July Literature

1. Genotyping and Molecular Characterization of Fluoroquinolone's Resistance Among Multidrug-Resistant Mycobacterium tuberculosis in Southwest of China.

Microb Drug Resist. 2021 Jul;27(7):865-870. doi: 10.1089/mdr.2019.0339. Epub 2020 Dec 10.

Hu Y(1), Liu J(1), Shen J(1), Feng X(1), Liu W(1), Zhu D(1), Zheng H(2), Hu D(1).

Although fluoroquinolones (FQs) are the backbone drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB), the knowledge about the resistance pattern and molecular characterization of new-generation FQs in Chongqing is limited. This study aimed to investigate the resistance rate and mutation types of later-generation FQs against MDR-TB in Chongqing, and further to explore the relationship between different genotypes and phenotypes. A total of 967 clinical strains were characterized using multilocus sequence typing and drug susceptibility testing, followed by analysis of genotype/phenotype association. The 229 (23.7%, 229/967) isolates were identified as MDR-TB. The most effective agent against MDR-TB was gatifloxacin (GFX) (20.1%, 46/229), and the highest resistant rate was observed in ofloxacin (OFX) (41.0%, 94/229). Of the 190 strains (83.0%) identified as Beijing genotype, 111 isolates were modern Beijing genotype (58.4%) and 79 isolates were ancient Beijing genotype (41.6%). By analyzing 94 OFX-resistant isolates, 13 isolates were clustered with the cumulative clustering rate of 13.8% (13/94). Of the 91 isolates (39.7%, 91/229) with a mutation in gyrA gene, mutation in codon 94 was the most prevalent. Only 15 isolates (6.6%, 15/229) harbored a mutation in gyrB gene. There was no significant difference in the mutation rate of gyrA gene between Beijing and non-Beijing genotype, clustered isolates, and nonclustered isolates ($p > 0.05$).

DOI: 10.1089/mdr.2019.0339
PMID: 33305990

2. Antituberculosis Activities of Lapachol and β-Lapachone in Combination with Other Drugs in Acidic pH.

Microb Drug Resist. 2021 Jul;27(7):924-932. doi: 10.1089/mdr.2020.0164. Epub 2020 Sep 1.

Ieque AL(1), Carvalho HC(2), Baldin VP(2), Santos NCS(2), Costacurta GF(1), Sampiron EG(1), Fernandez de Andrade CMM(3), Siqueira VLD(2), Caleffi Ferracioli

KR(2), Cardoso RF(1)(2), Cortez DAG (in memoriam)(3), Silva EL(4), Scodro RBL(1).

Background: The treatment of multidrug-resistant tuberculosis (MDR-TB) is a challenge to be overcome. The increase of resistant isolates associated with serious side effects during therapy leads to the search for substances that have anti-TB activity, which make treatment less toxic, and also act in the macrophage acidic environment promoted by the infection. Objective: The aim of this study was to investigate lapachol and β-lapachone activities in combination with other drugs against Mycobacterium tuberculosis at neutral and acidic pH and its cytotoxicity. Design: Inhibitory and bactericidal activities against M. tuberculosis and clinical isolates were determined. Drug combination and cytotoxicity assay were carried out using standard TB drugs and/or N-acetylcysteine (NAC). Results: Both naphthoquinones presented activity against MDR clinical isolates. The combinations with the first-line TB drugs demonstrated an additive effect and β-lapachone+NAC were synergic against H37Rv. Lapachol activity at acidic pH and its association with NAC improved the selectivity index. Lapachol and β-lapachone produced cell morphological changes in bacilli at pH 6.0 and 6.8, respectively. Conclusion: Lapachol revealed promising anti-TB activity, especially associated with NAC.

DOI: 10.1089/mdr.2020.0164
PMID: 33275860

3. Pyrosequencing for diagnosis of multidrug and extensively drug-resistant tuberculosis: A systemic review and meta-analysis.

J Clin Tuberc Other Mycobact Dis. 2021 Jun 29;24:100254. doi: 10.1016/j.jctube.2021.100254. eCollection 2021 Aug.

Getachew E(1)(2), Adebeta T(3), Gebrie D(1)(4), Charlie L(1), Said B(1)(5), Assefa DG(1)(6), Wanjiru CL(1), Zeleke ED(1)(7), Tesfahunei HA(1)(8), Abebe M(1)(9), Joseph M(1), Manyazewal T(1).

BACKGROUND: Multidrug and extensively drug-resistant tuberculosis (M/XDR-TB) pose major threats to global health. Diagnosis accuracy and delay have been the major drivers for the upsurge of M/XDR-TB. Pyrosequencing (PSQ) is a novel, real-time DNA sequencing for rapid detection of mutations associated with M/XDR-TB. We aimed to systematically synthesize the evidence on the diagnostic accuracy of PSQ for M/XDR-TB.
METHODS: We conducted an electronic search of PubMed, Embase, Biosis, Web of Science, and Google Scholar up to March 2020. We used the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool to assess the quality of

studies, the BRMA (bivariate random-effects meta-analysis) model to synthesize diagnostic accuracies, and the Rev-Man 5.4 software to perform the meta-analyses. We analyzed dichotomous data using the risk ratio (RR) with a 95% confidence interval. PROSPERO Registration ID: CRD42020200817.
RESULTS: The analysis included seven studies, with a total sample of 3,165. At 95% confidence interval, the pooled sensitivity and specificity of PSQ were 89.7 (CI: 83.5-93.8) and 97.8 (CI: 94.9-99.1) for Isoniazid, 94.6 (CI: 90.9-96.8) and 98.5 (CI: 96.5-99.3) for Rifampicin, 87.9 (CI: 81.2-92.4) and 98.8 (CI: 97.2-99.5) for Fluoroquinolone, 83.5 (CI: 72.8-90.5) and 99.4 (CI: 98.3-99.8) for Amikacin, 79 (CI: 67-8-87) and 97.9 (CI: 95.5-99) for Capreomycin, and 69.6 (CI: 57-79.8) and 98.2 (CI: 95.9-99.2) for Kanamycin. The overall pooled sensitivity and specificity were 85.8 (CI: 76.7-91.7) and 98.5 (CI: 96.5-99.3), respectively.
CONCLUSION: According to the pooled data, PSQ is highly sensitive and specific for detecting M/XDR-TB, both from clinical specimens and culture isolates, and within a shorter turnaround time. We suggest a continued synthesis of the evidence on the cost-effectiveness and technical feasibilities of PSQ in low-income countries context, including sub-Saharan Africa.

DOI: 10.1016/j.jctube.2021.100254
PMCID: PMC8267485
PMID: 34278006

4. Neoteric advancements in TB diagnostics and its future frame.

Indian J Tuberc. 2021 Jul;68(3):313-320. doi: 10.1016/j.ijtb.2020.10.004. Epub 2020 Oct 12.

Kajal(1), Sharma D(2), Rai R(3).

Tuberculosis (TB) is one of the major infectious disease that causes threat to human health and leads to death in most of the cases. Mycobacterium tuberculosis is the causative agent that can affect both pulmonary and extra pulmonary regions of the body. This infection can be presented either as an active or latent form in the patients. Although this disease has been declared curable and preventable by WHO, it still holds its position as a global emergency. Over the past decade many hurdles such as low immunity, co-infections like HIV, autoimmune disorders, poverty, malnutrition and emerging trends in drug resistance patterns are hindering the eradication of this infection. However, many programmes have been launched by WHO with involvement of governments at various level to put a full stop over the disease. Under the Revised National

Tuberculosis Control Programme (RNTCP) which was recently renamed as National Tuberculosis Elimination Programme (NTEP), the major focus is on eliminating tuberculosis by the year 2025. The main aim of the programme is to identify feasible quality testing, evaluate through NIKSHYA poshak yozana, restrict through BCG vaccination and assemble with public awareness to eradicate MTB. Numerous novel diagnostic techniques and molecular tools have been developed to elucidate and differentiate report of various suspected and active tuberculosis patients. However, improvements are still required to cut short the duration of the overall process ranging from screening of patients to their successful treatment.

DOI: 10.1016/j.ijtb.2020.10.004
PMID: 34099195

5. Xpert Mycobacterium tuberculosis/Rifampicin-Detected Rifampicin Resistance is a Suboptimal Surrogate for Multidrug-resistant Tuberculosis in Eastern Democratic Republic of the Congo: Diagnostic and Clinical Implications.

Clin Infect Dis. 2021 Jul 15;73(2):e362-e370. doi: 10.1093/cid/ciaa873.

Bisimwa BC(1)(2), Nachega JB(3)(4)(5), Warren RM(6), Theron G(6), Metcalfe JZ(7), Shah M(8), Diacon AH(9), Sam-Agudu NA(10)(11), Yotebieng M(12), Bulabula ANH(13)(14), Katoto PDMC(15)(16), Chirambiza JP(17), Nyota R(17), Birembano FM(17), Musafiri EM(17), Byadunia S(2), Bahizire E(18)(19)(20), Kaswa MK(21), Callens S(22), Kashongwe ZM(1)(2)(23).

BACKGROUND: Rifampicin (RIF) resistance is highly correlated with isoniazid (INH) resistance and used as proxy for multidrug-resistant tuberculosis (MDR-TB). Using MTBDRplus as a comparator, we evaluated the predictive value of Xpert MTB/RIF (Xpert)-detected RIF resistance for MDR-TB in eastern Democratic Republic of the Congo (DRC).
METHODS: We conducted a cross-sectional study involving data from new or retreatment pulmonary adult TB cases evaluated between July 2013 and December 2016. Separate, paired sputa for smear microscopy and MTBDRplus were collected. Xpert testing was performed subject to the availability of Xpert cartridges on sample remnants after microscopy.
RESULTS: Among 353 patients, 193 (54.7%) were previously treated and 224 (63.5%) were MTBDRplus TB positive. Of the 224, 43 (19.2%) were RIF monoresistant, 11 (4.9%) were INH monoresistant, 53 (23.7%) had MDR-TB, and 117 (52.2%) were RIF and INH susceptible. Overall, among the 96 samples detected by MTBDRplus as RIF resistant, 53 (55.2%) had MDR-TB. Xpert testing was performed in 179 (50.7%) specimens; among these, 163 (91.1%) were TB positive and 73 (44.8%) RIF

resistant. Only 45/73 (61.6%) Xpert-identified RIF-resistant isolates had concomitant MTBDRplus-detected INH resistance. Xpert had a sensitivity of 100.0% (95% CI, 92.1-100.0) for detecting RIF resistance but a positive-predictive value of only 61.6% (95% CI, 49.5-72.8) for MDR-TB. The most frequent mutations associated with RIF and INH resistance were S531L and S315T1, respectively. CONCLUSIONS: In this high-risk MDR-TB study population, Xpert had low positive-predictive value for the presence of MDR-TB. Comprehensive resistance testing for both INH and RIF should be performed in this setting.

DOI: 10.1093/cid/ciaa873
PMCID: PMC8282324
PMID: 32590841

6. Transient Bartter-like syndrome in a child with extensively drug-resistant tuberculosis: Questions.

Pediatr Nephrol. 2021 Jul;36(7):1973-1974. doi: 10.1007/s00467-020-04813-y. Epub 2020 Nov 5.

Poojari VS(1), Shah I(2), Shetty NS(2), Jaiswal A(2).

DOI: 10.1007/s00467-020-04813-y
PMID: 33151405

7. Transient Bartter-like syndrome in a child with extensively drug-resistant tuberculosis: Answers.

Pediatr Nephrol. 2021 Jul;36(7):1975-1976. doi: 10.1007/s00467-020-04822-x. Epub 2020 Nov 5.

Poojari VS(1), Shah I(2), Shetty NS(2), Jaiswal A(2).

DOI: 10.1007/s00467-020-04822-x
PMID: 33151404

8. Tuberculosis of the spine and drug resistance: a review article.

Neurosurg Rev. 2021 Jun 26. doi: 10.1007/s10143-021-01595-1. Online ahead of print.

Kumar V(1), Neradi D(1), Sherry B(1), Gaurav A(1), Dhatt SS(2).

Pott's spine is tuberculosis of spine caused due to hematogenous spread of mycobacterium from a primary focus. It constitutes about 50% of skeletal tuberculosis cases. Paradiscal type is the most common type of spinal tuberculosis. Untreated cases can lead to complications like a cold abscess, paraplegia, and deformity which may require surgical intervention. Rapid molecular methods have made the diagnosis of spinal tuberculosis and drug resistance faster and easier but it still remains a problem due to difficulties in sample collection and the paucibacillary nature of the Pott spine. Antitubercular drug therapy forms the mainstay of management. The emergence of MDR TB and XDR TB has posed a big challenge in the management of spinal tuberculosis. The literature regarding drug resistance in spinal tuberculosis and its management is lacking. We conducted a literature review of 29 studies and presented information on pathogenesis, diagnosis, and management of spinal tuberculosis and drug resistance. New shorter regimens for MDR and XDR TB are under trial in different parts of the world. We believe this article will provide information on spinal tuberculosis and drug resistance and help clinicians outline important research areas.

DOI: 10.1007/s10143-021-01595-1
PMID: 34176000

9. Anti-tuberculosis chemotherapy alters TNFR2 expression on CD4+ lymphocytes in both drug-sensitive and -resistant tuberculosis: however, only drug-resistant tuberculosis maintains a pro-inflammatory profile after a long time.

Mol Med. 2021 Jul 14;27(1):76. doi: 10.1186/s10020-021-00320-4.

Téllez-Navarrete NA(1), Ramon-Luing LA(1), Muñoz-Torrico M(2), Preciado-García M(1), Medina-Quero K(3), Hernandez-Pando R(4), Chavez-Galan L(5).

BACKGROUND: Tuberculosis (TB) is an infectious disease. During TB, regulatory T cells (Treg) are related to poor prognosis. However, information about conventional and unconventional Treg (cTreg and uTreg, respectively) is limited. The tumour necrosis factor (TNF) and its receptors (TNFR1 and TNFR2) are necessary for mycobacterial infection, and TNFR2 signalling is required to maintain Treg.
METHODS: A blood sample of drug-susceptible (DS-TB) and drug-resistant tuberculosis (DR-TB) patients was obtained before (basal) and after 2 and 6

months of anti-TB therapy. Expression of TNF, TNFR1, and TNFR2 (transmembrane form, tm) on cTreg, uTreg, activated CD4+ (actCD4+), and CD4+ CD25- (CD4+) T cell subpopulations were evaluated. The main objective was to identify immunological changes associated with sensitive/resistant Mtb strains and with the use of anti-TB therapy.
RESULTS: We found that after 6 months of anti-TB therapy, both DS- and DR-TB patients have decreased the frequency of cTreg tmTNF+, CD4+ tmTNFR1+ and CD4+ tmTNFR2+. Nevertheless, after 6 months of therapy, only DR-TB patients decreased the frequency of actCD4+ tmTNF+ and actCD4+ tmTNFR2+, exhibited a systemic inflammatory status (high levels of TNF, IFN-γ and IL-12), and their purified CD4+ T cells showed that TNF and TNFR2 are up-regulated at the transcriptional level. Moreover, DS- and DR-TB down-regulated TNFR1 and other proteins associated with Treg (FOXP3 and TGFβ1) in response to the anti-TB therapy.
CONCLUSION: These results partially explain the differences in the immune response of DS-TB vs DR-TB. The frequency of actCD4+ tmTNFR2+ cells and inflammatory status should be considered in the follow-up of therapy in DR-TB patients.

DOI: 10.1186/s10020-021-00320-4
PMCID: PMC8278684
PMID: 34261449

10. Characterization of Differentially Detectable Mycobacterium tuberculosis in the Sputum of Subjects with Drug-Sensitive or Drug-Resistant Tuberculosis before and after Two Months of Therapy.

Antimicrob Agents Chemother. 2021 Jul 16;65(8):e0060821. doi: 10.1128/AAC.00608-21. Epub 2021 Jul 16.

Zainabadi K(1)(2), Walsh KF(1)(3), Vilbrun SC(4), Mathurin LD(4), Lee MH(1), Saito K(2), Mishra S(2), Ocheretina O(1), Pape JW(1)(4), Nathan C(#)(2), Fitzgerald DW(#)(1).

Standard methods for enumerating Mycobacterium tuberculosis in patient sputum can miss large populations of viable M. tuberculosis cells that are unable to grow either on solid medium or in liquid medium unless the medium has been extensively diluted. Because these bacteria can be detected in liquid medium after limiting dilution, they have been termed differentially culturable or differentially detectable M. tuberculosis (DD-Mtb). Treatment with isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) (HRZE) for 1 to 2 weeks has been shown to increase the representation of DD-Mtb in the sputum of

drug-sensitive (DS) tuberculosis (TB) patients. However, little is known about DD-Mtb after longer periods of treatment with HRZE or in patients with drug-resistant (DR) TB who receive second-line therapies. Here, we measured the proportion of DD-Mtb cells in the sputum of 47 subjects, 29 with DS TB and 18 with DR TB, before initiation of treatment and at 2 weeks and 2 months thereafter. Prior to treatment, DD-Mtb cells represented the majority of M. tuberculosis cells in the sputum of 21% of subjects with DS TB, and this proportion rose to 65% after 2 weeks of treatment with first-line drugs. In subjects with DR TB, DD-Mtb cells were found in the sputum of 29% of subjects prior to treatment initiation, and this proportion remained steady at 31% after 2 weeks of treatment with second-line drugs. By 2 months, DD-Mtb cells were detected in the sputum of only 2/15 (13.3%) subjects with DS TB and in 0/15 of subjects with DR TB. One of the DS subjects whose sputum was positive for DD-Mtb at month 2 later experienced treatment failure.

DOI: 10.1128/AAC.00608-21
PMID: 34060896

11. Linezolid resistance among multidrug-resistant Mycobacterium tuberculosis clinical isolates in Iran.

Acta Microbiol Immunol Hung. 2021 Jun 24. doi: 10.1556/030.2021.01490. Online ahead of print.

Khosravi AD(1)(2)(3), Tabandeh MR(4), Shahi F(1)(2), Salmanzadeh S(1)(5).

The management of multidrug-resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB) presents a main challenge and the drug options for treating these infections are very limited. Linezolid (LNZ) has recently been approved for the treatment of MDR and XDR-TB. But, there are narrow data on genotypic and phenotypic LNZ resistance in clinical isolates. So, we aimed to determine the prevalence of LNZ resistance and to identify the mutations associated with LNZ resistance among clinical MDR-TB isolates. The minimum inhibitory concentration (MIC) values of LNZ for 22 MDR-TB isolates were determined by broth microdilution method. All MDR-TB isolates were sequenced in the rrl and rplC genes conferring LNZ resistance. LNZ resistance was found in 3 (13.6%) of 22 MDR-TB isolates. The MICs of LNZ were 8 μg/mL for two isolates and 16 μg/mL for one isolate. The 421 (A/G) and 449 (T/A) mutations in rplC gene were detected in one of the LNZ-resistant isolates. There was no mutation in rrl gene. The results reveal that the prevalence of LNZ-resistant isolates is 13.6% among MDR-TB isolates and drug susceptibility testing (DST) against LNZ is useful in the management of complicated and drug-resistant cases. However, further studies could identify other possible genetic mechanism of resistance in

TB.

DOI: 10.1556/030.2021.01490
PMID: 34174037

12. Phenotypic and molecular characterization of pyrazinamide resistance among multidrug-resistant Mycobacterium tuberculosis isolates in Ningbo, China.

BMC Infect Dis. 2021 Jun 25;21(1):605. doi: 10.1186/s12879-021-06306-1.

Che Y(1), Bo D(2), Lin X(1), Chen T(1), He T(3), Lin Y(4).

BACKGROUND: Detection of pyrazinamide (PZA) resistance in Mycobacterium tuberculosis (TB) patients is critical, especially in dealing with multidrug-resistant Mycobacterium tuberculosis (MDR-TB) case. Up to date, PZA drug susceptibility testing (DST) has not been regularly performed in China. The prevalence and molecular characteristics of PZA resistance in M.tuberculosis isolates, especially MDR-TB have not been studied in Ningbo, China. This study aimed to analyze the phenotypic and molecular characterization of PZA resistance among MDR-TB isolates in Ningbo.
METHODS: A total of 110 MDR-TB isolates were collected from the TB patients who were recorded at local TB dispensaries in Ningbo. All clinical isolates were examined by drug susceptibility testing and genotyping. DNA sequencing was used to detect mutations in the pncA gene associated with PZA resistance.
RESULTS: The prevalence of PZA resistance among MDR-TB strains in Ningbo was 59.1%. With regard to the history and the outcome of treatments among MDR-TB cases, the percentages of re-treated MDR-TB patients in the PZA-resistant group and of successful patients in PZA-susceptible group were significantly higher than the ones in the PZA-susceptible group and in the PZA-resistant group, respectively (P = 0.027, P = 0.020). The results showed that the resistance of streptomycin (67.7% vs 46.7%, P = 0.027), ethambutol (56.9% vs 33.3%, P = 0.015), ofloxacin (43.1% vs 11.1%, P = 0.000), levofloxacin (43.1% vs 11.1%, P = 0.000), pre-XDR (pre-Xtensively Drug Resistance) (38.5% vs 15.6%, P = 0.009), were more frequently adverted among PZA-resistant isolates compared with PZA-susceptible isolates. In addition, 110 MDR-TB was composed of 87 (PZA resistant, 78.5%) Beijing strains and 23 (PZA resistant, 21.5%) non-Beijing strains. Fifty-four out of 65 (83.1%) PZA-resistant MDR strains harbored a mutation located in the pncA gene and the majority (90.7%) were point mutations. Compared with the phenotypic characterization, DNA sequencing of pncA has sensitivity and specificity of 83.1 and 95.6%.
CONCLUSION: The mutations within pncA gene was the primary mechanism of PZA resistance among MDR-TB and DNA sequencing of pncA gene could provide a rapid detection evidence in PZA drug resistance of MDR-TB in Ningbo.

DOI: 10.1186/s12879-021-06306-1
PMCID: PMC8228925
PMID: 34171989 [Indexed for MEDLINE]

13. Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients.

BMC Public Health. 2021 Jul 16;21(1):1404. doi: 10.1186/s12889-021-11427-y.

van de Berg SEJ(#)(1), Pelzer PT(#)(2), van der Land AJ(1), Abdrakhmanova E(3), Ozi AM(4), Arias M(1), Cook-Scalise S(5), Dravniece G(1)(6), Gebhard A(1), Juneja S(5), Handayani R(7), Kappel D(5), Kimerling M(1), Koppelaar I(1), Malhotra S(5), Myrzaliev B(8), Nsa B(9), Sugiharto J(10), Engel N(11), Mulder C(#)(1)(12), van den Hof S(#)(1)(13).

BACKGROUND: BPaL, a 6 month oral regimen composed of bedaquiline, pretomanid, and linezolid for treating extensively drug-resistant tuberculosis (XDR-TB) is a potential alternative for at least 20 months of individualized treatment regimens (ITR). The ITR has low tolerability, treatment adherence, and success rates, and hence to limit patient burden, loss to follow-up and the emergence of resistance it is essential to implement new DR-TB regimens. The objective of this study was to assess the acceptability, feasibility, and likelihood of implementing BPaL in Indonesia, Kyrgyzstan, and Nigeria.
METHODS: We conducted a concurrent mixed-methods study among a cross-section of health care workers, programmatic and laboratory stakeholders between May 2018 and May 2019. We conducted semi-structured interviews and focus group discussions to assess perceptions on acceptability and feasibility of implementing BPaL. We determined the proportions of a recoded 3-point Likert scale (acceptable; neutral; unacceptable), as well as the overall likelihood of implementing BPaL (likely; neutral; unlikely) that participants graded per regimen, pre-defined aspect and country. We analysed the qualitative results using a deductive framework analysis.
RESULTS: In total 188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria The majority were health care workers (110). Overall, 88% (146/166) of the stakeholders would likely implement BPaL once available. Overall acceptability for BPaL was high, especially patient friendliness was often rated as acceptable (93%, 124/133). In contrast, patient friendliness of the ITR was rated as acceptable by 45%. Stakeholders appreciated that BPaL would reduce workload and financial burden on the health care system. However, several stakeholders expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements regarding introduction of the regimen. Stakeholders stressed the importance of addressing

current health systems constraints as well, especially in treatment and safety monitoring systems.
CONCLUSIONS: Acceptability and feasibility of the BPaL regimen is high among TB stakeholders in Indonesia, Kyrgyzstan, and Nigeria. The majority is willing to start using BPaL as the standard of care for eligible patients despite country-specific health system constraints.

DOI: 10.1186/s12889-021-11427-y
PMCID: PMC8284025
PMID: 34271884

14. Reducing the risk of tuberculosis transmission for HCWs in high incidence settings.

Antimicrob Resist Infect Control. 2021 Jul 19;10(1):106. doi: 10.1186/s13756-021-00975-y.

Paleckyte A(1), Dissanayake O(2), Mpagama S(3), Lipman MC(4), McHugh TD(5).

Globally, tuberculosis (TB) is a leading cause of death from a single infectious agent. Healthcare workers (HCWs) are at increased risk of hospital-acquired TB infection due to persistent exposure to Mycobacterium tuberculosis (Mtb) in healthcare settings. The World Health Organization (WHO) has developed an international system of infection prevention and control (IPC) interventions to interrupt the cycle of nosocomial TB transmission. The guidelines on TB IPC have proposed a comprehensive hierarchy of three core practices, comprising: administrative controls, environmental controls, and personal respiratory protection. However, the implementation of most recommendations goes beyond minimal physical and organisational requirements and thus cannot be appropriately introduced in resource-constrained settings and areas of high TB incidence. In many low- and middle-income countries (LMICs) the lack of knowledge, expertise and practice on TB IPC is a major barrier to the implementation of essential interventions. HCWs often underestimate the risk of airborne Mtb dissemination during tidal breathing. The lack of required expertise and funding to design, install and maintain the environmental control systems can lead to inadequate dilution of infectious particles in the air, and in turn, increase the risk of TB dissemination. Insufficient supply of particulate respirators and lack of direction on the re-use of respiratory protection is associated with unsafe working practices and increased risk of TB transmission between patients and HCWs. Delayed diagnosis and initiation of treatment are commonly influenced by the effectiveness of healthcare systems to

identify TB patients, and the availability of rapid molecular diagnostic tools. Failure to recognise resistance to first-line drugs contributes to the emergence of drug-resistant Mtb strains, including multidrug-resistant and extensively drug-resistant Mtb. Future guideline development must consider the social, economic, cultural and climatic conditions to ensure that recommended control measures can be implemented in not only high-income countries, but more importantly low-income, high TB burden settings. Urgent action and more ambitious investments are needed at both regional and national levels to get back on track to reach the global TB targets, especially in the context of the COVID-19 pandemic.

DOI: 10.1186/s13756-021-00975-y
PMID: 34281623

15. Novel treatments in multidrug-resistant tuberculosis.

Curr Opin Pharmacol. 2021 Jun 26;59:103-115. doi: 10.1016/j.coph.2021.05.007. Online ahead of print.

Mondoni M(1), Saderi L(2), Sotgiu G(3).

The management of multidrug-resistant tuberculosis (TB) is associated with low treatment success, high mortality and failure rates. New drugs and novel short-therapeutic regimens have only recently helped overcome these obstacles. We carried out a narrative literature review aimed at summarizing the scientific evidence on the recent therapeutic advances in the field of drug-resistant TB. Experimental and observational studies on novel (i.e. bedaquiline, delamanid, pretomanid) drugs and novel regimens and the main pharmacological characteristics of the newest compounds are described. We also highlight the main scientific evidence on therapeutic strategies complementary to standard chemotherapy (i.e. new approaches to drug delivery, host-directed therapy, surgery, new collapse therapy, rehabilitation, and palliative care).

DOI: 10.1016/j.coph.2021.05.007
PMID: 34186381

16. Genotypic diversity of multi- and pre-extremely drug-resistant Mycobacterium tuberculosis isolates from Morocco.

PLoS One. 2021 Jul 2;16(7):e0253826. doi: 10.1371/journal.pone.0253826. eCollection 2021.

Oudghiri A(1)(2), Momen G(3)(4), Aainouss A(3)(5), Laglaoui A(2), El Messaoudi MD(3), El Mzibri M(1), Chaoui I(1).

In Morocco, the prevalence of multidrug resistant tuberculosis (MDR-TB) continues to increase especially within previously treated cases; these MDR cases may evolve to extensively drug resistant tuberculosis (XDR-TB) raising major concern to TB control programs. From an epidemiological window, scarce informations are available about the genetic diversity of Mycobacterium tuberculosis (MTB) strains fueling these forms of resistance. The aim of this study was to assess to genetic diversity of MDR-MTB strains. Hence, this prospective study was conducted on patients diagnosed with MDR-TB at Pasteur Institute of Casablanca from 2010 to 2013. A total of 70 MDR-MTB isolates were genotyped by spoligotyping and 15-loci MIRU-VNTR methods. Spoligotyping generated four orphan patterns, five unique profiles whereas 61 strains were grouped in nine clusters (2 to 25 strains per cluster), the clustering rates being 87.1%. Subtyping by 15 loci MIRU-VNTR splitted all clusters already established by spoligotyping and generated 70 unique profiles not recognized in SITVIT2 database; clustering rate was equal to zero. HGDI analysis of 15 loci MIRU demonstrated that eight out of 15 loci were highly discriminant. Of note, all pre-XDR strains belongs to many clades, meaning that there no association between gyrA mutants and particular clade. Overall, the data generated by this study (i) describe the population structure of MDR MTBC in Morocco which is highly homogenous, (ii) confirm that TB in Morocco is almost exclusively transmitted by modern and evolutionary lineages with high level of biodiversity seen by MIRU, and (iii) validate the use of optimized 15-loci MIRU-VNTR format for future investigations in Morocco.

DOI: 10.1371/journal.pone.0253826
PMCID: PMC8253442
PMID: 34214120

17. Molecular Epidemiology of Drug-Resistant Mycobacterium Tuberculosis in Japan.

mSphere. 2021 Jul 7:e0097820. doi: 10.1128/mSphere.00978-20. Online ahead of print.

Mizukoshi F(1), Kobayashi N(2)(3), Kirikae F(4), Ohta K(2)(5), Tsuyuguchi K(6), Yamada N(7), Inoue Y(6), Horiba M(8), Kawata N(9), Ichinose A(10)(11), Miyoshi-Akiyama T(11), Kiritani R(1), Funatogawa K(1), Kirikae T(4).

Clinical isolates of drug-resistant (isoniazid and/or rifampicin-resistant) Mycobacterium tuberculosis were obtained from 254 patients diagnosed with drug-resistant tuberculosis in Japan from April 2015 to March 2017 in National Hospital Organization hospitals. The 254 patients were approximately 32% of all 795 patients who were diagnosed with culture-confirmed drug-resistant tuberculosis from 2015 to 2016 nationwide in Japan. The whole-genome sequences of all the isolates from the 254 patients and the lineages of these isolates were determined, and phylogenetic trees were constructed based on single nucleotide polymorphism concatemers. Of these patients, 202 (79.5%) were born in Japan and 52 (20.5%) were born elsewhere. Of the 254 drug-resistant isolates, 54 (21.3%) were multidrug resistant, being resistant to both isoniazid and rifampicin. The percentages of multidrug-resistant isolates were significantly higher in foreign-born (38.5% [20/52]) than Japanese-born patients (16.8% [34/202]). Of the 54 multidrug-resistant isolates, nine were extensively drug resistant, which were all obtained from Japanese-born patients. Five extensively drug-resistant isolates were obtained from patients with incipient tuberculosis. A significant number of multidrug-resistant M. tuberculosis strains were isolated from foreign-born patients from Asian countries that have a high tuberculosis burden. Foreign-derived isolates affect the nationwide genetic diversity of drug-resistant M. tuberculosis in Japan. Extensively drug-resistant M. tuberculosis isolates were transmitted among the Japanese population. IMPORTANCE The incidence rate of tuberculosis (TB) in Japan was 11.5 per 100,000 of the population in 2019. Of TB patients in Japan, 61.1% were aged >70 years, and 10.7% were born outside Japan, mostly in Asian countries with a high burden of tuberculosis. Of the tuberculosis patients in the present study, 5.4% and 1.0% showed resistance to isoniazid and rifampicin, respectively, and 0.7% were multidrug resistant. The objective of this study was to clarify the molecular epidemiological properties of drug-resistant tuberculosis in Japan. Molecular epidemiology provides several clues to inform potential measures to control drug-resistant tuberculosis in Japan.

DOI: 10.1128/mSphere.00978-20
PMID: 34232083

18. Prevalence of drug resistance-conferring mutations associated with isoniazid and rifampicin-resistant Mycobacterium tuberculosis in Ethiopia: A systematic review and meta-analysis.

J Glob Antimicrob Resist. 2021 Jun 29:S2213-7165(21)00162-4. doi: 10.1016/j.jgar.2021.06.009. Online ahead of print.

Reta MA(1), Alemnew B(2), Abate BB(3), Fourie PB(4).

OBJECTIVES: Globally, tuberculosis (TB) incidence and mortality are declining; however, low detection of drug-resistant disease threatens to reverse current progress toward global TB control. Multiple, rapid molecular diagnostic tests have recently been developed to detect genetic mutations in Mycobacterium tuberculosis (Mtb) known to confer anti-TB drug resistance. Their utility, though, depends on the frequency and distribution of the resistance-associated mutations in the pathogen population. Therefore, this review aimed to assess the prevalence of the gene mutations associated with rifampicin (RIF) and isoniazid (INH) resistant Mtb in Ethiopia.
METHODS: Using PRISMA guidelines, we searched the literature on PubMed/MEDLINE, Web of Science, Scopus, and Cochrane library databases. Data analysis was conducted in STATA 11.
RESULTS: In total, 909 (95.8%) of 949 INH resistant Mtb isolates had detectable gene mutations: 95.8% in katG315 and 5.9% in the inhA-promoter region. The meta-analysis resulting an estimated prevalence of katGMUT1(S315T1) was 89.2% (95%CI:81.94-96.43%), while a pooled prevalence of inhAMUT1 (C15T) was 77.5% (95%CI:57.84-97.13%). Besides, 769 (90.8%) of 847 RIF resistant strains had detectable rpoB gene mutations, and the meta-analysis resulting in a pooled prevalence of rpoBMUT3 (S531L) was 74.2% (95%CI: 66.39-82.00%).
CONCLUSIONS: RIF-resistant Mtb isolates were spread widely, particularly those harboring S531L mutations. Similarly, INH-resistant Mtb strains with S315T1 and C15T mutations were common. Tracking S531L, S315T1, and C15T mutations among RIF and INH resistant isolates, respectively, would be diagnostically and epidemiologically valuable. Rapid diagnosis of RIF and INH-resistant Mtb in TB patients would expedite alteration of treatment regimens, and proper timely infection control interventions could reduce the risk of progression and transmission of multidrug-resistant TB (MDR-TB).

DOI: 10.1016/j.jgar.2021.06.009
PMID: 34214698

19. Concordance of Drug-resistance Profiles Between Persons With Drug-resistant Tuberculosis and Their Household Contacts: A Systematic Review and Meta-analysis.

Clin Infect Dis. 2021 Jul 15;73(2):250-263. doi: 10.1093/cid/ciaa613.

Chiang SS(1)(2), Brooks MB(3), Jenkins HE(4), Rubenstein D(1), Seddon JA(5)(6), van de Water BJ(3), Lindeborg MM(3), Becerra MC(3)(7), Yuen CM(3)(7).

BACKGROUND: Household contacts of patients with drug-resistant tuberculosis (TB) are at high risk for being infected with Mycobacterium tuberculosis and for developing TB disease. To guide regimen composition for the empirical treatment of TB infection and disease in these household contacts, we estimated drug-resistance profile concordance between index patients with drug-resistant TB and their household contacts.
METHODS: We performed a systematic review and meta-analysis of studies published through 24 July 2018 that reported resistance profiles of drug-resistant TB index cases and secondary cases within their households. Using a random-effects meta-analysis, we estimated resistance profile concordance, defined as the percentage of secondary cases whose M. tuberculosis strains were resistant to the same drugs as strains from their index cases. We also estimated isoniazid/rifampin concordance, defined as whether index and secondary cases had identical susceptibilities for isoniazid and rifampin only.
RESULTS: We identified 33 eligible studies that evaluated resistance profile concordance between 484 secondary cases and their household index cases. Pooled resistance profile concordance was 54.3% (95% confidence interval [CI], 40.7-67.6%; I2 = 85%). Pooled isoniazid/rifampin concordance was 82.6% (95% CI, 72.3-90.9%; I2 = 73%). Concordance estimates were similar in a subanalysis of 16 studies from high-TB-burden countries. There were insufficient data to perform a subanalysis among pediatric secondary cases.
CONCLUSIONS: Household contacts of patients with drug-resistant TB should receive treatment for TB infection and disease that assumes that they, too, are infected with a drug-resistant M. tuberculosis strain. Whenever possible, drug susceptibility testing should be performed for secondary cases to optimize regimen composition.

DOI: 10.1093/cid/ciaa613
PMID: 32448887

20. Immunomodulatory Agents Combat Multidrug-Resistant Tuberculosis by Improving Antimicrobial Immunity.

J Infect Dis. 2021 Jul 15;224(2):332-344. doi: 10.1093/infdis/jiab100.

Rao Muvva J(1), Ahmed S(2), Rekha RS(2), Kalsum S(1), Groenheit R(3), Schön T(4), Agerberth B(2), Bergman P(2), Brighenti S(1).

BACKGROUND: Multidrug-resistant (MDR) tuberculosis has low treatment success

rates, and new treatment strategies are needed. We explored whether treatment with active vitamin D3 (vitD) and phenylbutyrate (PBA) could improve conventional chemotherapy by enhancing immune-mediated eradication of Mycobacterium tuberculosis.
METHODS: A clinically relevant model was used consisting of human macrophages infected with M. tuberculosis isolates (n = 15) with different antibiotic resistance profiles. The antimicrobial effect of vitD+PBA, was tested together with rifampicin or isoniazid. Methods included colony-forming units (intracellular bacterial growth), messenger RNA expression analyses (LL-37, β-defensin, nitric oxide synthase, and dual oxidase 2), RNA interference (LL-37-silencing in primary macrophages), and Western blot analysis and confocal microscopy (LL-37 and LC3 protein expression).
RESULTS: VitD+PBA inhibited growth of clinical MDR tuberculosis strains in human macrophages and strengthened intracellular growth inhibition of rifampicin and isoniazid via induction of the antimicrobial peptide LL-37 and LC3-dependent autophagy. Gene silencing of LL-37 expression enhanced MDR tuberculosis growth in vitD+PBA-treated macrophages. The combination of vitD+PBA and isoniazid were as effective in reducing intracellular MDR tuberculosis growth as a >125-fold higher dose of isoniazid alone, suggesting potent additive effects of vitD+PBA with isoniazid.
CONCLUSIONS: Immunomodulatory agents that trigger multiple immune pathways can strengthen standard MDR tuberculosis treatment and contribute to next-generation individualized treatment options for patients with difficult-to-treat pulmonary tuberculosis.

DOI: 10.1093/infdis/jiab100
PMCID: PMC8280489
PMID: 33606878

21. Patient- and provider-related factors in the success of multidrug-resistant tuberculosis treatment in Colombia.

Rev Panam Salud Publica. 2021 Jun 21;45:e74. doi: 10.26633/RPSP.2021.74. eCollection 2021.

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

OBJECTIVE: To identify patient- and provider-related factors associated with the success of multidrug-resistant tuberculosis (MDR-TB) treatment in the six municipalities of Colombia with the highest number of MDR-TB cases.

METHODS: Bivariate and multivariate logistic regressions were used to analyze the association between treatment success (cure or treatment completion) and characteristics of the patients and physicians, nursing professionals, and psychologists involved in their treatment. The importance of knowledge in the management of MDR-TB cases was explored through focus groups with these providers.
RESULTS: Of 128 cases of TB-MDR, 63 (49.2%) experienced treatment success. Only 52.9% of the physicians and nursing professionals had satisfactory knowledge about MDR-TB. Logistic regression showed that being HIV negative, being affiliated with the contributory health insurance scheme, being cared for by a male physician, and being cared for by nursing professionals with sufficient knowledge were associated with a successful treatment outcome ($p \leq 0.05$). Qualitative analysis showed the need for in-depth, systematic training of health personnel who care for patients with MDR-TB.
CONCLUSIONS: Some characteristics of patients and healthcare providers influence treatment success in MDR-TB cases. Physicians' and nurses' knowledge about MDR-TB must be improved, and follow-up of MDR-TB patients who are living with HIV and of those affiliated with the subsidized health insurance scheme in Colombia must be strengthened, as these patients have a lower likelihood of a successful treatment outcome.

DOI: 10.26633/RPSP.2021.74
PMCID: PMC8216496
PMID: 34168683

22. Genetic diversity and primary drug resistance transmission in Mycobacterium tuberculosis in southern Mexico.

Infect Genet Evol. 2021 Jul 7;93:104994. doi: 10.1016/j.meegid.2021.104994. Online ahead of print.

Ordaz-Vázquez A(1), Torres-González P(1), Cruz-Hervert P(2), Ferreyra-Reyes L(3), Delgado-Sánchez G(3), García-García L(3), Kato-Maeda M(4), Ponce-De-León A(1), Sifuentes-Osornio J(5), Bobadilla-Del-Valle M(6).

Tuberculosis is a global human health threat, especially in developing countries. The present study aimed to describe the genetic diversity of Mycobacterium tuberculosis and to measure the transmission rates of primary and acquired resistance. A total of 755 M. tuberculosis isolates from a cohort study of patients with culture-confirmed pulmonary tuberculosis in Orizaba, Veracruz, performed between 1995 and 2010 were genotyped by the 24-locus mycobacterial interspersed repetitive unit-variable number of tandem repeats (MIRU-VNTR) method. Drug susceptibility was determined. Logistic regression models were

constructed to identify the variables associated with resistance and clusters. The recent transmission index (RTI), the Hunter-Gaston discrimination index (HGDI) for the MIRU-VNTR test and allelic diversity (h) were calculated. The Haarlem and LAM lineages were the most common in the population. A total of 519 isolates were grouped into 128 clusters. The overall drug resistance rate was 19%, isoniazid monoresistance (10%) was the most common, and 3.4% of the isolates were multidrug resistant. Among the 116 isolates resistant to at least one drug, the primary and acquired resistance rates were 81.9% and 18.1%, respectively. Primary resistance was associated with belonging to a cluster (aOR 4.05, 95% CI 1.5-11.2, p = 0.007). Previous treatment history (aOR 9.05, 95% CI 3.6-22.5, p < 0.001) and LAM lineage (aOR 4.25, 95% CI 1.4-12.7, p = 0.010) were associated with multidrug-resistant tuberculosis (MDR-TB). The RTI was 51.7%, and the 24-locus MIRU-VNTR HGDI was 0.98. The alleles with the greatest diversity were 4056-QUB26 (h = 0.84), 2163b-QUB11b (h = 0.79), and 424-Mtub04 (h = 0.72). Primary resistance transmission, high LAM lineage prevalence and its association with MDR-TB represent public health problems. The implementation of molecular tools is needed to improve the existing control surveillance tuberculosis program.

DOI: 10.1016/j.meegid.2021.104994
PMID: 34245908

23. Study of treatment outcomes of multidrug-resistant tuberculosis under programmatic conditions and factors influencing the outcomes in Hyderabad District.

Indian J Tuberc. 2021 Jul;68(3):379-383. doi: 10.1016/j.ijtb.2020.12.008. Epub 2021 Jan 4.

Kandi S(1), K TK(2), Kandi SR(3), Mathur N(4), D CD(5), Adepu R(6).

BACKGROUND: Treatment outcomes for Multidrug-Resistant Tuberculosis (MDR TB) is generally poor. The study aims to know about the treatment outcomes of MDR-TB under programmatic conditions in Hyderabad District and to analyze the factors influencing the treatment outcomes.
METHODS: This is a retrospective study in which 377 patients of Hyderabad district, Telangana state who were diagnosed with MDR TB and registered at Drug Resistance TB Treatment site of Government General & Chest Hospital, Hyderabad from 4th quarter 2008 to 4th quarter 2013 were included in the study. Impact of Demographic factors (age, sex; Nutritional status (BMI); Co-morbid condition (Diabetes, HIV, Hypothyroidism); Programmatic factors (time delay in the

initiation of treatment); Initial Resistance pattern on the outcomes were studied and analyzed.
RESULTS: The treatment outcomes of Multidrug-Resistant Tuberculosis under Programmatic Conditions were: 57% cured, 21.8% died, 19.6% defaulted, 1.1% failed and 0.5% switched to XDR. Age, Sex, BMI had a statistically significant impact on treatment outcomes. Hypothyroidism and Delay in the initiation of treatment >1 a month had an impact on the outcomes though not statistically significant. NO impact on treatment outcomes was found when Rifampicin resistance & INH sensitive patients were compared with those resistant to both INH and Rifampicin.
CONCLUSION: To reduce MDR-TB transmission in the community, improvement of treatment outcomes, via ensuring adherence, paying special attention to elderly patients is required. The Programmatic Management of Drug Resistance Tuberculosis (PMDT) should seriously think of providing Nutritional support to patients with low BMI to improve outcomes. In the programmatic conditions if we could address the problems like delay in initiation of treatment and proper management of comorbidities like HIV, Diabetes, Hypothyroidism would definitely improve the treatment outcomes.

DOI: 10.1016/j.ijtb.2020.12.008
PMID: 34099204

24. Additional Drug Resistance in Patients with Multidrug-resistant Tuberculosis in Korea: a Multicenter Study from 2010 to 2019.

J Korean Med Sci. 2021 Jul 5;36(26):e174. doi: 10.3346/jkms.2021.36.e174.

Lee T(#)(1), Lee SJ(#)(2), Jeon D(3), Lee HY(4), Kim HJ(5), Kang BH(6), Mok J(7)(8).

BACKGROUND: Drug-resistance surveillance (DRS) data provide key information for building an effective treatment regimen in patients with multidrug-resistant tuberculosis (MDR-TB). This study was conducted to investigate the patterns and trends of additional drug resistance in MDR-TB patients in South Korea.
METHODS: Phenotypic drug susceptibility test (DST) results of MDR-TB patients collected from seven hospitals in South Korea from 2010 to 2019 were retrospectively analyzed.
RESULTS: In total, 633 patients with MDR-TB were included in the analysis. Of all patients, 361 (57.0%) were new patients. All patients had additional resistance to a median of three anti-TB drugs. The resistance rates of any fluoroquinolone (FQ), linezolid, and cycloserine were 26.2%, 0.0%, and 6.3%,

respectively. The proportions of new patients and resistance rates of most anti-TB drugs did not decrease during the study period. The number of additional resistant drugs was significantly higher in FQ-resistant MDR-TB than in FQ-susceptible MDR-TB (median of 9.0 vs. 2.0). Among 26 patients with results of minimum inhibitory concentrations for bedaquiline (BDQ) and delamanid (DLM), one (3.8%) and three (11.5%) patients were considered resistant to BDQ and DLM with interim critical concentrations, respectively. Based on the DST results, 72.4% and 24.8% of patients were eligible for the World Health Organization's longer and shorter MDR-TB treatment regimen, respectively.
CONCLUSION: The proportions of new patients and rates of additional drug resistance in patients with MDR-TB were high and remain stable in South Korea. A nationwide analysis of DRS data is required to provide effective treatment for MDR-TB patients in South Korea.

DOI: 10.3346/jkms.2021.36.e174
PMCID: PMC8258238
PMID: 34227261

25. Adverse drug reaction and its management in tuberculosis patients with multidrug resistance: a retrospective study.

J Basic Clin Physiol Pharmacol. 2021 Jun 25;32(4):783-787. doi: 10.1515/jbcpp-2020-0447.

Nilamsari WP(1), Rizqi MF(1), Regina NO(1), Wulaningrum PA(2), Fatmawati U(3).

OBJECTIVES: This study was conducted to assess adverse drug reactions and their management in MDR-TB patients. Indonesia is the fifth highest country with multidrug-resistant tuberculosis (MDR-TB) high burden around the world. The number of MDR-TB patients in Indonesia is increasing every year, but the data regarding ADRs are still limited. Therefore, more data on their characteristics and their management is very valuable for clinicians and pharmacists.
METHODS: The study is a descriptive study, using retrospective data of MDR-TB patients who completed therapy from January 1st, 2015 to December 31st, 2015 at the Tuberculosis Outpatient unit at the Dr. Soetomo Teaching Hospital Indonesia. Each adverse effect was judged with standards of the clinic and was documented in patients' medical records.
RESULTS: There were 40 patients included in this study. During therapy, 70% of patients developed at least one adverse drug reaction. The five most prevalent adverse effects found in this study were hyperuricemia (52.5%) followed by gastrointestinal (GI) disturbances (40%), ototoxicity (37.5%), hypokalemia

(27.5%), and athralgia (12.5%). Managements that were undertaken to overcome the adverse drug reactions were adding symptomatic drugs and/or modifying the treatment regimen.
CONCLUSIONS: Because of the small samples we cannot attain a general conclusion. However, the result of this study is very imperative as this data gives us insight regarding adverse effects in MDR-TB patients in Indonesia.

DOI: 10.1515/jbcpp-2020-0447
PMID: 34214373

26. Rapid Detection of Extensively Drug-Resistant Tuberculosis in Clinical Samples Using a Novel Tabletop Platform: Protocol for a Prospective Clinical Study.

JMIR Res Protoc. 2021 Jul 14;10(7):e26748. doi: 10.2196/26748.

Hillery N(1), Seifert M(1), Catanzaro DG(2), McKinnon S(1), Colman RE(1), Chiles PG(1), Chesov D(3)(4), Ciobanu N(3)(5), Hagan C(1), Crudu V(3)(5), Catanzaro A(1), Rodwell TC(1).

BACKGROUND: The lack of accurate and efficient diagnostic devices for extensively drug-resistant tuberculosis (XDR-TB) makes it a severe threat to global public health. A prospective clinical study in an intended-use cohort was designed to evaluate the Akonni Biosystems XDR-TB TruArray and lateral flow cell (XDR-LFC) to address this gap in tuberculosis diagnostics.
OBJECTIVE: This paper presents the protocol for a study that aims to document the conceptualization and design of this evaluation method for early dissemination while data collection and analysis are ongoing.
METHODS: The clinical study was conducted in three phases. The first phase was to observe changes in bacterial load and culture positivity in patient sputa over time and better understand the diversity of prospective clinical samples. The second phase was to prospectively collect clinical samples for sensitivity and specificity testing of the Akonni Biosystems XDR-LFC device. Lastly, the third phase was to explore the anti-TB drug concentrations in serum throughout the drug-resistant tuberculosis treatment.
RESULTS: The methodology described includes the study design, laboratory sample handling, data collection, and the protection elements of human subjects of this clinical study to evaluate a potential new XDR-TB diagnostic device. A total of 664 participants were enrolled across the three phases. The implemented complex systems facilitated a thorough clinical data collection for an objective evaluation of the device. The study is closed to recruitment. The follow-up data collection and analysis are in progress.

CONCLUSIONS: This paper outlined a prospective cohort study protocol to evaluate a rapid XDR-TB detection device, which may be informative for other researchers with similar goals.
INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): DERR1-10.2196/26748.

DOI: 10.2196/26748
PMID: 34259165

27. Characterization of rifampicin-resistant Mycobacterium tuberculosis in Khyber Pakhtunkhwa, Pakistan.

Sci Rep. 2021 Jul 9;11(1):14194. doi: 10.1038/s41598-021-93501-4.

Khan AS(1)(2), Phelan JE(3), Khan MT(4), Ali S(2), Qasim M(1), Napier G(3), Campino S(3), Ahmad S(5), Cabral OM(6)(7)(8), Zhang S(9), Rahman H(10), Wei DQ(11), Clark TG(12)(13), Khan TA(14).

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is endemic in Pakistan. Resistance to both firstline rifampicin and isoniazid drugs (multidrug-resistant TB; MDR-TB) is hampering disease control. Rifampicin resistance is attributed to rpoB gene mutations, but rpoA and rpoC loci may also be involved. To characterise underlying rifampicin resistance mutations in the TB endemic province of Khyber Pakhtunkhwa, we sequenced 51 M. tuberculosis isolates collected between 2016 and 2019; predominantly, MDR-TB (n = 44; 86.3%) and lineage 3 (n = 30, 58.8%) strains. We found that known mutations in rpoB (e.g. S405L), katG (e.g. S315T), or inhA promoter loci explain the MDR-TB. There were 24 unique mutations in rpoA, rpoB, and rpoC genes, including four previously unreported. Five instances of within-host resistance diversity were observed, where two were a mixture of MDR-TB strains containing mutations in rpoB, katG, and the inhA promoter region, as well as compensatory mutations in rpoC. Heteroresistance was observed in two isolates with a single lineage. Such complexity may reflect the high transmission nature of the Khyber Pakhtunkhwa setting. Our study reinforces the need to apply sequencing approaches to capture the full-extent of MDR-TB genetic diversity, to understand transmission, and to inform TB control activities in the highly endemic setting of Pakistan.

DOI: 10.1038/s41598-021-93501-4
PMCID: PMC8270973
PMID: 34244539

28. Ambispective study of adverse drug reactions in multi-drug resistant tuberculosis patients in Warangal, Telangana.

Lung India. 2021 Jul-Aug;38(4):330-337. doi: 10.4103/lungindia.lungindia_118_19.

Fatima S(1), Syeda MF(1), Adla N(1), Devi R(2).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) has become a global threat concerning to a risk of high mortality with the potential to cause adverse drug reactions (ADRs) which if not managed properly may affect patient compliance, resulting in below par treatment outcome.
AIM: The aim of the study was to study, assess, and report the ADRs of patients diagnosed with MDR-TB.
SUBJECTS AND METHODS: An ambispective, observational study was conducted among confirmed cases of MDR-TB patients without any comorbidities during the period of January 2015-December 2018 in patients of age 15 years and above.
STATISTICAL ANALYSIS: Data were analyzed descriptively using MS-Excel sheet 2013 and Chi-square test in GraphPad Prism 8.2.1. Results were expressed as either frequency, percentage, or mean ± standard deviation. ADRs were evaluated for causality, severity, and preventability attributes.
RESULTS: In the sample size of 400 patients, 236 (ADRs) were reported among 136 patients. The proportion of ADRs was higher in males (P = 0.0001) and in the age group of 36-75 years (P = 0.0211). Most commonly encountered ADRs include nausea and vomiting (35.31%) and arthralgia (14.04%), followed by peripheral neuropathy (8.93%) and giddiness (8.93%). Overall, 53% were of possible category and 60% of moderate level severity and 85% were unpreventable ADRs.
CONCLUSION: Our study included 13 types of ADRs, of which most commonly reported were nausea and vomiting, arthralgia, and peripheral neuropathy and least common were psychosis, nephrotoxicity, and gynecomastia with a higher incidence in males. Majority of ADRs were moderate, unpreventable ADRs and had a possible relationship with the suspected drugs.

DOI: 10.4103/lungindia.lungindia_118_19
PMID: 34259171

29. Predictors of mortality in patients with drug-resistant tuberculosis: A systematic review and meta-analysis.

PLoS One. 2021 Jun 28;16(6):e0253848. doi: 10.1371/journal.pone.0253848. eCollection 2021.

Alemu A(1), Bitew ZW(2), Worku T(3), Gamtesa DF(1), Alebel A(4)(5).

BACKGROUND: Even though the lives of millions have been saved in the past decades, the mortality rate in patients with drug-resistant tuberculosis is still high. Different factors are associated with this mortality. However, there is no comprehensive global report addressing these risk factors. This study aimed to determine the predictors of mortality using data generated at the global level.
METHODS: We systematically searched five electronic major databases (PubMed/Medline, CINAHL, EMBASE, Scopus, Web of Science), and other sources (Google Scholar, Google). We used the Joanna Briggs Institute Critical Appraisal tools to assess the quality of included articles. Heterogeneity assessment was conducted using the forest plot and I2 heterogeneity test. Data were analyzed using STATA Version 15. The pooled hazard ratio, risk ratio, and odd's ratio were estimated along with their 95% CIs.
RESULT: After reviewing 640 articles, 49 studies met the inclusion criteria and were included in the final analysis. The predictors of mortality were; being male (HR = 1.25,95%CI;1.08,1.41,I2;30.5%), older age (HR = 2.13, 95%CI;1.64,2.62,I2;59.0%,RR = 1.40,95%CI; 1.26, 1.53, I2; 48.4%) including a 1 year increase in age (HR = 1.01, 95%CI;1.00,1.03,I2;73.0%), undernutrition (HR = 1.62,95%CI;1.28,1.97,I2;87.2%, RR = 3.13, 95% CI; 2.17,4.09, I2;0.0%), presence of any type of co-morbidity (HR = 1.92,95%CI;1.50-2.33,I2;61.4%, RR = 1.61, 95%CI;1.29, 1.93,I2;0.0%), having diabetes (HR = 1.74, 95%CI; 1.24,2.24, I2;37.3%, RR = 1.60, 95%CI;1.13,2.07, I2;0.0%), HIV co-infection (HR = 2.15, 95%CI;1.69,2.61, I2; 48.2%, RR = 1.49, 95%CI;1.27,1.72, I2;19.5%), TB history (HR = 1.30,95%CI;1.06,1.54, I2;64.6%), previous second-line anti-TB treatment (HR = 2.52, 95% CI;2.15,2.88, I2;0.0%), being smear positive at the baseline (HR = 1.45, 95%CI;1.14,1.76, I2;49.2%, RR = 1.58,95%CI;1.46,1.69, I2;48.7%), having XDR-TB (HR = 2.01, 95%CI;1.50,2.52, I2;60.8%, RR = 2.44, 95%CI;2.16,2.73,I2;46.1%), and any type of clinical complication (HR = 2.98, 95%CI; 2.32, 3.64, I2; 69.9%). There are differences and overlaps of predictors of mortality across different drug-resistance categories. The common predictors of mortality among different drug-resistance categories include; older age, presence of any type of co-morbidity, and undernutrition.
CONCLUSION: Different patient-related demographic (male sex, older age), and clinical factors (undernutrition, HIV co-infection, co-morbidity, diabetes, clinical complications, TB history, previous second-line anti-TB treatment, smear-positive TB, and XDR-TB) were the predictors of mortality in patients with drug-resistant tuberculosis. The findings would be an important input to the global community to take important measures.

DOI: 10.1371/journal.pone.0253848
PMCID: PMC8238236
PMID: 34181701

30. Profiling Pretomanid as a Therapeutic Option for TB Infection: Evidence to Date.

Drug Des Devel Ther. 2021 Jun 28;15:2815-2830. doi: 10.2147/DDDT.S281639. eCollection 2021.

Stancil SL(1)(2)(3), Mirzayev F(4), Abdel-Rahman SM(2)(3).

Tuberculosis (TB) is the most deadly infectious disease globally. Although most individuals achieve a cure, a substantial portion develop multi-drug resistant TB which is exceedingly difficult to treat, and the number of effective agents is dwindling. Development of new anti-tubercular medications is imperative to combat existing drug resistance and accelerate global eradication of TB. Pretomanid (PA-824) represents one of the newest drug classes (ie, nitroimidazooxazines) approved in 2019 by the United States Food and Drug Administration as part of a multi-drug regimen (with bedaquiline and linezolid, BPaL) and recommended by the World Health Organization (WHO) to treat extensively-resistant (XR-TB) and multi-drug resistant tuberculosis (MDR-TB). Approval was granted through the FDA's Limited Population Pathway for Antibacterial and Antifungal Drugs, which accelerates approval for antimicrobial drugs used to treat life-threatening or serious infections in a limited population with unmet need. This review details the pharmacology, efficacy, and safety of this new agent and describes evidence to date for its role in the treatment of drug resistant TB including published, ongoing, and planned studies.

DOI: 10.2147/DDDT.S281639
PMCID: PMC8253981
PMID: 34234413

31. Costs of multidrug-resistant TB treatment in Finland and Estonia affected by the 2019 WHO guidelines.

Int J Tuberc Lung Dis. 2021 Jul 1;25(7):554-559. doi: 10.5588/ijtld.20.0892.

Feuth T(1), Patovirta RL(2), Grierson S(3), Danilovits M(4), Viiklepp P(5), Aaltonen HK(6), Vauhkonen M(3), Pehme L(4), Vasankari T(3).

BACKGROUND: Multidrug-resistant TB (MDR-TB) is a growing problem in the effort to end the global TB epidemic. In 2019, the WHO adopted a new standardised regiment for MDR-TB, consisting of only oral medications.METHODS: We estimated the impact of the new guidelines on the costs of TB treatment in Estonia and Finland. For both countries, the costs of the two most common new drug regimens were calculated, including drug costs, as well as care- and monitoring-related costs.RESULTS: In Turku, Finland, treatment costs with the old regimen were €178,714; this could either increase by 10% or decrease by 18%, depending on the duration of bedaquiline use (6 months vs. 20 months). In Estonia, treatment costs with the old regimen were €33,664, whereas the new regimens were associated with a 40% increase in overall costs.CONCLUSIONS: The 2019 WHO guidelines have led to significant changes in the costs of MDR-TB treatment in Finland and Estonia. These changes depend mostly on the drug regimen administered and on care-related practices, with important differences between countries and even within the same country due to local practices.

CONTEXTE : La TB multirésistante (MDR-TB) constitue un problème croissant dans les efforts de mettre fin à l'épidémie mondiale de TB. En 2019, l'OMS a adopté un nouveau protocole standardisé pour la MDR-TB, consistant seulement en médicaments oraux.
MÉTHODES : Nous avons estimé l'impact des nouvelles directives sur le coût du traitement de la TB en Estonie et en Finlande. Dans ces deux pays, les coûts des deux nouveaux protocoles les plus fréquents ont été calculés, y compris le coût des médicaments ainsi que celui de la prise en charge et du suivi.
RÉSULTATS : A Turku, Finlande, les coûts ont été de 178 714€ avec le protocole ancien et ils pourraient augmenter de 10% ou diminuer de 18% selon la durée d'administration de la bédaquiline (6 mois contre 20 mois). En Estonie, les coûts du protocole ancien étaient de 30 131€, tandis que les nouveaux protocoles étaient associés à une augmentation de 40% de l'ensemble des coûts.
CONCLUSION : Les directives OMS 2019 ont abouti à des modifications significatives du coût de traitement de la MDR-TB en Finlande et en Estonie. Ces modifications dépendent surtout du protocole et des pratiques de soins associées, avec des différences importantes entre pays et même à l'intérieur d'un pays en fonction des pratiques locales.

DOI: 10.5588/ijtld.20.0892
PMCID: PMC8259121
PMID: 34183100

32. Prevalence of Mycobacterium tuberculosis resistant to Bedaquiline and Delamanid in China.

J Glob Antimicrob Resist. 2021 Jun 29:S2213-7165(21)00160-0. doi:

10.1016/j.jgar.2021.06.007. Online ahead of print.

He W(1), Liu C(2), Liu D(3), Ma A(3), Song Y(4), He P(1), Bao J(5), Li Y(4), Zhao B(2), Fan J(2), Cheng Q(2), Zhao Y(6).

OBJECTIVES: New anti-TB drugs delamanid and bedaquiline appear as the last line to defense drug-resistant tuberculosis. Understanding the background prevalence of resistance to new drugs can help predict the lifetime of these drugs' effectiveness and inform regimen design.
METHODS: TB strains without prior exposure to novel anti-TB drugs were analyzed retrospectively. Drug susceptibility testing was conducted for TB strains with bedaquiline, delamanid, linezolid, clofazimine, and widely-used first- and second-line anti-TB drugs. All TB isolates with resistance to new or repurposed drugs were subjected to whole-genome sequencing to explore molecular characteristics of resistance and perform the phylogenetic analysis.
RESULTS: Overall, resistance to delamanid, bedaquiline, linezolid and clofazimine were observed in 0.7% (11/1603), 0.4% (6/1603), 0.4% (7/1603) and 0.4% (6/1603) of strains, respectively. Moreover, 1.0% (1/102) and 2.9% (3/102), 3.9% (4/102) and 1.0% (1/102) of MDR-TB strains were resistant to bedaquiline, delamanid, linezolid and clofazimine, respectively. Whereas 22.22% (2/9) of XDR-TB strains were resistant to both delamanid and linezolid, and none was resistant to bedaquiline or clofazimine. Phylogenetic analysis showed that recent transmission occurred in two XDR-TB strains with additional resistance to delamanid and linezolid. None known gene mutation associated with delamanid resistance was detected. All four strains with cross-resistance between bedaquiline and clofazimine were identified with a related gene mutation in Rv0678. Three out of five strains with linezolid resistance were detected gene mutation in rplC.
CONCLUSIONS: The detection of resistance to new anti-TB drugs emphasizes the pressing need for intensive surveillance for such resistance before wide-usage.

DOI: 10.1016/j.jgar.2021.06.007
PMID: 34214699

33. Drug-Lead Anti-tuberculosis Phytochemicals: A Systematic Review.

Curr Top Med Chem. 2021 Jul 5. doi: 10.2174/1568026621666210705170510. Online ahead of print.

Swain SS(1), Hussain T(1), Pati S(1).

Today, the occurrence and recurrence of multidrug-resistant tuberculosis (MDR-TB) strains and TB-comorbidity incidence are the main reasons for long-term morbidity and mortality from tuberculosis (TB) caused by the nasty acid-fast pathogen, Mycobacterium tuberculosis, globally. Therefore, discovering and developing well-tolerated and non-toxic anti-TB regimens are directly needed to defend the gruesome MDR-TB strains and support WHO's 'END-TB' campaign. Alternatively, phytochemicals from various common and medicinal plants have always been vital therapeutic agents since the primitive era. Thus, to promote phytochemical-based anti-TB drug development, scientific documentation of biological activities, structural-cum-drug chemistry analyses are essential. In the present review, we have used some specific keywords such as 'antituberculosis phytochemicals', 'antituberculosis phytochemicals from plant source', 'natural products against tuberculosis' in Google, PubMed, ScienceDirect sites to get more appropriate research reports/ publications. Further, based on lower minimum inhibitory concentration (MIC) within 50 μg/mL, a total of two-hundred-twenty-one bioactive anti-TB phytochemicals were selected for critical drug-chemistry and structural activity relationship (SAR) analyses to accelerate the anti-TB drug development with most drug lead anti-TB candidates. Among all, abietane, ethyl-p-methoxycinnamate, ergosterol peroxide, mono-O-methyl curcumin isoxazole, 7-methyljuglone, 12-demethylmulticaulin, 12-methyl-5-dehy droacetylhorminone, tryptanthrin, etc. are some of the potential anti-TB phytochemicals display at the minimum concentration ≤ 1 μg/mL. Remarkably, existing and clinical drug pipelines for TB contain more than one phytochemical scaffold/ pharmacophores illustrated from the SAR analysis. Thus, updated experimental documentation and critical drug-chemistry analysis on isolated phytochemicals are more beneficial for drug developers, R & D centres and pharmaceutical companies to accelerate the anti-TB drug development.

DOI: 10.2174/1568026621666210705170510
PMID: 34225624

34. Prevalence of aminoglycoside-induced hearing loss in drug-resistant tuberculosis patients: A systematic review.

J Infect. 2021 Jul;83(1):27-36. doi: 10.1016/j.jinf.2021.05.010. Epub 2021 May 17.

Dillard LK(1), Martinez RX(2), Perez LL(2), Fullerton AM(3), Chadha S(2), McMahon CM(3).

Objectives estimate the prevalence of ototoxic hearing loss in drug-resistant tuberculosis (DR-TB) patients treated with aminoglycoside antibiotics via a systematic review and meta-analysis. Estimate the annual preventable cases of hearing loss in DR-TB patients and leverage findings to discuss primary, secondary and tertiary prevention. Methods studies published between 2005 and 2018 that reported prevalence of post-treatment hearing loss in DR-TB patients were included. We performed a random effects meta-analysis to determine pooled prevalence of ototoxic hearing loss overall and by medication type. Preventable hearing loss cases were estimated using World Health Organization (WHO) data on DR-TB treatment and prevalence determined by the meta-analysis. Results eighteen studies from 10 countries were included. Pooled prevalence of ototoxic hearing loss and the corresponding 95% confidence interval (CI) was 40.62% CI [32.77-66.61%] for all drugs (kanamycin: 49.65% CI [32.77- 66.61%], amikacin: 38.93% CI [26.44-53.07%], capreomycin: 10.21% CI [4.33-22.21%]). Non-use of aminoglycosides may result in prevention of approximately 50,000 hearing loss cases annually. Conclusions aminoglycoside use results in high prevalence of ototoxic hearing loss. Widespread prevention of hearing loss can be achieved by following updated WHO guidelines for DR-TB treatment. When hearing loss cannot be avoided, secondary and tertiary prevention should be prioritized.

DOI: 10.1016/j.jinf.2021.05.010
PMID: 34015383

35. Pharmacokinetics and target attainment of SQ109 in plasma and human-like tuberculosis lesions in rabbits.

Antimicrob Agents Chemother. 2021 Jul 6:AAC0002421. doi: 10.1128/AAC.00024-21. Online ahead of print.

Egbelowo O(1), Sarathy JP(2), Gausi K(1), Zimmerman MD(2), Wang H(2), Wijnant GJ(2), Kaya F(2), Gengenbacher M(2), Van N(3), Degefu Y(3), Nacy C(4), Aldridge BB(3), Carter CL(2), Denti P(1), Dartois V(2)(5).

SQ109 is a novel well-tolerated drug candidate in clinical development for the treatment of drug resistant tuberculosis (TB). It is the only inhibitor of the MmpL3 mycolic acid transporter in clinical development. No SQ109 resistant mutant has been directly isolated thus far, in vitro, in mice or in patients, tentatively attributed to its multiple targets. It is considered as a potential replacement for poorly tolerated components of multidrug-resistant TB regimens. To prioritize SQ109-containing combinations with best potential for cure and treatment shortening, one must understand its contribution against different

bacterial populations in pulmonary lesions. Here we have characterized the pharmacokinetics of SQ109 in the rabbit model of active TB and its penetration at the sites of disease: lung tissue, cellular and necrotic lesions, and caseum. A two-compartment model with first-order absorption and elimination described the plasma pharmacokinetics. At the human-equivalent dose, parameter estimates fell within the ranges published for preclinical species. Tissue concentrations were modelled using an "effect" compartment, showing high accumulation in lung and cellular lesion areas with penetration coefficients in excess of 1,000, and lower passive diffusion in caseum after 7 daily doses. These results, together with the hydrophobic nature and high non-specific caseum binding of SQ109, suggest that multi-week dosing would be required to reach steady state in caseum and poorly vascularized compartments, similar to bedaquiline. Linking lesion pharmacokinetics to SQ109 potency in assays against replicating, non-replicating, and intracellular M. tuberculosis showed SQ109 concentrations markedly above pharmacokinetic-pharmacodynamic targets in lung and cellular lesions throughout the dosing interval. IMPORTANCE Drug-resistant tuberculosis (TB) accounts for over 20% of all fatalities due to drug-resistant pathogens. With recently approved drugs and a promising drug candidate pipeline, the challenge faced by clinical developers is prioritization of drug combinations with the best potential to improve cure rates and shorten treatment duration. To this end, one must understand the contribution of each partner drug against different bacterial populations in pulmonary TB lesions. SQ109 is a safe drug candidate in clinical development for the treatment of multidrug resistant TB. It is active against replicating and non-replicating Mycobacterium tuberculosis persisters in vitro, in mouse models and in patients. SQ109 exhibits extremely low frequency of resistance, unprecedented among all TB drugs so far. Here we characterize the pharmacokinetics and activity of SQ109 at the site of TB disease to inform the selection of drug regimens that account for its lesion-centric pharmacokinetic-pharmacodynamic parameters and best leverage its contribution to efficient disease cure.

DOI: 10.1128/AAC.00024-21
PMID: 34228540

36. Prevalence of primary anti-tuberculosis drug resistance at the tertiary center in Saudi Arabia and associated risk factors.

Saudi Med J. 2021 Jul;42(7):728-734. doi: 10.15537/smj.2021.42.7.20200797.

Al-Shahrani MS(1), Hakami MI(1), Younis MA(1), Fan HA(1), Jeraiby MA(1), Alraey Y(1).

OBJECTIVES: To estimate the prevalence mono-resistant tuberculosis (MR-TB) and

multidrug resistant TB (MDR-TB), and evaluate the risk factors associated with the drug-resistant tuberculosis (DR-TB).
METHODS: A descriptive, retrospective study was applied, utilizing the TB patients' medical records at King Fahd Armed Forces Hospital (KFAFH), Jeddah, Saudi Arabia. The records of patients notified between 2000 and 2018 were reviewed and culture positive cases for Mycobacterium tuberculosis species were included. Moreover, the risk factors included were age, gender, smoking history, renal disease, liver disease, hyperbilirubinemia, diabetes mellitus, and human immunodeficiency virus (HIV).
RESULTS: Nine hundred and one cases in entirety were involved in the research, out of which 193 had drug-resistant tuberculosis (DR-TB) (21.4%). Out of the 21.4% DR-TB, 91.7% were MR-TB and 8.3% were MDR-TB. The highest MR prevalence was for pyrazinamide at 33.4%, while the lowest resistance was for ethambutol at 7.1%. For the risk factors of drug-resistant TB, only age depicted a statistically significant ($p<0.01$) but weak negative ($r= -0.145$) correlation with anti-TB drug resistance.
CONCLUSION: Rates of DR-TB reported in the study are considered higher compared to the recently reported national and international rates. According to the results, only younger people are at risk of developing DR-TB. Moreover, genetic mutation may play a role in drug resistance among our cases specifically for pyrazinamide monoresistance.

DOI: 10.15537/smj.2021.42.7.20200797
PMID: 34187916

37. Multidisciplinary management of difficult-to-treat drug resistant tuberculosis: a review of cases presented to the national consilium in Uganda.

BMC Pulm Med. 2021 Jul 10;21(1):220. doi: 10.1186/s12890-021-01597-1.

Baluku JB(1)(2), Katuramu R(3), Naloka J(4), Kizito E(5), Nabwana M(6), Bongomin F(7).

BACKGROUND: Patients with drug resistant tuberculosis (DR-TB) with comorbidities and drug toxicities are difficult to treat. Guidelines recommend such patients to be managed in consultation with a multidisciplinary team of experts (the "TB consilium") to optimise treatment regimens. We describe characteristics and treatment outcomes of DR-TB cases presented to the national DR-TB consilium in Uganda between 2013 and 2019.
METHODS: We performed a secondary analysis of data from a nation-wide retrospective cohort of DR-TB patients with poor prognostic indicators in

Uganda. Patients had a treatment outcome documented between 2013 and 2019. Characteristics and treatment outcomes were compared between cases reviewed by the consilium with those that were not reviewed.
RESULTS: Of 1,122 DR-TB cases, 189 (16.8%) cases from 16 treatment sites were reviewed by the consilium, of whom 86 (45.5%) were reviewed more than once. The most frequent inquiries (N = 308) from DR-TB treatment sites were construction of a treatment regimen (38.6%) and management of side effects (24.0%) while the most frequent consilium recommendations (N = 408) were a DR-TB regimen (21.7%) and "observation while on current regimen" (16.6%). Among the cases reviewed, 152 (80.4%) were from facilities other than the national referral hospital, 113 (61.1%) were aged ≥ 35 years, 72 (40.9%) were unemployed, and 26 (31.0%) had defaulted antiretroviral therapy. Additionally, 141 (90.4%) had hepatic injury, 55 (91.7%) had bilateral hearing loss, 20 (4.8%) had psychiatric symptoms and 14 (17.7%) had abnormal baseline systolic blood pressure. Resistance to second-line drugs (SLDs) was observed among 9 (4.8%) cases while 13 (6.9%) cases had previous exposure to SLDs. Bedaquiline (13.2%, n = 25), clofazimine (28.6%, n = 54), high-dose isoniazid (22.8%, n = 43) and linezolid (6.7%, n = 13) were more frequently prescribed among cases reviewed by the consilium than those not reviewed. Treatment success was observed among 126 (66.7%) cases reviewed.
CONCLUSION: Cases reviewed by the consilium had several comorbidities, drug toxicities and a low treatment success rate. Consilia are important "gatekeepers" for new and repurposed drugs. There is need to build capacity of lower health facilities to construct DR-TB regimens and manage adverse effects.

DOI: 10.1186/s12890-021-01597-1
PMCID: PMC8272325
PMID: 34246234

38. Health-Related Quality of Life in Tuberculosis Patients in Eritrea: Comparison Among Drug-Susceptible and Rifampicin/Multidrug-Resistant Tuberculosis Patients.

Patient Relat Outcome Meas. 2021 Jun 29;12:205-212. doi: 10.2147/PROM.S316337. eCollection 2021.

Araia ZZ(1), Mesfin AB(2), Mebrahtu AH(1), Tewelde AG(3), Tewelde AT(3), Ngusbrhan Kidane S(4).

BACKGROUND: Despite the negative impact of tuberculosis (TB) on patients' quality of life, TB control programs focus on biological and clinical parameters to manage and monitor TB patients. In our setting, patients' perception of their experience with TB and the impacts of TB on patients' physical, mental, and

social wellbeing remain unknown.
OBJECTIVE: The objective of this study was to evaluate the health-related quality of life (HRQOL) among rifampicin/multidrug-resistant TB (RR/MDR-TB) in comparison to drug-susceptible TB (DS-TB) patients in Eritrea.
METHODS: A cross-sectional study was conducted in RR/MDR-TB and DS-TB patients under treatment. Anonymized data collected using the WHOQOL-BREF questionnaire were analyzed using SPSS version 23. Frequency, mean and standard deviation were used to describe the data. Mean group score comparison and relationship between variables were assessed using t-test. Domain score was calculated with a mean score of items within each domain and scaled positively, a higher (increasing) score denoting a higher quality of life. Internal consistency was measured using Cronbach's alpha and statistical significance was set at $p < 0.05$.
RESULTS: A total of 92 patients (46 RR/MDR-TB and 46 DS-TB) participated in the study. Environmental (40.63 ± 10.72) and physical domains (61.80 ±17.18) were the two most affected domains in RR/MDR-TB and DS-TB patients, respectively. The psychological domain was the least affected domain in RR/MDR-TB (48.28 ± 20.83) and DS-TB patients (76.63 ±15.32). RR/MDR-TB patients had statistically lower mean scores in all domains than DS-TB patients.
CONCLUSION: HRQOL was impaired in both groups, but RR/MDR-TB patients had a worse health-related quality of life.

DOI: 10.2147/PROM.S316337
PMCID: PMC8254609
PMID: 34234605

39. Ambient air pollutants, diabetes and risk of newly diagnosed drug-resistant tuberculosis.

Ecotoxicol Environ Saf. 2021 Aug;219:112352. doi: 10.1016/j.ecoenv.2021.112352. Epub 2021 May 25.

Song WM(1), Liu Y(2), Zhang QY(1), Liu SQ(1), Xu TT(3), Li SJ(1), An QQ(1), Liu JY(4), Tao NN(5), Liu Y(6), Yu CB(7), Yu CX(8), Li YF(9), Li HC(10).

BACKGROUND: Drug-resistant tuberculosis (DR-TB), diabetes and exposure to air pollution are thought to be important threat to human health, but no studies have explored the effects of ambient air pollutants on DR-TB when adjusting diabetes status so far.
METHODS: We performed a study among 3759 newly diagnosed TB cases with drug-susceptibility testing results, diabetes status, and individual air pollution data in Shandong from 2015 to 2019. Generalized linear mixed models

(GLMM) including three models (Model 1: without covariates, Model 2: adjusted by diabetes status only, Model 3: with all covariates) were applied.
RESULTS: Of 3759 TB patients enrolled, 716 (19.05%) were DR-TB, and 333 (8.86%) had diabetes. High exposure to O3 was associated with an increased risk of RFP-resistance (Model 2 or 3: odds ratio (OR) = 1.008, 95% confidence intervals (CI): 1.002-1.014), ethambutol-resistance (Model 3: OR = 1.015, 95%CI: 1.004-1.027) and any rifampicin+streptomycin resistance (Model 1,2,3: OR = 1.01, 95%CI: 1.002-1.018) at 90 days. In contrast, NO2 was associated with a reduced risk of DR-TB (Model 3: OR = 0.99, 95%CI: 0.981-0.999) and multidrug-resistant TB (MDR-TB) (Model 3: OR = 0.977, 95%CI: 0.96-0.994) at 360 days. Additionally, SO2 (Model 1, 2, 3: OR = 0.987, 95%CI: 0.977-0.998) showed a protective effect on MDR-TB at 90 days. PM2.5 (90 days, Model 2: OR = 0.991, 95%CI: 0.983-0.999), PM10 (360 days, Model 2: OR = 0.992, 95%CI: 0.985-0.999) had protective effects on any RFP+SM resistance.
CONCLUSIONS: O3 contributed to an elevated risk of TB resistance but PM2.5, PM10, SO2, NO2 showed an inverse effect. Air pollutants may affect the development of drug resistance among TB cases by adjusting the status of diabetes.

DOI: 10.1016/j.ecoenv.2021.112352
PMID: 34044311 [Indexed for MEDLINE]

40. HIV-associated tuberculosis.

Int J STD AIDS. 2021 Aug;32(9):780-790. doi: 10.1177/0956462421992257. Epub 2021 Feb 20.

Hamada Y(1)(2), Getahun H(3), Tadesse BT(3), Ford N(4).

Tuberculosis (TB) remains a leading cause of morbidity and mortality among people living with HIV. HIV-associated TB disproportionally affects African countries, particularly vulnerable groups at risk for both TB and HIV. Currently available TB diagnostics perform poorly in people living with HIV; however, new diagnostics such as Xpert Ultra and lateral flow urine lipoarabinomannan assays can greatly facilitate diagnosis of TB in people living with HIV. TB preventive treatment has been underutilized despite its proven benefits independent of antiretroviral therapy (ART). Shorter regimens using rifapentine can support increased availability and scale-up. Mortality is high in people with HIV-associated TB, and timely initiation of ART is critical. Programs should provide decentralized and integrated TB and HIV care in settings with high burden of both diseases to improve access to services that diagnose TB and HIV

as early as possible. The new prevention and diagnosis tools recently recommended by WHO offer an immense opportunity to advance our fight against HIV-associated TB. They should be made widely available and scaled up rapidly supported by adequate funding with robust monitoring of the uptake to advance global TB elimination.

DOI: 10.1177/0956462421992257
PMCID: PMC8236666
PMID: 33612015

41. Screening of Compounds for Anti-tuberculosis Activity, and in vitro and in vivo Evaluation of Potential Candidates.

Front Microbiol. 2021 Jun 30;12:658637. doi: 10.3389/fmicb.2021.658637. eCollection 2021.

Zhou W(1)(2), Yang B(1)(2), Zou Y(1)(2), Rahman K(1)(2), Cao X(1)(2), Lei Y(1)(2), Lai R(3), Fu ZF(1)(2), Chen X(1)(2), Cao G(1)(2)(4)(5).

Tuberculosis (TB) is a debilitating infectious disease responsible for more than one million deaths per year. The emergence of drug-resistant TB poses an urgent need for the development of new anti-TB drugs. In this study, we screened a library of over 4,000 small molecules and found that orbifloxacin and the peptide AK15 possess significant bactericidal activity against Mycobacterium tuberculosis (Mtb) in vitro. Orbifloxacin also showed an effective ability on the clearance of intracellular Mtb and protect mice from a strong inflammatory response but not AK15. Moreover, we identified 17 nucleotide mutations responsible for orbifloxacin resistance by whole-genome sequencing. A critical point mutation (D94G) of the DNA gyrase (gyrA) gene was found to be the key role of resistance to orbifloxacin. The computational docking revealed that GyrA D94G point mutation can disrupt the orbifloxacin-protein gyrase interactions mediated by magnesium ion bridge. Overall, this study indicated the potential ability of orbifloxacin as an anti-tuberculosis drug, which can be used either alone or in combination with first-line antibiotics to achieve more effective therapy on TB.

DOI: 10.3389/fmicb.2021.658637
PMCID: PMC8278749
PMID: 34276592

42. Rapid Molecular Diagnosis of Tuberculosis and Its Resistance to Rifampicin and

Isoniazid with Automated MDR/MTB ELITe MGB(®) Assay.

Antibiotics (Basel). 2021 Jun 30;10(7):797. doi: 10.3390/antibiotics10070797.

Ok V(1)(2), Aubry A(1)(2), Morel F(1)(2), Bonnet I(1)(2), Robert J(1)(2), Sougakoff W(1)(2).

The MDR/MTB ELITe MGB® kit (ELITech) carried on the ELITe InGenius® platform is a new real-time PCR assay allowing automated extraction and detection of DNA of the Mycobacterium tuberculosis complex (MTB) and mutations in the rpoB and katG genes and inhA promoter region (pro-inhA) associated to resistance to rifampicin and isoniazid, the two markers of multidrug-resistant TB (MDR). We assessed the performances of the test on a collection of strains (n = 54) and a set of clinical samples (n = 242) from routine practice, comparatively to TB diagnosis and genotypic drug susceptibility testing (gDST) as references. Regarding the 242 clinical samples, the sensitivity and specificity of MTB detection by ELITe were 90.9% and 97.5%, respectively. For the detection of resistance-conferring mutations on positive clinical samples, we observed perfect agreement with gDST for katG and pro-inhA (κ = 1.0) and two discordant results for rpoB (κ = 0.82). Considering the 54 cultured strains, very good agreement with gDST was observed for the detection of the 25 distinct mutations in rpoB, katG, and pro-inhA, (κ = 0.95, 0.88, and 0.95, respectively). In conclusion, the automated MDR/MTB ELITe MGB® assay shows great promise and appears to be a valuable tool for rapid detection of pre-MDR- and MDR-TB directly from clinical specimens.

DOI: 10.3390/antibiotics10070797
PMID: 34208899

43. Khat Chewing and Clinical Conditions Determine the Epidemiology of Primary Drug Resistance Tuberculosis in Amhara Region of Ethiopia: A Multicenter Study.

Infect Drug Resist. 2021 Jun 30;14:2449-2460. doi: 10.2147/IDR.S316268. eCollection 2021.

Kassa GM(1), Merid MW(1), Muluneh AG(1).

BACKGROUND: Rifampicin and/or multidrug-resistant tuberculosis (RR/MDR-TB) remains an uncontrolled public health emergency that has been synergized by the recently increased person-to-person transmission in the community as primary RR/MDR-TB, which is defined as RR/MDR-TB in new TB patients with no prior exposure to anti-TB treatment for more than one month. This study aimed to measure the prevalence and associated factors of primary drug-resistance among drug-resistant tuberculosis patients, as evidenced by the Amhara region

treatment initiating centers.
METHODS: An institutional-based multicenter cross-sectional study was conducted from September 2010 to December 2017, among 580 RR/MDR-TB patients on the second-line anti-TB drug in the Amhara regional state. Data were collected from patient charts and registration books using a standardized data abstraction sheet. The data were entered using Epi-data 4.2.0.0 and transferred to Stata 14 software for further data management and analysis. A bivariable and multivariable binary logistic model was run subsequently, and finally, a p-value of less than 0.05 with a 95% confidence interval (CI) was used to declare the significance of the explanatory variable.
RESULTS: The magnitude of primary drug resistance among drug-resistant tuberculosis patients was 15.69% (95% CI: 12.94, 18.89). Alcohol drinking (adjusted odds ratio [AOR] = 0.31, 95% CI: 0.12-0.82), khat chewing (AOR = 4.43; 95% CI: 1.67-11.76), ambulatory and bedridden functional status (AOR = 0.43; 95% CI: 0.24-0.76) and (AOR = 0.41; 95% CI: 0.19-0.91), respectively, positive sputum smear result (AOR = 0.48; 95% CI: 0.26-0.90), and HIV coinfection (AOR= 2.31; 95% CI: 1.31-4.06) remained statistically significant associated factors of primary RR/MDR-TB.
CONCLUSION: Primary drug resistance is a public health problem in the study setting. Different behavioral and clinical conditions were significant factors of primary drug-resistant development. Mitigation strategies targeted on the patient's clinical condition, substance-related behaviors, and universal DST coverage might be very important for early detection and treatment of RR/MDR-TB to prevent community-level transmission.

DOI: 10.2147/IDR.S316268
PMCID: PMC8255900
PMID: 34234475

44. Anti-mycobacterial natural products and mechanisms of action.

Nat Prod Rep. 2021 Jul 6. doi: 10.1039/d1np00011j. Online ahead of print.

Han J(1), Liu X(2), Zhang L(2), Quinn RJ(1), Feng Y(1).

Covering: up to June, 2020Tuberculosis (TB) continues to be a major disease with high mortality and morbidity globally. Drug resistance and long duration of treatment make antituberculosis drug discovery more challenging. In this review, we summarize recent advances on anti-TB natural products (NPs) and their potential molecular targets in cell wall synthesis, protein production, energy generation, nucleic acid synthesis and other emerging areas. We highlight

compounds with activity against drug-resistant TB, and reveal several novel targets including Mtb biotin synthase, ATP synthase, 1,4-dihydroxy-2-naphthoate prenyltransferase and biofilms. These anti-TB NPs and their targets could facilitate target-based screening and accelerate TB drug discovery.

DOI: 10.1039/d1np00011j
PMID: 34226909

45. Perspectives for systems biology in the management of tuberculosis.

Eur Respir Rev. 2021 May 25;30(160):200377. doi: 10.1183/16000617.0377-2020. Print 2021 Jun 30.

Kontsevaya I(1)(2)(3), Lange C(1)(2)(3), Comella-Del-Barrio P(4), Coarfa C(5)(6), DiNardo AR(7), Gillespie SH(8), Hauptmann M(1)(2), Leschczyk C(1)(2), Mandalakas AM(7), Martinecz A(9)(10)(11), Merker M(1)(2), Niemann S(1)(2), Reimann M(1)(2)(3), Rzhepishevska O(12)(13), Schaible UE(1)(2), Scheu KM(1), Schurr E(14), Abel Zur Wiesch P(9)(10), Heyckendorf J(15)(2)(3).

Standardised management of tuberculosis may soon be replaced by individualised, precision medicine-guided therapies informed with knowledge provided by the field of systems biology. Systems biology is a rapidly expanding field of computational and mathematical analysis and modelling of complex biological systems that can provide insights into mechanisms underlying tuberculosis, identify novel biomarkers, and help to optimise prevention, diagnosis and treatment of disease. These advances are critically important in the context of the evolving epidemic of drug-resistant tuberculosis. Here, we review the available evidence on the role of systems biology approaches - human and mycobacterial genomics and transcriptomics, proteomics, lipidomics/metabolomics, immunophenotyping, systems pharmacology and gut microbiomes - in the management of tuberculosis including prediction of risk for disease progression, severity of mycobacterial virulence and drug resistance, adverse events, comorbidities, response to therapy and treatment outcomes. Application of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach demonstrated that at present most of the studies provide "very low" certainty of evidence for answering clinically relevant questions. Further studies in large prospective cohorts of patients, including randomised clinical trials, are necessary to assess the applicability of the findings in tuberculosis prevention and more efficient clinical management of patients.

DOI: 10.1183/16000617.0377-2020

PMID: 34039674

46. Collateral Sensitivity to β-Lactam Drugs in Drug-Resistant Tuberculosis Is Driven by the Transcriptional Wiring of BlaI Operon Genes.

mSphere. 2021 Jun 30;6(3):e0024521. doi: 10.1128/mSphere.00245-21. Epub 2021 May 28.

Trigos AS(1)(2), Goudey BW(3)(4), Bedő J(3)(5), Conway TC(1), Faux NG(6)(7), Wyres KL(8).

The evolution of resistance to one antimicrobial can result in enhanced sensitivity to another, known as "collateral sensitivity." This underexplored phenomenon opens new therapeutic possibilities for patients infected with pathogens unresponsive to classical treatments. Intrinsic resistance to β-lactams in Mycobacterium tuberculosis (the causative agent of tuberculosis) has traditionally curtailed the use of these low-cost and easy-to-administer drugs for tuberculosis treatment. Recently, β-lactam sensitivity has been reported in strains resistant to classical tuberculosis therapy, resurging the interest in β-lactams for tuberculosis. However, a lack of understanding of the molecular underpinnings of this sensitivity has delayed exploration in the clinic. We performed gene expression and network analyses and in silico knockout simulations of genes associated with β-lactam sensitivity and genes associated with resistance to classical tuberculosis drugs to investigate regulatory interactions and identify key gene mediators. We found activation of the key inhibitor of β-lactam resistance, blaI, following classical drug treatment as well as transcriptional links between genes associated with β-lactam sensitivity and those associated with resistance to classical treatment, suggesting that regulatory links might explain collateral sensitivity to β-lactams. Our results support M. tuberculosis β-lactam sensitivity as a collateral consequence of the evolution of resistance to classical tuberculosis drugs, mediated through changes to transcriptional regulation. These findings support continued exploration of β-lactams for the treatment of patients infected with tuberculosis strains resistant to classical therapies. IMPORTANCE Tuberculosis remains a significant cause of global mortality, with strains resistant to classical drug treatment considered a major health concern by the World Health Organization. Challenging treatment regimens and difficulty accessing drugs in low-income communities have led to a high prevalence of strains resistant to multiple drugs, making the development of alternative therapies a priority. Although Mycobacterium tuberculosis is naturally resistant to β-lactam drugs, previous studies have shown sensitivity in strains resistant to classical drug treatment, but we currently lack understanding of the molecular underpinnings behind this phenomenon. We found that genes involved in β-lactam susceptibility

are activated after classical drug treatment resulting from tight regulatory links with genes involved in drug resistance. Our study supports the hypothesis that β-lactam susceptibility observed in drug-resistant strains results from the underlying regulatory network of M. tuberculosis, supporting further exploration of the use of β-lactams for tuberculosis treatment.

DOI: 10.1128/mSphere.00245-21
PMID: 34047652

47. Spectrum of Drug Resistance in Musculoskeletal Tuberculosis.

Indian J Orthop. 2021 Mar 1;55(4):907-911. doi: 10.1007/s43465-021-00378-6. eCollection 2021 Aug.

Sural S(1), Soni A(1), Kashyap A(1), Ahmad V(2), Hanif M(2), Khanna A(3).

BACKGROUND: Very few studies report resistance pattern exclusively in musculoskeletal tuberculosis (MSK-TB).
METHODS: This study of 100 pus samples from patients of MSK-TB with active disease in whom Mycobacterium tuberculosis (MTB) was detected by cartridge-based nucleic acid amplification test (CBNAAT), revealed the pattern of resistance among newly diagnosed and previously treated cases. Liquid culture and drug susceptibility testing (DST) using MGIT 960 was done for 11 anti-tubercular drugs.
RESULTS: Among these 100 cases; 22% were AFB positive; MGIT 960 detected MTB in 58.33% (35/60) new cases and 30.0% (12/40) previously treated cases. Five new and 10 previously treated cases had drug resistance and 12 were detected rifampicin resistance (Rif-R) by CBNAAT. Among new cases MGIT-DST detected mono-INH resistant in 2.86% (1/35), mono-STR resistant in 2.86% (1/35), MDR-TB in 5.7% (2/35) and pre-XDR in 2.9%(1/35).Among previously treated cases Rif-R was found in 10% (4/40) where MTB was not detected by MGIT and MGIT-DST detected mono-INH resistant in 8.33% (1/12); MDR-TB in 8.33% (1/12) and pre-XDR in 33.3%. There were no cases of XDR-TB.
CONCLUSION: High disease burden of various type drug resistance were seen more commonly in previously treated cases and was not uncommon in new cases of MSK-TB. Both CBNAAT and DST are essential for detecting resistance pattern in MSK-TB.

DOI: 10.1007/s43465-021-00378-6
PMCID: PMC8192612
PMID: 34194646

48. Whole-genome analysis of drug-resistant Mycobacterium tuberculosis reveals novel mutations associated with fluoroquinolone resistance.

Int J Antimicrob Agents. 2021 Jun 20:106385. doi: 10.1016/j.ijantimicag.2021.106385. Online ahead of print.

Chaiyachat P(1), Chaiprasert A(2), Nonghanphithak D(1), Smithtikarn S(3), Kamolwat P(3), Pungrassami P(3), Reechaipichitkul W(4), Ong RT(5), Teo YY(6), Faksri K(7).

Multidrug-resistant and extensively drug-resistant tuberculosis (M/XDR-TB) remains a global public-health challenge. Known mutations in quinolone resistance-determination regions cannot fully explain phenotypic fluoroquinolone (FQ) resistance in Mycobacterium tuberculosis (Mtb). The aim of this study was to look for novel mutations in Mtb associated with resistance to FQ drugs using whole-genome sequencing analysis. Whole-genome sequences of 659 Mtb strains, including 214 with phenotypic FQ resistance and 445 pan-susceptible isolates, were explored for mutations associated with FQ resistance overall and with resistance to individual FQ drugs (ofloxacin, levofloxacin, moxifloxacin and gatifloxacin). Three novel genes (recC, Rv2005c and PPE59) associated with FQ resistance were identified ($P < 0.00001$ based on screening analysis and absence of relevant mutations in a pan-susceptible validation set of 360 strains). Nine novel single nucleotide polymorphisms (SNPs), including in gyrB (G5383A and G6773A), gyrA (G7892A), recC (G725900C and G726857T/C), Rv2005c (C2251373G, G2251420C and C2251725T) and PPE59 (C3847269T), were used for diagnostic performance analysis. Enhancing the known SNP set with five of these novel SNPs, including gyrA [G7892A (Leu247Leu)], recC [G725900C (Leu893Leu) and G726857T/C (Arg484Arg)], Rv2005c [G2251420C (Pro205Arg)] and PPE59 [C3847269T (Asn35Asn)] increased the sensitivity of detection of FQ-resistant Mtb from 83.2% (178/214) to 86.9% (186/214) while maintaining 100% specificity (360/360). No specific mutation associated with resistance to only a single drug (ofloxacin, levofloxacin, moxifloxacin or gatifloxacin) was found. In conclusion, this study reports possible additional mutations associated with FQ resistance in Mtb.

DOI: 10.1016/j.ijantimicag.2021.106385
PMID: 34161790

49. Experiences of introducing new drugs for drug-resistant TB at the ALERT

Hospital, Addis Ababa, Ethiopia, 2017-2019.

Public Health Action. 2021 Jun 21;11(2):50-52. doi: 10.5588/pha.20.0065.

Tesema E(1), Wares F(2), Bedru A(1), Negeri C(1), Molla Y(1), Gemechu D(3), Kassa A(4), Tsegaye F(5), Taye L(6).

BACKGROUND: Drug-resistant TB (DR-TB) remains a major public health concern. DR-TB patient data from ALERT (All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre) Hospital, Addis Ababa, Ethiopia, who received bedaquiline (BDQ) and/or delamanid (DLM) containing regimens were analysed. RESULTS: From 2017 to 2019, 51 DR-TB patients were enrolled. Of 33 patients, 31 (93.9%) had culture converted at 6 months. Of those with final outcomes, 77% (n = 10) were cured. Thirty (58.8%) developed adverse events, the most frequent of which were gastrointestinal disorders (70%), haematological disorders (16.7%) and QTc prolongation (16.7%). Twenty patients discontinued the offending drug permanently.
CONCLUSION: With close monitoring, introduction of new DR-TB regimens brought good early results, which encouraged wider programmatic implementation in Ethiopia.

DOI: 10.5588/pha.20.0065
PMCID: PMC8202633
PMID: 34159060

50. Prisons as ecological drivers of fitness-compensated multidrug-resistant Mycobacterium tuberculosis.

Nat Med. 2021 Jul;27(7):1171-1177. doi: 10.1038/s41591-021-01358-x. Epub 2021 May 24.

Gygli SM(#)(1)(2), Loiseau C(#)(1)(2), Jugheli L(1)(2)(3), Adamia N(3), Trauner A(1)(2), Reinhard M(1)(2), Ross A(1)(2), Borrell S(1)(2), Aspindzelashvili R(3), Maghradze N(1)(2)(3), Reither K(1)(2), Beisel C(4), Tukvadze N(1)(2)(3), Avaliani Z(3), Gagneux S(5)(6).

Multidrug-resistant tuberculosis (MDR-TB) accounts for one third of the annual deaths due to antimicrobial resistance1. Drug resistance-conferring mutations frequently cause fitness costs in bacteria2-5. Experimental work indicates that these drug resistance-related fitness costs might be mitigated by compensatory mutations6-10. However, the clinical relevance of compensatory evolution remains

poorly understood. Here we show that, in the country of Georgia, during a 6-year nationwide study, 63% of MDR-TB was due to patient-to-patient transmission. Compensatory mutations and patient incarceration were independently associated with transmission. Furthermore, compensatory mutations were overrepresented among isolates from incarcerated individuals that also frequently spilled over into the non-incarcerated population. As a result, up to 31% of MDR-TB in Georgia was directly or indirectly linked to prisons. We conclude that prisons fuel the epidemic of MDR-TB in Georgia by acting as ecological drivers of fitness-compensated strains with high transmission potential.

DOI: 10.1038/s41591-021-01358-x
PMID: 34031604

51. Treatment and pregnancy outcomes of pregnant women exposed to second-line anti-tuberculosis drugs in South Africa.

BMC Pregnancy Childbirth. 2021 Jun 28;21(1):453. doi: 10.1186/s12884-021-03956-6.

Mokhele I(1), Jinga N(2), Berhanu R(2)(3), Dlamini T(4), Long L(2)(3), Evans D(2).

BACKGROUND: Multi-drug resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) in pregnant women is a cause for concern globally; few data have described the safety of second-line anti-TB medications during pregnancy. We aim to describe TB treatment and pregnancy outcomes among pregnant women receiving second-line anti-tuberculosis treatment for MDR/RR-TB in Johannesburg, South Africa.
METHODS: We conducted a retrospective record review of pregnant women (≥ 18 years) who received treatment for MDR/RR-TB between 01/2010-08/2016 at three outpatient treatment sites in Johannesburg, South Africa. Demographic, treatment and pregnancy outcome data were collected from available medical records. Preterm birth (< 37 weeks), and miscarriage were categorized as adverse pregnancy outcomes.
RESULTS: Out of 720 women of child-bearing age who received MDR/RR-TB treatment at the three study sites, 35 (4.4%) pregnancies were identified. Overall, 68.7% (24/35) were HIV infected, 83.3% (20/24) were on antiretroviral therapy (ART). Most women, 88.6% (31/35), were pregnant at the time of MDR/RR-TB diagnosis and four women became pregnant during treatment. Pregnancy outcomes were available for 20/35 (57.1%) women, which included 15 live births (11 occurred prior to 37 weeks), 1 neonatal death, 1 miscarriage and 3 pregnancy terminations.

Overall, 13/20 (65.0%) women with known pregnancy outcomes had an adverse pregnancy outcome. Of the 28 women with known TB treatment outcomes 17 (60.7%) completed treatment successfully (4 were cured and 13 completed treatment), 3 (10.7%) died and 8 (28.6%) were lost-to-follow-up.
CONCLUSIONS: Pregnant women with MDR/RR-TB suffer from high rates of adverse pregnancy outcomes and about 60% achieve a successful TB treatment outcome. These vulnerable patients require close monitoring and coordinated obstetric, HIV and TB care.

DOI: 10.1186/s12884-021-03956-6
PMCID: PMC8240388
PMID: 34182944

52. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance?

Ann Pharmacother. 2021 Jul 14:10600280211031390. doi: 10.1177/10600280211031390. Online ahead of print.

Chahine EB(1), Dougherty JA(1), Thornby KA(1), Guirguis EH(1).

OBJECTIVE: To review the spectrum of activity, efficacy, safety, and role in therapy of all antibiotics and related biologics approved by the Food and Drug Administration (FDA) in the last decade.
DATA SOURCES: A literature search was performed using PubMed and Google Scholar (2010 to end May 2021) with the search terms' name of the antibiotic or the biologic. Data were also obtained from the prescribing information, FDA, and ClinicalTrials.gov websites.
STUDY SELECTION: All relevant English-language, late phase clinical trials assessing the safety and efficacy of the identified drugs were included. Review articles and references of retrieved articles were evaluated for relevant data.
DATA SYNTHESIS: Antibiotic resistance is a public health crisis, and antibiotic development is imperative to outpace the ability of bacteria to develop resistance. Only 17 new systemic antibiotics and 1 related biologic have been approved by the FDA since 2010. Among these drugs, 14 were approved for common bacterial infections, 1 was approved for Clostridioides difficile infection (CDI), 1 was licensed to prevent CDI recurrence, and 2 were approved for drug-resistant tuberculosis. Very few antibiotics are in clinical development.
RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE: The arrival of these new antibiotics was welcomed with great enthusiasm, particularly when they met previously unmet medical needs. Unfortunately, the majority of them represent modifications to existing chemical structures rather than new drug classes. Despite the availability of these antibiotics, managing patients with deep-seated infections and those with extensively resistant gram-negative organisms remains challenging.

CONCLUSIONS: The number of new antibiotics and their indications are not keeping up with resistance and the needs of the patients.

DOI: 10.1177/10600280211031390
PMID: 34259076

53. Population pharmacokinetics of oral levofloxacin in healthy volunteers and dosing optimization for multidrug-resistant tuberculosis therapy.

Biopharm Drug Dispos. 2021 Jul;42(7):329-337. doi: 10.1002/bdd.2294. Epub 2021 Jun 19.

Boonpeng A(1), Jaruratanasirikul S(2), Wattanavijitkul T(3), Nawakitrangsan M(2), Samaeng M(2).

Levofloxacin is considered a key component of a multidrug-resistant tuberculosis (MDR-TB) regimen. However, there is considerable concern regarding the subtherapeutic concentrations of the currently used doses and the development of drug resistance. Therefore, this study aimed to describe the population pharmacokinetics (PPK) of oral levofloxacin in healthy volunteers and to evaluate the probability of target attainment (PTA) in an attempt to optimize the dosing regimens for MDR-TB therapy. Data of levofloxacin in healthy volunteers from a previous study were used to construct a PPK model. Monte Carlo simulations were performed to derive the PTAs of various regimens. A two-compartment model with linear elimination and transit absorption compartments best described the pharmacokinetics (PK) of levofloxacin. The estimated PK parameters (interindividual variability, %) were: apparent clearance 8.32 L h-1 (22.6%), apparent central volume of distribution 35.8 L (45.2%), apparent peripheral volume of distribution 39.7 L, intercompartmental clearance 40.6 L h-1 (43.8%), absorption rate constant 7.45 h-1 (150%), mean absorption transit time 0.355 h (52.4%), and total number of transit compartments 6.01 (131.9%). Monte Carlo simulations using levofloxacin 750-1000 mg yielded a probability of achieving a target free area under the concentration-time curve/minimum inhibitory concentration (MIC) of 100 at greater than 90% for Mycobacterium tuberculosis with an MIC < 0.5 mg L-1 , while a dose of 1500 mg was required for strains with an MIC of 1 mg L-1 . A higher dose of levofloxacin might be needed to treat tuberculosis. However, further studies on the efficacy and safety of this dose are needed to confirm our findings.

DOI: 10.1002/bdd.2294

PMID: 34117648

54. Catastrophic costs among tuberculosis affected households in Zimbabwe: a national health facility-based survey.

Trop Med Int Health. 2021 Jun 30. doi: 10.1111/tmi.13647. Online ahead of print.

Timire C(1)(2)(3), Ngwenya M(4), Chirenda J(5), Metcalfe JZ(6), Kranzer K(3), Pedrazzoli D(7)(8), Takarinda KC(1)(2), Nguhiu P(9), Madzingaidzo G(1), Ndlovu K(1), Mapuranga T(1), Cornell M(10), Sandy C(1).

OBJECTIVES: To determine the incidence and major drivers of catastrophic costs among TB-affected households in Zimbabwe.
METHODS: We conducted a nationally representative health facility-based survey with random cluster sampling among consecutively enrolled drug-susceptible (DS-TB) and drug-resistant TB (DR-TB) patients. Costs incurred and income lost due to TB illness were captured using an interviewer-administered standardised questionnaire. We used multivariable logistic regression to determine the risk factors for experiencing catastrophic costs.
RESULTS: A total of 841 patients were enrolled and were weighted to 900 during data analysis. There were 500 (56%) males and 46 (6%) DR-TB patients. 35 (72%) DR-TB patients were HIV co-infected. Overall, 80% (95% CI:77-82) of TB patients and their households experienced catastrophic costs. The major cost drivers pre-TB diagnosis were direct medical costs. Nutritional supplements were the major cost driver post-TB diagnosis, with a median cost of US$360 (IQR: 240-600). Post-TB median diagnosis costs were three times higher among DR-TB (US$1,659 [653-2,787]) than drug DS-TB affected households (US$537 [204-1,134]). Income loss was five times higher among DR-TB than DS-TB patients. In multivariable analysis, household wealth was the only covariate that remained significantly associated with catastrophic costs: the poorest households had 16 times the odds of incurring catastrophic costs versus the wealthiest households (adjusted odds ratio [aOR:15.7 95% CI:7.5-33.1]).
CONCLUSION: The majority of TB-affected households, especially those affected by DR-TB, experienced catastrophic costs. Since the major cost drivers fall outside the healthcare system, multi-sectoral approaches to TB control and linking TB patients to social protection may reduce catastrophic costs.

DOI: 10.1111/tmi.13647
PMID: 34192392

55. Factors Associated with Medical Follow-Up Adherence for Patients on All-Oral Regimen for Multidrug-Resistant Tuberculosis in Shenzhen, China.

Patient Prefer Adherence. 2021 Jul 5;15:1491-1496. doi: 10.2147/PPA.S316253. eCollection 2021.

Li H(#)(1), Zhang H(#)(1), Xiong J(#)(2), Wang Y(1), Wang W(1), Wang J(1), Lin Y(1), Zhang P(1).

PURPOSE: The aim of this study is to identify factors affecting medical follow-up adherence of pulmonary multidrug-resistant tuberculosis (MDR-TB) patients on an all-oral regimen in Shenzhen, China to enhance intervention measures for increased treatment success.
METHODS: A cohort study was conducted in The Third People's Hospital of Shenzhen on MDR-TB patients switched to an all-oral regimen to evaluate effectiveness following the WHO's recommendation in late 2018. We recruited patients in the group for an opinion survey on medical follow-up adherence from May 2019 to June 2020. The survey was designed with socio-demographic questions in collecting baseline characteristics and importance and Likert closed-ended questions for measuring opinions and relevance of different factors to adherence. Linear regression model was used to analyze data collected.
RESULTS: The findings revealed that gender difference (P = 0.828) had no correlation with adherence. Marital status (P = 0.014), financial situation (P <0.001) and difficulties encountered with medical appointment booking procedures (P = 0.001) were significantly associated with medical follow-up adherence. Single (including widowed and divorced) patients, those with low household income and patients having difficulties making online medical appointment booking, were at higher risk of defaulting from routine MDR-TB medical follow-up.
CONCLUSION: Our survey revealed that financial burden, being single and a non-user friendly medical appointment booking system are the main barriers to patients' medical follow-up compliance. More financial assistance, better patient support and simplifying medical appointment booking procedures are facilitators of better treatment adherence.

DOI: 10.2147/PPA.S316253
PMCID: PMC8275170
PMID: 34267504

56. MDR tuberculosis, Alpha-1-anti-trypsin Deficiency, Cough in a Geriatric Nurse

Pneumologie. 2021 Jul 7. doi: 10.1055/a-1493-1206. Online ahead of print.

Hoheisel A(1), Vogt G(2), Nagel S(2), Bonitz A(3), Müller C(4), Köhnlein T(5), Hoheisel G(3).

Multidrug-resistant tuberculosis (MDR-TB) is of low proportion in comparison to the total number of TB patients, however, due to the necessity of a complex medication with potentially severe and life threatening adverse reactions, long term sequelae, and unfavorable outcome special attention is essential. We report the case of a 30-year-old geriatric nurse with a history of chronic cough and hereditary alpha-1-anti-trypsin deficiency (AATD), who suffered from MDR-TB and experienced a number of severe adverse reactions.

DOI: 10.1055/a-1493-1206
PMID: 34233361

57. Analysis of the side effect of QTc interval prolongation in the bedaquiline regimen in drug resistant tuberculosis patients.

J Basic Clin Physiol Pharmacol. 2021 Jun 25;32(4):421-427. doi: 10.1515/jbcpp-2020-0415.

Ardhianto D(1), Suharjono(1), Soedarsono(2), Fatmawati U(3).

OBJECTIVES: Indonesia is one of the top 20 countries with the highest prevalence of drug resistant tuberculosis (DR-TB) worldwide with a percentage of new cases of 2.4% and retreatment of 13%. Bedaquiline (BDQ) is one of the drugs that used in the individual long regimen treating DR-TB. BDQ is also combined with levofloxacin (LFX) and/or clofazimine (CFZ) that can cause QTc interval prolongation. The aim was to study the differences in the use of BDQ regimens to the lengthening of the QTc interval and to study risk factors (diabetes, hypokalemia, sex, BMI, and age) in BDQ regimen.
METHODS: This study was an observational retrospective study with a total sampling method, which was conducted at Dr. Soetomo General Hospital Surabaya. Samples from this study were patients diagnosed with DR-TB at Dr. Soetomo General Hospital Surabaya in the period of January 2015-December 2019 who used BDQ regimen and met the inclusion criteria. The ECG data were analyzed from the mean of each group (BDQ regimen and risk factors), also analyzed using statistical analysis.
RESULTS: Data obtained from total sample in this study were 73 patients. The most widely used different regimens in this study were the combination of BDQ + LFX by 36 patients (49.3%), BDQ + LFX + CFZ by 16 patients (21.9%), BDQ by 11 patients (15.1%) and BDQ + CFZ 10 patients (13.7%). Out of 73 patients, 52

patients (71.2%) experienced lengthening of the QT interval and grade 1 of QTc interval prolongation occurred in most patients and also the onset was mostly one month after using BDQ regimen. The side effects of QTc interval prolongation from groups of combination and risk factors were no difference in each month ($p>0.05$).
CONCLUSIONS: This study can be concluded that there were no differences in the QTc prolongation between the groups of BDQ regimen (BDQ, BDQ + LFX, BDQ + CFZ and BDQ + LFX + CFZ) and the groups of risk factors.

DOI: 10.1515/jbcpp-2020-0415
PMID: 34214323

58. Design and synthesis of 2-(2-isonicotinoylhydrazineylidene)propanamides as InhA inhibitors with high antitubercular activity.

Eur J Med Chem. 2021 Jun 23;223:113668. doi: 10.1016/j.ejmech.2021.113668. Online ahead of print.

Pflégr V(1), Horváth L(2), Stolaříková J(3), Pál A(4), Korduláková J(4), Bősze S(2), Vinšová J(1), Krátký M(5).

Based on successful antitubercular isoniazid scaffold we have designed its "mee-too" analogues by a combination of this drug linked with substituted anilines through pyruvic acid as a bridge. Lipophilicity important for passive diffusion through impenetrable mycobacterial cell wall was increased by halogen substitution on the aniline. We prepared twenty new 2-(2-isonicotinoylhydrazineylidene)propanamides that were assayed against susceptible Mycobacterium tuberculosis H37Rv, nontuberculous mycobacteria, and also multidrug-resistant tuberculous strains (MDR-TB). All the compounds showed excellent activity not only against Mtb. (minimum inhibitory concentrations, MIC, from ≤0.03 μM), but also against M. kansasii (MIC ≥2 μM). The most active molecules have CF_3 and OCF_3 substituent in the position 4 on the aniline ring. MIC against MDR-TB were from 8 μM. The most effective derivatives were used for the mechanism of action investigation. The treatment of Mtb. H37Ra with tested compounds led to decreased production of mycolic acids and the strains overproducing InhA were more resistant to them. These results confirm that studied compounds inhibit the enoyl-acyl carrier protein reductase (InhA) in mycobacteria. The compounds did not show any cytotoxic and cytostatic activity for HepG2 cells. The amides can be considered as a promising scaffold for antitubercular drug discovery having better antimicrobial properties than original isoniazid together with a significantly improved pharmaco-toxicological

profile.

DOI: 10.1016/j.ejmech.2021.113668
PMID: 34198149

59. Health care seeking patterns of rifampicin-resistant tuberculosis patients in Harare, Zimbabwe: A prospective cohort study.

PLoS One. 2021 Jul 16;16(7):e0254204. doi: 10.1371/journal.pone.0254204. eCollection 2021.

Tadokera R(1), Huo S(2), Theron G(1), Timire C(3)(4), Manyau-Makumbirofa S(5), Metcalfe JZ(2).

BACKGROUND: Delays in seeking and accessing treatment for rifampicin-resistant tuberculosis (RR-TB) and multi-drug resistant (MDR-TB) are major impediments to TB control in high-burden, resource-limited settings.
METHOD: We prospectively determined health-seeking behavioural patterns and associations with treatment outcomes and costs among 68 RR-TB patients attending conveniently selected facilities in a decentralised system in Harare, Zimbabwe.
RESULTS: From initial symptoms to initiation of effective treatment, patients made a median number of three health care visits (IQR 2-4 visits) at a median cost of 13% (IQR 6-31%) of their total annual household income (mean cost, US$410). Cumulatively, RR-TB patients most frequently first visited private facilities, i.e., private pharmacies (30%) and other private health care providers (24%) combined. Median patient delay was 26 days (IQR 14-42 days); median health system delay was 97 days (IQR 30-215 days) and median total delay from symptom onset to initiation of effective treatment was 132 days (IQR 51-287 days). The majority of patients (88%) attributed initial delay in seeking care to "not feeling sick enough." Total delay, total cost and number of health care visits were not associated with treatment or clinical outcomes, though our study was not adequately powered for these determinations.
CONCLUSIONS: Despite the public availability of rapid molecular TB tests, patients experienced significant delays and high costs in accessing RR-TB treatment. Active case finding, integration of private health care providers and enhanced service delivery may reduce treatment delay and TB associated costs.

DOI: 10.1371/journal.pone.0254204
PMID: 34270593

60. Computational identification and characterization of antigenic properties of Rv3899c of Mycobacterium tuberculosis and its interaction with human leukocyte antigen (HLA).

Immunogenetics. 2021 Jul 6. doi: 10.1007/s00251-021-01220-x. Online ahead of print.

Das R(1), Eniyan K(2)(3), Bajpai U(4).

A rise in drug-resistant tuberculosis (TB) cases demands continued efforts towards the discovery and development of drugs and vaccines. Secretory proteins of Mycobacterium tuberculosis (H37Rv) are frequently studied for their antigenicity and their scope as protein subunit vaccines requires further analysis. In this study, Rv3899c of H37Rv emerges as a potential vaccine candidate on its evaluation by several bioinformatics tools. It is a non-toxic, secretory protein with an 'immunoglobulin-like' fold which does not show similarity with a human protein. Through BlastP and MEME suite analysis, we found Rv3899c homologs in several mycobacterial species and its antigenic score (0.54) to compare well with the known immunogens such as ESAT-6 (0.56) and Rv1860 (0.52). Structural examination of Rv3899c predicted ten antigenic peptides, an accessibility profile of the antigenic determinants constituting B cell epitope-rich regions and a low abundance of antigenic regions (AAR) value. Significantly, STRING analysis showed ESX-2 secretion system proteins and antigenic PE/PPE proteins of H37Rv as the interacting partners of Rv3899c. Further, molecular docking predicted Rv3899c to interact with human leukocyte antigen HLA-DRB1*04:01 through its antigenically conserved motif (RAAEQQRLQRIVDAVARQEPRISWAAGLRDDGTT). Interestingly, the binding affinity was observed to increase on citrullination of its Arg1 residue. Taken together, the computational characterization and predictive information suggest Rv3899c to be a promising TB vaccine candidate, which should be validated experimentally.

DOI: 10.1007/s00251-021-01220-x
PMID: 34228167

61. Profiling and identification of novel rpoB mutations in rifampicin-resistant Mycobacterium tuberculosis clinical isolates from Pakistan.

J Infect Chemother. 2021 Jul 6:S1341-321X(21)00181-1. doi: 10.1016/j.jiac.2021.06.020. Online ahead of print.

Qadir M(1), Tahseen S(2), McHugh TD(3), Hussain A(2), Masood F(2), Ahmed N(2), Faryal R(4).

INTRODUCTION: Rifampicin (RIF) is one of the most effective anti-tuberculosis first-line drugs prescribed along with isoniazid. However, the emergence of RIF resistance Mycobacterium tuberculosis (MTB) isolates is a major issue towards tuberculosis (TB) control program in high MDR TB-burdened countries including Pakistan. Molecular data behind phenotypic resistance is essential for better management of RIF resistance which has been linked with mutations in rpoB gene. Since molecular studies on RIF resistance is limited in Pakistan, the current study was aimed to investigate the molecular data of mutations in rpoB gene behind phenotypic RIF resistance isolates in Pakistan.
METHOD: A total of 322 phenotypically RIF-resistant isolates were randomly selected from National TB Reference Laboratory, Pakistan for sequencing while 380 RIF resistance whole-genome sequencing (WGS) of Pakistani isolates (BioProject PRJEB25972), were also analyzed for rpoB mutations.
RESULT: Among the 702 RIF resistance samples, 675 (96.1%) isolates harbored mutations in rpoB in which 663 (94.4%) were detected within the Rifampicin Resistance Determining Region (RRDR) also known as a mutation hot spot region, including three novel. Among these mutations, 657 (97.3%) were substitutions including 603 (89.3%) single nucleotide polymorphism, 49 (7.25%) double and five (0.8%) triple. About 94.4% of Phenotypic RIF resistance strains, exhibited mutations in RRDR, which were also detectable by GeneXpert.
CONCLUSION: Mutations in the RRDR region of rpoB is a major mechanism of RIF resistance in MTB circulating isolates in Pakistan. Molecular detection of drug resistance is a faster and better approach than phenotypic drug susceptibility testing to reduce the time for transmission of RIF resistance strains in population. Such insights will inform the deployment of anti-TB drug regimens and disease control tools and strategies in high burden settings, such as Pakistan.

DOI: 10.1016/j.jiac.2021.06.020
PMID: 34244055

62. Lesion penetration and activity limit the utility of second-line injectable agents in pulmonary tuberculosis.

Antimicrob Agents Chemother. 2021 Jul 12:AAC0050621. doi: 10.1128/AAC.00506-21. Online ahead of print.

Ernest JP(1), Sarathy J(2), Wang N(2), Kaya F(2), Zimmerman MD(2), Strydom N(1), Wang H(2), Xie M(2), Gengenbacher M(2)(3), Via LE(4), Barry CE 3rd(4), Carter CL(2), Savic RM(1), Dartois V(2)(3).

Amikacin and kanamycin are second line injectables used in the treatment of multidrug resistant tuberculosis (MDR-TB), based on the clinical utility of streptomycin, another aminoglycoside and first line anti-TB drug. While streptomycin was tested as a single agent in the first controlled TB clinical trial, introduction of amikacin and kanamycin into MDR-TB regimens was not preceded by randomized controlled trials. A recent large retrospective meta-analysis revealed that compared with regimens without any injectable drug, amikacin provided modest benefits, and kanamycin was associated with worse outcomes. Although their long-term use can cause irreversible ototoxicity, they remain part of MDR-TB regimens because they have a role in preventing emergence of resistance to other drugs. To quantify the contribution of amikacin and kanamycin to second-line regimens, we applied 2-dimensional MALDI mass spectrometry imaging in large lung lesions, quantified drug exposure in lung and lesions of rabbits with active TB, and measured the concentrations required to kill or inhibit growth of the resident bacterial populations. Using these metrics, we applied site-of-action pharmacokinetic and pharmacodynamic (PK-PD) concepts and simulated drug coverage in patients' lung lesions. The results provide a pharmacological explanation for the limited clinical utility of both agents and reveal better PK-PD lesion coverage for amikacin than kanamycin, consistent with retrospective data of contribution to treatment success. Together with recent mechanistic studies dissecting antibacterial activity from aminoglycoside ototoxicity, the limited but rapid penetration of streptomycin, amikacin and kanamycin to the sites of TB disease supports the development of analogs with improved efficacy and tolerability.

DOI: 10.1128/AAC.00506-21
PMID: 34252307

63. A systematic review of pharmacoeconomic evaluations on oral diarylquinoline-based treatment for drug-resistant tuberculosis: from high to low burden countries.

Expert Rev Pharmacoecon Outcomes Res. 2021 Jun 23:1-14. doi: 10.1080/14737167.2021.1925111. Online ahead of print.

Fekadu G(1), Yao J(1), You JHS(1).

Introduction: There is a rising global interest in the pharmacoeconomic evaluations of bedaquiline (BDQ), a novel oral diarylquinoline, for treatment of drug-resistant tuberculosis (DR-TB).Areas covered: This article systematically reviewed publications retrieved from Medline, American Psychological Association-Psychology information, Web of Science, Embase, Scopus, Science direct, Center for Reviews and Dissemination, and CINAHL Complete during

2010-2020 on pharmacoeconomic studies on BDQ for DR-TB treatment. Ten Markov model-based cost-effectiveness analyses identified were conducted in high (n = 4), intermediate (n = 2), and low (n = 4) TB burden countries.Expert opinion: The paucity of model-based health economic analyses on BDQ-containing regimens for DR-TB indicated that further pharmacoeconomic research of BDQ-based regimens, on the aspects of duration of BDQ treatment, types of DR-TB indicated, and settings of regions and health-systems, is highly warranted to inform global cost-effective use of BDQ-based regimens for DR-TB treatment.

DOI: 10.1080/14737167.2021.1925111
PMID: 33931005

64. Hematological side effect analysis of linezolid in MDR-TB patients with individual therapy.

J Basic Clin Physiol Pharmacol. 2021 Jun 25;32(4):777-781. doi: 10.1515/jbcpp-2020-0468.

Pratama NYI(1), Zulkarnain BS(1), Soedarsono(2), Fatmawati U(3).

OBJECTIVES: This study aimed to estimate the prevalence and analyze the risk factors for linezolid-induced hematological side effects in multidrug-resistant tuberculosis (MDR-TB) patients.
METHODS: Data were collected from medical records of MDR-TB patients who received linezolid between January 2018 and May 2020. Statistical significance analysis and multivariate analysis were performed with SPSS version 24 software.
RESULTS: Hematological side effects were identified in 27 out of 93 patients (29.0%). The most prevalent effect was anemia (29.0%), while the less prevalent effects were thrombocytopenia (3.2%) and leukopenia (2.2%). These side effects were reported after 2 weeks of linezolid treatment. The drug dose was more than 11 mg/kgBW/day or patient weighing less than 54 kg was identified as an independent risk factor for anemia in multivariate analysis.
CONCLUSIONS: Anemia was the most prevalent of linezolid-induced hematological side effects in MDR-TB patients. Therefore, hemoglobin monitoring might be recommended in patients weighing less than 54 kg and after receiving linezolid therapy for at least 2 weeks.

DOI: 10.1515/jbcpp-2020-0468
PMID: 34214355

65. Detection of pyrazinamide heteroresistance in Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2021 Jun 28:AAC0072021. doi: 10.1128/AAC.00720-21. Online ahead of print.

Werngren J(1), Mansjö M(1), Glader M(1), Hoffner S(2), Davies Forsman L(3)(4).

Heteroresistance is defined as the coexistence of both susceptible and resistant bacteria in a bacterial population. Previously published data show that it may occur in 9-57% of Mycobacterium tuberculosis isolates for various drugs. Pyrazinamide (PZA) is an important first-line drug used for treatment of both drug-susceptible and PZA-susceptible multidrug-resistant TB. Clinical PZA resistance is defined as a proportion of resistant bacteria in the isolate exceeding 10%, when the drug is no longer considered clinically effective. The capability of traditional drug susceptibility testing techniques to detect PZA heteroresistance has not yet been evaluated. The aim of this study was to compare the capacity of BACTEC MGIT 960, Wayne's test and whole genome sequencing (WGS) to detect PZA resistant subpopulations in bacterial suspensions prepared with different proportions of mutant strains. Both BACTEC MGIT 960 and WGS were able to detect the critical level of 10% PZA heteroresistance whereas Wayne's test failed to do so, with the latter falsely reporting highly resistant samples as PZA susceptible. Failure to detect drug resistant subpopulations may lead to inadvertently weak treatment regimens if ineffective drugs are included, with the risk of treatment failure with the selective growth of resistant subpopulations. We need clinical awareness of heteroresistance as well as evaluation of new diagnostic tools in their capacity in detecting heteroresistance in TB.

DOI: 10.1128/AAC.00720-21
PMID: 34181476

66. Comparative Performance of Line Probe Assay (Version 2) and Xpert MTB/RIF Assay for Early Diagnosis of Rifampicin-Resistant Pulmonary Tuberculosis.

Tuberc Respir Dis (Seoul). 2021 Jul;84(3):237-244. doi: 10.4046/trd.2020.0171. Epub 2021 Mar 3.

Yadav RN(1), Kumar Singh B(1), Sharma R(1), Chaubey J(1), Sinha S(1), Jorwal P(1).

BACKGROUND: The emergence of drug-resistant tuberculosis (TB), is a major menace to cast off TB worldwide. Line probe assay (LPA; GenoType MTBDRplus ver. 2) and Xpert MTB/RIF assays are two rapid molecular TB detection/diagnostic tests. To

compare the performance of LPA and Xpert MTB/RIF assay for early diagnosis of rifampicin-resistant (RR) TB in acid-fast bacillus (AFB) smear-positive and negative sputum samples.
METHODS: A total 576 presumptive AFB patients were selected and subjected to AFB microscopy, Xpert MTB/RIF assay and recent version of LPA (GenoType MTBDRplus assay version 2) tests directly on sputum samples. Results were compared with phenotypic culture and drug susceptibility testing (DST). DNA sequencing was performed with rpoB gene for samples with discordant rifampicin susceptibility results.
RESULTS: Among culture-positive samples, Xpert MTB/RIF assay detected Mycobacterium tuberculosis (Mtb) in 97.3% (364/374) of AFB smear-positive samples and 76.5% (13/17) among smear-negative samples, and the corresponding values for LPA test (valid results with Mtb control band) were 97.9% (366/374) and 58.8% (10/17), respectively. For detection of RR among Mtb positive molecular results, the sensitivity of Xpert MTB/RIF assay and LPA (after resolving discordant phenotypic DST results with DNA sequencing) were found to be 96% and 99%, respectively. Whereas, specificity of both test for detecting RR were found to be 99%.
CONCLUSION: We conclude that although Xpert MTB/RIF assay is comparatively superior to LPA in detecting Mtb among AFB smear-negative pulmonary TB. However, both tests are equally efficient in early diagnosis of AFB smear-positive presumptive RR-TB patients.

DOI: 10.4046/trd.2020.0171
PMID: 33657709

67. Infectious diseases screening approach among refugees: results from a single-center study.

J Infect Dev Ctries. 2021 Jun 30;15(6):847-852. doi: 10.3855/jidc.15030.

Fiore V(1), De Vito A(2), Martineková P(3), Princic E(2), Geremia N(2), Madeddu G(2), Babudieri S(2).

INTRODUCTION: Our aim was to evaluate a screening program, with active case-finding and treatment for active tuberculosis (TB), latent tuberculosis infection (LTBI), blood-borne viruses (BBV), and sexually transmitted diseases (STDs) among refugees living in facility centers.
METHODOLOGY: We collected data on refugees arriving to our attention in migrant centers in Sardinia, Italy. Socio-demographical data, anamnesis, and clinical features were collected. TST Mantoux was conducted, and X-ray chest (XRC) was performed if TST was positive. Blood-borne virus screening was proposed to all patients. Screening for STDs was offered according to guidelines, anamnesis, and

physical examination.
RESULTS: Eighty-one patients were included. Seventy (86.4%) were male, and the mean age was 24.8±5.7 years. Thirty-three (40.7%) had scabies. Overall, 40/81 (49.4%) had a positive TST Mantoux. One (2.5%) was hospitalized and died for multi-drug-resistant TB. One (2.5%) patient had intestinal-TB. 52/81 (64.2%) refused HIV screening, whereas no positivity was found among tested migrants. Sixty-two (76.5%) accepted HCV screening, and one (1.6%) had a positive test. Fifty-eight (71.6%%) accepted HBV testing, and 29 (50%) of them had positive serology. Ten (12.3%) patients had anal or genital lesions due to syphilis, Molluscum contagiosum, and HPV in 7 (70%), 2 (20%), and one (10%) case, respectively.
CONCLUSIONS: Infectious diseases control and prevention are a key strategy among refugees. The stay in a migrant center is an extraordinary occasion for healthcare provision. This condition could allow a broad screening program in which quick BBV screening tests could be a good method to implement uptake. More information and educational programs would allow a higher understanding and acceptance of HIV screening.

DOI: 10.3855/jidc.15030
PMID: 34242196

68. Is the new WHO definition of extensively drug-resistant tuberculosis easy to apply in practice?

Eur Respir J. 2021 Jul 1;58(1):2100959. doi: 10.1183/13993003.00959-2021. Print 2021 Jul.

Alagna R(1), Cabibbe AM(1), Miotto P(1), Saluzzo F(1), Köser CU(2), Niemann S(3)(4), Gagneux S(5)(6), Rodrigues C(7), Rancoita PVM(8), Cirillo DM(9).

DOI: 10.1183/13993003.00959-2021
PMID: 34215664

69. Sputum culture conversion definitions and analytic practices for multidrug-resistant TB.

Int J Tuberc Lung Dis. 2021 Jul 1;25(7):596-598. doi: 10.5588/ijtld.21.0090.

Rodriguez CA(1), Brooks MB(1), Aibana O(2), Mitnick CD(1), Franke MF(1).

DOI: 10.5588/ijtld.21.0090
PMCID: PMC8259120
PMID: 34183109

70. Expression profiling of TRIM gene family reveals potential diagnostic biomarkers for rifampicin-resistant tuberculosis.

Microb Pathog. 2021 Aug;157:104916. doi: 10.1016/j.micpath.2021.104916. Epub 2021 May 15.

Liu S(1), Sun Y(2), Yang R(3), Ren W(4), Li C(5), Tang S(6).

The epidemic of pulmonary tuberculosis (TB), especially rifampin-resistant tuberculosis (RR-TB) presents a major challenge for TB control today. However, there is a lack of reliable and specific biomarkers for the early diagnosis of RR-TB. We utilized reverse transcription-quantitative polymerase chain reaction (RT-qPCR) to profile the transcript levels of 72 tripartite motif (TRIM) genes from a discovery cohort of 10 drug-sensitive tuberculosis (DS-TB) patients, 10 RR-TB patients, and 10 healthy controls (HCs). A total of 35 differentially expressed genes (DEGs) were screened out, all of which were down-regulated. The bio functions and pathways of these DEGs were enriched in protein ubiquitination, regulation of the viral process, Interferon signaling, and innate immune response, etc. A protein-protein interaction network (PPI) was constructed and analyzed using STRING and Cytoscape. Twelve TRIM genes were identified as hub genes, and seven (TRIM1, 9, 21, 32, 33, 56, 66) of them were verified by RT-qPCR in a validation cohort of 95 subjects. Moreover, we established the RR-TB decision tree models based on the 7 biomarkers. The receiver operating characteristic (ROC) analyses showed that the models exhibited the areas under the curve (AUC) values of 0.878 and 0.868 in discriminating RR-TB from HCs and DS-TB, respectively. Our study proposes potential biomarkers for RR-TB diagnosis, and also provides a new experimental basis to understand the pathogenesis of RR-TB.

DOI: 10.1016/j.micpath.2021.104916
PMID: 34000303 [Indexed for MEDLINE]

71. Prediction of Human Pharmacokinetic Profiles of the Antituberculosis Drug Delamanid from Nonclinical Data: Potential Therapeutic Value against Extrapulmonary Tuberculosis.

Antimicrob Agents Chemother. 2021 Jul 16;65(8):e0257120. doi: 10.1128/AAC.02571-20. Epub 2021 Jul 16.

Shibata M(1), Masuda M(2), Sasahara K(1), Sasabe H(1), Sasaki T(2), Kim S(2), Takeuchi K(1), Umehara K(1), Kashiyama E(1).

Delamanid has been studied extensively and approved for the treatment of pulmonary multidrug-resistant tuberculosis; however, its potential in the treatment of extrapulmonary tuberculosis remains unknown. We previously reported that, in rats, delamanid was broadly distributed to various tissues in addition to the lungs. In this study, we simulated human plasma concentration-time courses (pharmacokinetic profile) of delamanid, which has a unique property of metabolism by albumin, using two different approaches (steady-state concentration of plasma-mean residence time [Css-MRT] and physiologically based pharmacokinetic [PBPK] modeling). In Css-MRT, allometric scaling predicted the distribution volume at steady state based on data from mice, rats, and dogs. Total clearance was predicted by in vitro-in vivo extrapolation using a scaled albumin amount. A simulated human pharmacokinetic profile using a combination of human-predicted Css and MRT was almost identical to the observed profile after single oral administration, which suggests that the pharmacokinetic profile of delamanid could be predicted by allometric scaling from these animals and metabolic capacity in vitro. The PBPK model was constructed on the assumption that delamanid was metabolized by albumin in circulating plasma and tissues, to which the simulated pharmacokinetic profile was consistent. Moreover, the PBPK modeling approach demonstrated that the simulated concentrations of delamanid at steady state in the lung, brain, liver, and heart were higher than the in vivo effective concentration for Mycobacterium tuberculosis. These results indicate that delamanid may achieve similar concentrations in various organs to that of the lung and may have the potential to treat extrapulmonary tuberculosis.

DOI: 10.1128/AAC.02571-20
PMID: 34097484

72. A Review on Nuclear Imaging as a Promising Modality for Efficient Diagnosis of Tuberculosis.

Curr Med Imaging. 2021 Jul 7. doi: 10.2174/1573405617666210707150811. Online ahead of print.

Rafique A(1), Rasheed R(2), Shamim S(3), Ijaz M(3), Murtaza G(4).

Tuberculosis (TB) is an infectious disease and is declared a global health issue

by the World Health Organization in 1993. Due to the complex pathophysiology of Mycobacterium tuberculosis, it remains a global threat. This article reviews the conventional diagnostic modalities for tuberculosis, their limitations to detect latent TB, multiple drug-resistant TB, human immunodeficiency virus co-infected TB lesions, and TB in children. Moreover, this review illustrates the importance of nuclear medicine imaging for early, non-invasive diagnosis of TB to detect disease stages and monitor therapy response. Currently, single-photon emission computed tomography and positron emission tomography with their specific radionuclides have been extensively used for a thorough assessment of TB.

DOI: 10.2174/1573405617666210707150811
PMID: 34238164

73. Rv0684/fusA1, an Essential Gene, Is the Target of Fusidic Acid and Its Derivatives in Mycobacterium tuberculosis.

ACS Infect Dis. 2021 Jul 1. doi: 10.1021/acsinfecdis.1c00195. Online ahead of print.

Singh V(1)(2)(3), Dziwornu GA(2)(4), Mabhula A(2)(3), Chibale K(1)(2)(3).

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is a major global health concern given the increase in multiple forms of drug-resistant TB. This underscores the importance of a continuous pipeline of new anti-TB agents. Drug repurposing has shown promise in expanding the therapeutic options for TB chemotherapy. Fusidic acid (FA), a natural product-derived antibiotic, is one such candidate for repurposing. The present study aimed to understand the mechanism of action of FA and its selected analogs in M. tuberculosis. By using chemical biology and genetics, we identified elongation factor G as the target of FA in M. tuberculosis. We showed essentiality of its encoding gene fusA1 in M. tuberculosis by demonstrating that the transcriptional silencing of fusA1 is bactericidal in vitro and in macrophages. Thus, this work validated a novel drug target FusA1 in M. tuberculosis.

DOI: 10.1021/acsinfecdis.1c00195
PMID: 34196521

74. A cohort study analyzing the impact of socioeconomic and spatial characteristics alongside treatment regimens on the environmental-health outcomes of the MDR-TB

treatment in Pakistan.

Environ Sci Pollut Res Int. 2021 Jul;28(26):34953-34967. doi: 10.1007/s11356-021-13196-y. Epub 2021 Mar 4.

Arif A(1), Ahmad E(2), Khan FN(2), Fatima R(3).

This study identifies and analyzes a number of factors that correlate with the environmental-health outcome of multi-drug resistance tuberculosis (MDR-TB) treatment in Pakistan. Survival analysis is carried out by applying the multivariable Cox Proportional Hazard model on secondary data of 369 patients registered at three main MDR-TB sites in Pakistan during 2012-2017. Results show that there is no difference in survival of patients between the two treatment arms, hospital and ambulatory care. Male gender and travel expenditure are found to be negatively associated with the environmental-health outcome, whereas spatial characteristic of time expenditure is positively related to it supporting distance bias approach. Medical expenditure is also positively related to the environmental-health outcome. The study concludes that availability of affordable and accessible health services, better environmental conditions, and ambulatory care based on WHO recommendation as well as health education along with social protection schemes should be ensured by the government to improve environmental-health outcome in the resource-scarce setting in Pakistan.

DOI: 10.1007/s11356-021-13196-y
PMID: 33661501 [Indexed for MEDLINE]

75. Factors associated with high-grade Erectile Dysfunction (ED) in tuberculosis patients from a hospital in Lima, Peru

Arch Esp Urol. 2021 Jul;74(6):579-586.

Reyes-Paredes M(1), Valladares-Garrido MJ(2)(3), Ichiro Peralta C(4), Dominguez-Troncos H(5), Grandez-Urbina A(2).

OBJECTIVE: To determine the prevalence and factors associated with high-grade ED in Lima, Peru.
MATERIAL AND METHODS: Analytical cross-sectional study in tuberculosis patients treated in an out patient clinic of a public hospital in Lima, Peru in 2018.
High grade SD was the dependent variable, using the IIEF-5 questionnaire and the

independent variables were sexual orientation, history of previous pathology, location of tuberculosis, type of treatment scheme and presence of hemoptysis. Prevalence ratios (PR) were estimated using simple and multiple regression models.
RESULTS: Of 189 patients, the majority presented pulmonary tuberculosis (98.9%), overweight (25.9%) and just over half had high-grade ED (52.9%). In the simple regression it was found that the factors associated with presenting high-grade SD were age in years (RP=1.11), reporting diabetes (RP=2.09), having multi-drug resistant TB (RP=1.51) and presenting a treatment time from 1 year to more (RP=1.87). In the multiple regression, the variables that were associated with a higher frequency of high-grade TB were age in years (RP=1.11), a history of diabetes (RP=1.66) and having MDR TB (RP=2.04).
CONCLUSIONS: This study suggests a high prevalence of ED in patients with TB, where four out of ten presented high-grade ED. Being older, having a history of diabetes and using an MDR treatment were positively associated with the development of high-grade ED. Studies with designs close to causality are required to know the real magnitude of the influence of clinical and therapeutic characteristics on the development of high-grade ED.

PMID: 34219060 [Indexed for MEDLINE]

76. WNT6/ACC2-induced storage of triacylglycerols in macrophages is exploited by Mycobacterium tuberculosis.

J Clin Invest. 2021 Jul 13:141833. doi: 10.1172/JCI141833. Online ahead of print.

Brandenburg J(1), Marwitz S(2), Tazoll SC(1), Waldow F(3), Kalsdorf B(4), Vierbuchen T(5), Scholzen T(6), Gross A(1), Goldenbaum S(1), Hölscher A(7), Hein M(6), Linnemann L(8), Reimann M(4), Kispert A(9), Leitges M(10), Rupp J(11), Lange C(4), Niemann S(12), Behrends J(6), Goldmann T(13), Heine H(5), Schaible UE(8), Hölscher C(7), Schwudke D(3), Reiling N(1).

In view of emerging drug-resistant tuberculosis (TB), host directed adjunct therapies are urgently needed to improve treatment outcomes with currently available anti-TB therapies. One approach is to interfere with the formation of lipid-laden "foamy" macrophages in the host, as they provide a nutrient-rich host cell environment for Mycobacterium tuberculosis (Mtb). Here, we provide evidence that Wnt family member 6 (WNT6), a ligand of the evolutionarily conserved Wingless/Integrase 1 (WNT) signaling pathway, promotes foam cell formation by regulating key lipid metabolic genes including acetyl-CoA carboxylase-2 (ACC2) during pulmonary TB. Using genetic and pharmacological approaches, we demonstrated that lack of functional WNT6 or ACC2 significantly

reduced intracellular triacylglycerol (TAG) levels and Mtb survival in macrophages. Moreover, treatment of Mtb-infected mice with a combination of a pharmacological ACC2 inhibitor and the anti-TB drug isoniazid (INH) reduced lung TAG and cytokine levels, as well as lung weights compared to treatment with INH alone. This combination also reduced Mtb bacterial numbers and the size of mononuclear cell infiltrates in livers of infected mice. In summary, our findings demonstrated that Mtb exploits WNT6/ACC2-induced storage of TAGs in macrophages to facilitate its intracellular survival, a finding opening new perspectives for host directed adjunctive treatment of pulmonary TB.

DOI: 10.1172/JCI141833
PMID: 34255743

77. Epidemiology of molecular probes in Xpert MTB/RIF assay in Khyber Pakhtunkhwa, Pakistan.

Arch Microbiol. 2021 Jul;203(5):2249-2256. doi: 10.1007/s00203-021-02242-5. Epub 2021 Feb 27.

Khan AS(1), Khan MT(2), Ali S(1), Khan TA(3), Qasim M(3), Malik A(4), Ali S(5), Sajjad W(6), Ain QU(7), Irfan M(8).

Regardless of a plethora of advanced diagnostics, TB and drug resistance remains a principal killer. We proposed gold nanoparticles (AuNPs) attached with probes to enhance the efficiency of GeneXpert MTB/RIF assay instead of conventional dye probes for molecular detection. A total of 15,000 samples were collected from TB suspects and subjected to Xpert MTB/RIF assay, where 6800 (45.3%) were detected as MTB positive, 280 (4.3%) were detected to harbor mutations in the RRDR, while invalid /errors were found in 690 (4.6%) cases. The mutations were detected by probe E, 199 (71.1%), while probes B and D, 30 and 26 (10% and 9%), respectively. In the Xpert MTB/RIF Assay were found mutations picked by probes E and B codons 529-533 (71%) and 512-518 (10%), respectively. The fast-rising works of TB nano-diagnostics, of Xpert probes, may improve by the applications of gold nanoparticle probes.

DOI: 10.1007/s00203-021-02242-5
PMID: 33640990 [Indexed for MEDLINE]

78. Rarity of rpoB Mutations Outside the Rifampicin Resistance-Determining Region of Mycobacterium tuberculosis Isolates from Patients Responding Poorly to First-Line Tuberculosis Regimens in Beijing, China: A Retrospective Study.

Infect Drug Resist. 2021 Jul 6;14:2607-2612. doi: 10.2147/IDR.S313717.
eCollection 2021.

Guo J(#)(1), Liu R(#)(1), Shi J(#)(1), Huo F(2), Shang Y(3), Wang F(2), Gao M(1), Li S(3).

BACKGROUND: Early and accurate diagnosis of rifampicin (RIF)-resistant Mycobacterium tuberculosis (MTB) is essential for controlling community spread of drug-resistant tuberculosis (TB). In order to discover mutations residing outside the rifampicin resistance-determining region (RRDR) of the MTB rpoB gene, we conducted this retrospective study.
METHODS: We retrospectively screened patient records to obtain Xpert MTB/RIF assay results for patients who received care at the Beijing Chest Hospital from 2016 to 2019 in order to identify subjects who met study selection criteria. Stored frozen patient isolates were cultured, harvested, and then subjected to drug susceptibility testing. Concurrently, entire rpoB gene DNA of each isolate was amplified and then sequenced to reveal rpoB mutations.
RESULTS: Overall, 104 RIF-susceptible tuberculosis patients who were tested using the Xpert MTB/RIF assay also had poor first-line regimen treatment responses. Isolates obtained from these cases included 101 MTB isolates that possessed wild-type rpoB allelic profiles, as demonstrated using Sanger sequencing. However, sequences from the other three isolates confirmed that rpoB of one isolate harbored a mutation encoding the amino acid substitution Ile491Phe and that rpoB genes of two isolates contained a mutation encoding the amino acid substitution Ser450Leu.
CONCLUSION: Our data demonstrated that mutations found outside the RRDR of MTB rpoB are rare in Beijing, China, indicating that World Health Organization-approved molecular diagnostics are generally suitable for diagnosing RIF resistance.

DOI: 10.2147/IDR.S313717
PMCID: PMC8275097
PMID: 34262305

79. Cardiac safety of multidrug-resistant tuberculosis treatment: moving towards individualised monitoring.

Lancet Infect Dis. 2021 Jul;21(7):894-895. doi: 10.1016/S1473-3099(20)30836-7.
Epub 2021 Feb 12.

Hewison C(1), Guglielmetti L(2).

DOI: 10.1016/S1473-3099(20)30836-7
PMID: 33587896 [Indexed for MEDLINE]

80. Sorry for the delay.

Clin Microbiol Infect. 2021 Jul;27(7):941-943. doi: 10.1016/j.cmi.2021.03.007. Epub 2021 Apr 3.

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

DOI: 10.1016/j.cmi.2021.03.007
PMCID: PMC8079284
PMID: 33823271

81. Complex effects of macrolide venturicidins on bacterial F-ATPases likely contribute to their action as antibiotic adjuvants.

Sci Rep. 2021 Jul 1;11(1):13631. doi: 10.1038/s41598-021-93098-8.

Milgrom YM(1), Duncan TM(2).

Bacterial energy metabolism is now recognized as a critical factor for the efficacy of antibiotics. The F-type ATPase/ATP synthase (FOF1) is a central player in cellular bioenergetics of bacteria and eukaryotes, and its potential as a selective antibiotic target has been confirmed by the success of bedaquiline in combatting multidrug-resistant tuberculosis. Venturicidin macrolides were initially identified for their antifungal properties and were found to specifically inhibit FOF1 of eukaryotes and bacteria. Venturicidins alone are not effective antibacterials but recently were found to have adjuvant activity, potentiating the efficacy of aminoglycoside antibiotics against several species of resistant bacteria. Here we discovered more complex effects of venturicidins on the ATPase activity of FOF1 in bacterial membranes from Escherichia coli and Pseudomonas aeruginosa. Our major finding is that higher concentrations of venturicidin induce time- and ATP-dependent decoupling of F1-ATPase activity from the venturicidin-inhibited, proton-transporting FO complex. This dysregulated ATPase activity is likely to be a key factor in the depletion of cellular ATP induced by venturicidins in prior studies with P. aeruginosa and Staphylococcus aureus. Further studies of how this functional decoupling occurs could guide development of new antibiotics and/or adjuvants that target the F-type ATPase/ATP synthase.

DOI: 10.1038/s41598-021-93098-8
PMCID: PMC8249445
PMID: 34211053

82. Impact of upfront Xpert testing on time to treatment initiation for multidrug-resistant TB.

Int J Tuberc Lung Dis. 2021 Jul 1;25(7):584-586. doi: 10.5588/ijtld.21.0092.

Habib SS(1), Malik AA(2), Khan U(3), Khowaja S(2), Hussain H(3), Ayub SM(1), Khan S(4), Creswell J(5), Khan AJ(2), Zaidi SMA(1).

DOI: 10.5588/ijtld.21.0092
PMID: 34183105

83. Semisynthetic modifications of antitubercular lanostane triterpenoids from Ganoderma.

J Antibiot (Tokyo). 2021 Jul;74(7):435-442. doi: 10.1038/s41429-021-00422-5. Epub 2021 May 12.

Chinthanom P(1), Vichai V(1), Dokladda K(1), Sappan M(1), Thongpanchang C(1), Isaka M(2).

Antitubercular lanostane triterpenoids isolated from mycelial cultures of the basidiomycete Ganoderma australe were structurally modified by semisynthesis. One of the synthetic compounds, named GA003 (9), showed more potent activity against Mycobacterium tuberculosis H37Ra than the lead natural lanostane (1). GA003 was also significantly active against the virulent strain (H37Rv) as well as extensively drug-resistant tuberculosis strains.

DOI: 10.1038/s41429-021-00422-5
PMCID: PMC8113785
PMID: 33981028