508-8517. doi: 10.1080/07391102.2021.1913230. Epub 2021 Apr 16.

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

Tuberculosis (TB) is one of the prominent cause of deaths across the world and multidrug-resistant and extensively drug-resistant TB continues to pose challenges for clinicians and public health centers. The risk of death is extremely high in individuals who have compromised immune systems, HIV infection, or diabetes. Research institutes and pharmaceutical companies have been working on repurposing existing drugs as effective therapeutic options against TB. The identification of suitable drugs with multi-target affinity profiles is a widely accepted way to combat the development of resistance. Flavin-dependent thymidylate synthase (FDTS), known as ThyX, is in the class of methyltransferases and is a possible target in the discovery of novel anti-TB

drugs. In this study, we aimed to repurpose existing drugs approved by Food and Drug Administration (FDA) that could be used in the treatment of TB. An integrated screening was performed based on computational procedures: high-throughput molecular docking techniques, followed by molecular dynamics simulations of the target enzyme, ThyX. After performing in silico screening using a library of 3,967 FDA-approved drugs, the two highest-scoring drugs, Carglumic acid and Mesalazine, were selected as potential candidates that could be repurposed to treat TB.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2021.1913230
PMID: 33860725 [Indexed for MEDLINE]

48. **Adherence to Recommendations for Bacillus Calmette-Guérin Vaccination of High-risk Neonates in Greece.**

Pediatr Infect Dis J. 2022 Oct 1;41(10):857-859. doi: 10.1097/INF.0000000000003623. Epub 2022 Jul 22.

Maltezou HC(1), Magaziotou I(2), Tseroni M(3), Syrigonaki K(2), Syrogiannopoulos GA(4), Tsolia M(5), Roilides E(6), Theodoridou M(7), Georgakopoulou T(2).

In 2016 a Bacillus Calmette-Guérin vaccination policy targeting high-risk neonates for tuberculosis before discharge from maternity hospital was adopted in Greece. Vaccination rates were 38.2% in 2019 and 24.7% in 2020. Vaccination coverage varied by risk group (higher for neonates in close contact with an active noncompliant or multidrug-resistant tuberculosis case and lower for Roma and immigrant neonates).

DOI: 10.1097/INF.0000000000003623
PMID: 35763676 [Indexed for MEDLINE]

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

49. **Whole-Genome Sequencing for Resistance Prediction and Transmission Analysis of Mycobacterium tuberculosis Complex Strains from Namibia.**

Microbiol Spectr. 2022 Sep 27:e0158622. doi: 10.1128/spectrum.01586-22. Online ahead of print.

Claassens M(#)(1), Dreyer V(#)(2)(3), Nepolo E(#)(1), Mokomele Q(4), van Rooyen G(4), Ruswa N(5), Günther G(#)(1)(6)(7), Niemann S(#)(1)(2)(3).

Namibia is among 30 countries with a high burden of tuberculosis (TB), with an estimated incidence of 460 per 100,000 population and around 800 new multidrug-resistant (MDR) TB cases per year. Still, data on the transmission and evolution of drug-resistant Mycobacterium tuberculosis complex (Mtbc) strains are not available. Whole-genome sequencing data of 136 rifampicin-resistant (RIFr) Mtbc strains obtained from 2016 to 2018 were used for phylogenetic classification, resistance prediction, and cluster analysis and linked with phenotypic drug susceptibility testing (pDST) data. Roughly 50% of the strains investigated were resistant to all first-line drugs. Furthermore, 13% of the MDR Mtbc strains were already pre-extensively drug resistant (pre-XDR). The cluster rates were high, at 74.6% among MDR and 85% among pre-XDR strains. A significant proportion of strains had borderline resistance-conferring mutations, e.g., inhA promoter mutations or rpoB L430P. Accordingly, 25% of the RIFr strains tested susceptible by pDST. Finally, we determined a potentially new bedaquiline resistance mutation (Rv0678 D88G) occurring in two independent clusters. High rates of resistance to first-line drugs in line with emerging pre-XDR and likely bedaquiline resistance linked with the ongoing recent transmission of MDR Mtbc clones underline the urgent need for the implementation of interventions that allow rapid diagnostics to break MDR TB transmission chains in the country. A borderline RIFr mutation in the dominant outbreak strain causing discrepancies between phenotypic and genotypic resistance testing results may require breakpoint adjustments but also may allow individualized regimens with high-dose treatment. IMPORTANCE The transmission of drug-resistant tuberculosis (TB) is a major problem for global TB control. Using genome sequencing, we showed that 13% of the multidrug-resistant (MDR) M. tuberculosis complex strains from Namibia are already pre-extensively drug resistant (pre-XDR), which is substantial in an African setting. Our data also indicate that the ongoing transmission of MDR and pre-XDR strains contributes significantly to the problem. In contrast to other settings with higher rates of drug resistance, we found a high proportion of strains having so-called borderline low-level resistance mutations, e.g., inhA promoter mutations or rpoB L430P. This led to the misclassification of 25% of the rifampicin-resistant strains as susceptible by phenotypic drug susceptibility testing. This observation potentially allows individualized regimens with high-dose treatment as a potential option for patients with few treatment options. We also found a potentially new bedaquiline resistance mutation in rv0678.

DOI: 10.1128/spectrum.01586-22
PMID: 36165641

50. **Feasibility, ease-of-use and operational characteristics of WHO-recommended moderate complexity automated NAATs for the detection of TB and resistance to rifampicin and isoniazid.**

J Mol Diagn. 2022 Oct 12:S1525-1578(22)00289-6. doi: 10.1016/j.jmoldx.2022.10.001. Online ahead of print.

David A(1), de Vos M(2), Scott L(3), da Silva P(4), Trollip A(2), Ruhwald M(2), Schumacher S(2), Stevens W(5).

Four moderate complexity automated Nucleic Acid Amplification Test for the diagnosis of tuberculosis are reported as having similar laboratory analytical and clinical performance to the Cepheid Xpert MTB/RIF assay. These assays are the Abbott RealTime MTB and RealTime MTB RIF/INH Resistance, Becton Dickinson MAX MDR-TB, the Hain Lifescience/Bruker FluoroType MTBDR and the Roche cobas MTB and MTB RIF/INH assay. The study compared feasibility, ease of use and operational characteristics of these assays/platforms. Manufacturer input was obtained for technical characteristics. Laboratory operators were requested to complete a questionnaire on their ease-of-use. A time-in-motion analysis was also undertaken for each platform. For ease-of-use and operational requirements, the BD MAX MDR-TB assay achieved the highest scores (86% and 90%) based on information provided by the user and manufacturer, respectively, followed by the cobas MTB and MTB-RIF/INH assay (68% and 86%), the FluoroType MTBDR assay (67% and 80%) and Abbott RT-MTB and RT MTB RIF/INH assays (64% and 76%). The time-in-motion analysis demonstrated that for 94 specimens, the RealTime MTB assay required the longest processing time, followed by the cobas MTB assay and the FluoroType MTBDR assay. The BD MAX MDR-TB assay required 4.6 hours for 22 specimens. These diagnostic assays exhibited different strengths and weaknesses. These should be taken into account, in addition to affordability, when considering placement of a new platform.

DOI: 10.1016/j.jmoldx.2022.10.001
PMID: 36243289

51. **Pediatric delamanid treatment for children with rifampicin-resistant TB.**

Int J Tuberc Lung Dis. 2022 Oct 1;26(10):986-988. doi: 10.5588/ijtld.22.0264.

Tyeku N(1), Apolisi I(1), Daniels J(1), Beko B(1), Memani B(1), Cengani L(2), Fatshe S(2), Gumede N(2), Joseph K(3), Mathee S(2), Furin J(4), Maugans C(5), Cox H(6), Reuter A(1).

DOI: 10.5588/ijtld.22.0264
PMCID: PMC9524514
PMID: 36163672 [Indexed for MEDLINE]

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

52. **Factors affecting the treatment outcome of injection based shorter MDR-TB regimen at a referral centre in India.**

Monaldi Arch Chest Dis. 2022 Oct 5. doi: 10.4081/monaldi.2022.2396. Online ahead of print.

B K(1), Singla R(2), Singla N(3), V V(4), Singh K(5), Choudhury MP(6), Bhattacherjee N(7).

Rifampicin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB) is a significant burden on global tuberculosis (TB) prevention and eradication efforts. MDR-TB can be treated, but it is expensive, takes a long time (typically two years), and contains potentially toxic drugs. Under certain conditions, the WHO recommends standard regimens lasting 9 to 11 months rather than individual regimens lasting at least 18-20 months. The current study sought to identify factors associated with treatment outcome in RR/MDR-TB patients receiving an injection-based regimen for 9-11 months. This ambispective (prospective and retrospective) observational study was conducted at a tertiary tuberculosis institute in New Delhi, India. Between February 2021 and March 2022, patients with RR/MDR-pulmonary TB who received an injection-based shorter regimen were enrolled. Factors related to treatment outcome were investigated and compared in patients who had a successful outcome versus those who did not. A total of 55 patients were enrolled, with 50.91% being successful (cured/treatment completed) and 49.09% failing (including failure, lost to follow up, death, and regimen changed). The following factors were significantly associated with the unsuccessful outcome, according to univariate analysis: BMI (18.5 kg/m2), anaemia, previous anti-TB treatment, bilateral chest X-ray involvement, and far advanced disease on chest X-ray BMI (18.5 kg/m2), anaemia, and far advanced disease on chest X-ray were all significantly associated with mortality. Anaemia was associated with an unsuccessful outcome (p=0.049) and mortality (p=0.048) in the multiple logistic regression analysis. Early treatment initiation, improved nutrition and anaemia, and regular monitoring can all improve RR/MDR-TB patients' outcomes and prognoses.

DOI: 10.4081/monaldi.2022.2396
PMID: 36200688

53. **Budget impact of next-generation sequencing for diagnosis of TB drug resistance in Moldova.**

Int J Tuberc Lung Dis. 2022 Oct 1;26(10):963-969. doi: 10.5588/ijtld.22.0104.

Cates L(1), Codreanu A(2), Ciobanu N(2), Fosburgh H(3), Allender CJ(4), Centner H(4), Engelthaler DM(4), Crudu V(2), Cohen T(3), Menzies NA(1).

BACKGROUND Diagnosing drug resistance is critical for choosing effective TB treatment regimens. Next-generation sequencing (NGS) represents an alternative approach to conventional phenotypic drug susceptibility testing (pDST) for diagnosing TB drug resistance.METHODS We undertook a budget impact analysis estimating the costs of introduction and routine use of NGS in the Moldovan National TB Programme. We conducted an empirical costing study and collated price and operating characteristics for NGS platforms. We examined multiple NGS scenarios in comparison to the current approach (pDST) for pre-treatment drug resistance testing over 2021-2025.RESULTS Annual testing volume ranged from 912 to 1,926 patients. For the pDST scenario, we estimated total costs of US$362,000 (2021 USD) over the 5-year study period. Total costs for NGS scenarios ranged from US$475,000 to US$1,486,000. Lowest cost NGS options involved targeted sequencing as a replacement for pDST, and excluded individuals diagnosed as RIF-susceptible on Xpert® MTB/RIF. For all NGS scenarios, the majority (55-80%) of costs were devoted to reagent kits. Start-up costs of NGS were small relative to routine costs borne each year.CONCLUSION NGS adoption will require expanded resources compared to conventional pDST. Further work is required to better understand the feasibility of NGS in settings such as Moldova.

DOI: 10.5588/ijtld.22.0104
PMID: 36163669 [Indexed for MEDLINE]

55. **[Expert consensus on the treatment of chronic kidney disease with tuberculosis (2022 version)].**

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Oct 12;45(10):996-1008. doi: 10.3760/cma.j.cn112147-20220327-00241.

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

Chinese Society for Tuberculosis, Chinese Medical Association.

China is a country with a high burden of chronic kidney disease(CKD) and tuberculosis. Patients with CKD are at increased risk of Mycobacterium

tuberculosis infection, and the prevalence of CKD is also significantly higher in patients with tuberculosis. The coexistence of the two diseases brings great difficulties for clinical treatment. In this consensus, the general situation, clinical characteristics, metabolic characteristics of anti-tuberculous drugs, and the principles of protocol formulation of such patients were discussed and summarized. When making anti-tuberculosis regimen for patients with chronic renal failure, drugs that metabolized through liver, liver and kidney channels or metabolic pathways other than liver and kidney should be selected as far as possible. Drugs with significant renal toxicity and mainly metabolized by the kidney should be avoided. For CKD patients with mild decrease in GFR (60-89 ml·min-1·1.73 m-2), anti-tuberculosis regimen should be carried out according to the national standards and guidelines, without reducing the dose of anti-tuberculosis drugs. For CKD patients with significantly reduced GFR, mainly CKD3b, stages 4-5, and those receiving dialysis, the anti-tuberculosis regimen must be adjusted according to the GFR. For CKD patients with GFR less than 30 ml·min-1·1.73 m-2, this consensus also recommended anti-tuberculous regimen for initial, retreated and multi-drug-resistant tuberculosis patients. This consensus aimed to improve clinicians' understanding of CKD complicated with tuberculosis, standardize the clinical treatment, improve the curative effect, and reduce adverse reactions. Data from previous trials of CKD combined with TB treatment are still scarce. We look forward to further investigation and evidence-based medical research on CKD with tuberculosis in the future, and make positive efforts for the control of CKD and tuberculosis in China.

DOI: 10.3760/cma.j.cn112147-20220327-00241
PMID: 36207956 [Indexed for MEDLINE]

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

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

Soetaert K(1), Ceyssens PJ(1), Boarbi S(1), Bogaerts B(2)(3), Delcourt T(2), Vanneste K(2), De Keersmaecker SCJ(2), Roosens NHC(2), Vodolazkaia A(4), Mukovnikova M(4), Mathys V(1).

OBJECTIVES: Since January 2019, the Belgian National Reference Center for Mycobacteria (NRC) has switched from conventional typing to prospective whole-genome sequencing (WGS) of all submitted Mycobacterium tuberculosis complex (MTB) isolates. The ISO17025 validated procedure starts with semi-automated extraction and purification of gDNA directly from the submitted MGIT tubes, without preceding subculturing. All samples are then sequenced on an

Illumina MiSeq sequencer and analyzed using an in-house developed and validated bioinformatics workflow to determine the species and antimicrobial resistance. In this study, we retrospectively compare results obtained via WGS to conventional phenotypic and genotypic testing, for all Belgian MTB strains analyzed in 2019 (n = 306).
RESULTS: In all cases, the WGS-based procedure was able to identify correctly the MTB species. Compared to MGIT drug susceptibility testing (DST), the sensitivity and specificity of genetic prediction of resistance to first-line antibiotics were respectively 100 and 99% (rifampicin, RIF), 90.5 and 100% (isoniazid, INH), 100 and 98% (ethambutol, EMB) and 61.1 and 100% (pyrazinamide, PZA). The negative predictive value was above 95% for these four first-line drugs. A positive predictive value of 100% was calculated for INH and PZA, 80% for RIF and 45% for EMB.
CONCLUSIONS: Our study confirms the effectiveness of WGS for the rapid detection of M. tuberculosis complex and its drug resistance profiles for first-line drugs even when working directly on MGIT tubes, and supports the introduction of this test into the routine workflow of laboratories performing tuberculosis diagnosis.

DOI: 10.1080/17843286.2021.1999588
PMID: 34751641 [Indexed for MEDLINE]

57. **Characterization of Genetic Variants Associated with Rifampicin Resistance Level in Mycobacterium tuberculosis Clinical Isolates Collected in Guangzhou Chest Hospital, China.**

Infect Drug Resist. 2022 Sep 27;15:5655-5666. doi: 10.2147/IDR.S375869. eCollection 2022.

Hameed HMA(#)(1)(2)(3)(4), Fang C(#)(1)(2)(3)(4), Liu Z(1)(2)(3), Ju Y(1)(2)(3), Han X(1)(2)(3)(4), Gao Y(1)(2)(3)(4), Wang S(1)(2)(3)(5), Chiwala G(1)(2)(3)(4), Tan Y(6), Guan P(6), Hu J(6), Xiong X(1)(2)(3), Peng J(3)(7), Lin Y(3)(7), Hussain M(4), Zhong N(3)(7)(8), Maslov DA(9), Cook GM(10)(11), Liu J(6), Zhang T(1)(2)(3)(4).

OBJECTIVE: Rifampicin (RIF)-resistance, a surrogate marker for multidrug-resistant tuberculosis (TB), is mediated by mutations in the rpoB gene. We aimed to investigate the prevalence of mutations pattern in the entire rpoB gene of Mycobacterium tuberculosis clinical isolates and their association with resistance level to RIF.
METHODS: Among 465 clinical isolates collected from the Guangzhou Chest Hospital, drug-susceptibility of 175 confirmed Mtb strains was performed via the proportion method and Bactec MGIT 960 system. GeneXpert MTB/RIF and sanger

sequencing facilitated in genetic characterization, whereas the MICs of RIF were determined by Alamar blue assay.
RESULTS: We found 150/175 (85.71%) RIF-resistant strains (MIC: 4 to >64 µg/mL) of which 57 were MDR and 81 pre-XDR TB. Genetic analysis identified 17 types of mutations 146/150 (97.33%) within RRDR (codons 426-452) of rpoB, mainly at L430 (P), D435 (V, E, G, N), H445 (N, D, Y, R, L), S450 (L, F) and L452 (P). D435V 12/146 (8.2%), H445N 16/146 (10.9%), and S450L 70/146 (47.94%) were the most frequently encountered mutations. Mutations Q432K, M434V, and N437D are rarely identified in RRDR. Deletions at (1284-1289 CCAGCT), (1295-1303 AATTCATGG), and insertion at (1300-1302 TTC) were detected within RRDR of three RIFR strains for the first time. We detected 47 types of mutations and insertions/deletions (indels) outside the RRDR. Four RIFR strains were detected with only novel mutations/indels outside the RRDR. Two of the four had (K274Q + C897 del + I491M) and (A286V + L494P), respectively. The other two had (G1687del + P454L) and (TT1835-6 ins + I491L) individually. Compared with phenotypic characterization, diagnostic sensitivities of GeneXpert MTB/RIF and sequencing analysis were 95.33% (143/150), and 100% (150/150) respectively.
CONCLUSION: Our findings underscore the key role of RRDR mutations and the contribution of non-RRDR mutations in rapid molecular diagnosis of RIFR clinical isolates. Such insights will support early detection of disease and recommend the appropriate anti-TB regimens in high-burden settings.

DOI: 10.2147/IDR.S375869
PMCID: PMC9526423
PMID: 36193294

Conflict of interest statement: Dr Dmitry A Maslov reports grants from Russian Science Foundation, during the conduct of the study. All authors approved the study to publish in your esteemed journal and declare no competing interests.

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

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

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

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

DOI: 10.1002/cpt.2685
PMCID: PMC9474693
PMID: 35687528 [Indexed for MEDLINE]

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

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

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

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

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

DOI: 10.1080/22221751.2021.2022439
PMCID: PMC8786254
PMID: 34935599 [Indexed for MEDLINE]

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

60. **Pyridine-N-Oxide Alkaloids from Allium stipitatum and Their Synthetic Disulfide Analogs as Potential Drug Candidates against Mycobacterium tuberculosis: A Molecular Docking, QSBAR, and ADMET Prediction Approach.**

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In this study, we consider pyridine-N-oxide alkaloids from Allium stipitatum and their synthetic disulfide analogs (PDAs) as candidates for next-generational antimycobacterial agents, in light of growing resistance to existing conventional therapies. In silico studies involving molecular docking simulations of 12 PDAs were carried out against 7 Mycobacterium tuberculosis target proteins (MTs) to determine their theoretical binding affinities. Compounds A3, A6, and B9 demonstrated stronger binding affinities on similar MTs. Molecular descriptors (MDs) describing structural and physicochemical properties of the compounds were also calculated using ChemDes, explored using Pearson's correlation analysis, and principal component analysis (PCA) in comparison with MDs from conventional antitubercular medicines. The PDAs possessed similar scores as isoniazid and pyrazinamide. The MDs were also used to conduct a quantitative structure-binding affinity relationship (QSBAR) study by building good fit and significant models through principal component regression (PCR) and partial least squares regression (PLSR). Leave-one-out cross-validation was adopted in the PLSR, resulting in good predictive models on all MTs (range of R 2 = 0.7541-0.8992; range of Q 2 = 0.6183-0.8162). Both PCR and PLSR models predicted the significant effects of ndonr, Hy, Mol wt, nhev, nring, ndb, Log P, W, Pol, ISIZ, TIAC, Getov, and UI on the binding of ligands to the MTs. In silico prediction of PDAs' ADMET profiles was conducted with QikProp utility. The ADMET profiles of the compounds were favorable. The outcome of the current study strengthens the significance of these compounds as promising lead candidates for the treatment of multidrug-resistant tuberculosis.

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61. **Development and Assessment of a Novel Whole-Gene-Based Targeted Next-Generation Sequencing Assay for Detecting the Susceptibility of Mycobacterium tuberculosis to 14 Drugs.**

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Targeted next-generation sequencing (tNGS) has emerged as an alternative method for detecting drug-resistant tuberculosis (DR-TB). To provide comprehensive drug susceptibility information and to address mutations missed by available commercial molecular diagnostics, we developed and evaluated a tNGS panel with 22 whole-gene targets using the Ion Torrent platform to predict drug resistance to 14 drugs, namely, rifampicin (RIF), isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA), moxifloxacin (MFX), levofloxacin (LFX), amikacin (AMK), capreomycin (CM), kanamycin (KM), streptomycin (SM), bedaquiline (BDQ), clofazimine (CFZ), linezolid (LZD), and delamanid (DLM). We selected 50 and 35 Mycobacterium tuberculosis isolates with various DR profiles as the training set and the challenge set, respectively. Comparative variant analyses of the DR genes were performed using Sanger sequencing and whole-genome sequencing (WGS). Phenotypic drug susceptibility testing (pDST) results were used as gold standards. Regarding the limit of detection, the tNGS assay detected 2.9 to 3.8% minority variants in 4% mutant mixtures. The sensitivity and specificity of tNGS were 97.0% (95% confidence interval [CI] = 93.1 to 98.7%) and 99.1% (95% CI = 97.7 to 99.7%), respectively. The concordance of tNGS with pDST was 98.5% (95% CI = 97.2 to 99.2%), which was comparable to that of WGS (98.7%, 95% CI = 97.4 to 99.3%) and better than that of Sanger sequencing (96.9%, 95% CI = 95.3 to 98.0%). The agreement between tNGS and pDST was almost perfect for RIF, INH, EMB, MFX, LFX, AMK, CM, KM, SM, BDQ, and LZD (kappa value = 0.807 to 1.000) and substantial for PZA (kappa value = 0.791). Our customized novel whole-gene-based tNGS panel is highly consistent with pDST and WGS for comprehensive and accurate prediction of drug resistance in a strengthened and streamlined DR-TB laboratory program. IMPORTANCE We developed and validated a tNGS assay that was the first to target 22 whole genes instead of regions of drug resistance genes and comprehensively detected susceptibility to 14 anti-TB drugs, with great flexibility to include new or repurposed drugs. Notably, we demonstrated that our custom-designed Ion AmpliSeq TB research panel platform had high concordance with pDST and could significantly reduce turnaround time (by approximately 70%) to meet a clinically actionable time frame. Our tNGS assay is a promising DST solution for providing needed clinical information for precision medicine-guided therapies for DR-TB and allows the rollout of active pharmacovigilance.

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62. **Disruption to TB services in Ukraine: less than feared.**

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Holt E.

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63. **In Vitro Activity of the Sudapyridine (WX-081) against Non-Tuberculous Mycobacteria Isolated in Beijing, China.**

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Zhu R(#)(1), Shang Y(#)(1)(2), Chen S(#)(1), Xiao H(1), Ren R(1), Wang F(1), Xue Y(1), Li L(3), Li Y(3), Chu N(2), Huang H(1).

Sudapyridine (WX-081) is a structural analog of bedaquiline (BDQ), which shows an anti-tuberculosis activity but, unlike BDQ, did not prolong QT interval (QT) in animal model studies. This study evaluated the antimicrobial activity of this novel drug against non-tuberculous mycobacteria (NTM). Fifty reference strains of different mycobacterial species, and 132 NTM clinical isolates from four commonly isolated NTM species were recruited. The microplate alamarBlue assay was performed to determine the MIC of WX-081 and BDQ. Cytotoxicity assay was performed for both drugs using the THP-1 cells, and the minimum bactericidal concentrations (MBCs) of both drugs against the reference strains of five selected NTM species were also determined. All the tested reference strains had MICs lower than 0.5 μg/mL, with the majority having MICs far below 0.1 μg/mL for WX-081. The epidemiological cut-offs of WX-081 ranged from 0.0156 μg/mL to 0.25 μg/mL against commonly isolated NTM, and this value was comparable with that of BDQ. The MBC/MIC ratios suggest a bacteriostatic activity for both drugs against the five selected NTM species. Cytotoxicity assays indicated that THP-1 cells had nearly 100% viability when exposed to WX-081 for 24 h below 4 μg/mL, 200- to 300-fold the MICs of Mycobacterium intracellulare, Mycobacterium avium, and Mycobacterium kansasii. WX-081 has a strong antimicrobial activity against different NTM species with low cytotoxicity and therefore has the potential to be used for treating NTM infections. IMPORTANCE Due to the rapidly increased cases globally, non-tuberculous mycobacteria (NTM) disease has become a significant public health problem. Over 200 species or subspecies of NTM have been reported, whereas pulmonary diseases in humans are caused mainly by M. avium complex (MAC), M. kansasii, and M. abscessus. Treatment of NTM infection is often challenging as natural resistance to most antibiotics is quite common among different NTM species. Hence, identifying highly active anti-NTM agents is a priority for potent regimen establishment. The pursuit of new drugs to treat multidrug-resistant-tuberculosis (MDR-TB) may also identify some agents with strong activity against NTM. Sudapyridine (WX-081) is a structural analog of bedaquiline (BDQ), which was developed to retain the antituberculosis efficacy

but eliminate the severe side effect of BDQ. This study initially evaluated the antimicrobial activity of this novel drug against non-tuberculous mycobacteria (NTM).

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64. **A glimpse into the genotype and clinical importance of non tuberculous mycobacteria among pulmonary tuberculosis patients: The case of Ethiopia.**

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Laboratory identification of nontuberculous mycobacteria (NTM) species is not regularly performed while, they have a public health importance with a prevalence of more than 5% among pulmonary tuberculosis (PTB) patients in Ethiopia. Hence, this study aimed to identify the NTM species and their clinical significance among PTB patients. A retrospective study was conducted at the Ethiopian Public Health Institution's (EPHI's) national TB referral laboratory. Stored NTM isolates were genotyped using GenoType Mycobacterium CM/AS kit (Hain Life science, Germany). Data pertinent to the study was extracted from the EPHI's database and patients' medical records. Between January 2 & December 28 of 2017, a total of 3,834 samples were processed from 698 TB patients of whom 50% were female. Among 3,317 samples with mycobacterial culture results 7.3% were NTM and majority of them were identified from smear negative TB patients. M. simiae was the /predominant NTM among the genotyped isolates. All the studied NTM species were not clinically important however, considering the similarity of clinical and radiologic findings between NTM and MTBC infected patients, integrating NTM species identification in the routine TB laboratory diagnosis may augment clinicians' decision particularly in DR-TB patients. Additional similar prospective study with a larger sample size is recommended. Moreover, urgent improvements on patients' record keeping practice are required in the studied hospitals.

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65. **Do unmanned aerial vehicles reduce the duration and costs in transporting sputum samples? A feasibility study conducted in Himachal Pradesh, India.**

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BACKGROUND: The feasibility of and advantages of using an unmanned aerial vehicle (UAV) for sputum transportation for TB in Chamba, Himachal Pradesh, India, were evaluated.
METHODS: We conducted a non-randomized interventional study and compared the advantages of sputum transport between UAVs and motorbikes (conventional).
RESULTS: We completed 151 transportations. Transportation by UAV (7.1±0.8 min) was faster than by motorbike (22.7±4.6 min, p<0.001). Motorbikes covered a greater distance (12.09±1.6 km) than UAVs (2.89±0.35 km, p<0.001). The recurrent cost per transport using an UAV (US${\$}$0.68) was less than by motorbike (US${\$}$1.4). All 26 stakeholders agreed that UAVs would reduce the turnaround time for diagnosis of drug-resistant TB.
CONCLUSIONS: Sputum transportation by UAVs was feasible, cheaper and an efficacious potential alternative to conventional modes of transportation.

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News

1. Smart pill box can help with TB treatment, but it's not for everyone
https://www.tbonline.info/posts/2022/10/6/smart-pill-box-can-help-tb-treatment-its-not-every/

Tuberculosis (TB) can be cured, but completing TB treatment can sometimes be difficult. Treatment for drug-susceptible forms of TB takes six months and some of the medicines have side effects. Treatment of drug-resistant TB typically takes more than six months and the risk of side effects is substantially higher. One way in which people with TB can be supported is with what is called Digital Adherence Technologies, or DAT. As explained by Nontobeko Mokone, study coordinator at the Aurum Institute (an NGO), there are different types of DAT, including smart pill boxes, video support, and 99DOTS.