June Literature

1. Multidrug-resistant tuberculosis during pregnancy and adverse birth outcomes: a systematic review and meta-analysis. FROM MAY ARTICLE

BJOG. 2021 Jun;128(7):1125-1133. doi: 10.1111/1471-0528.16573. Epub 2020 Nov 23.

Alene KA(1)(2)(3), Jegnie A(4), Adane AA(3)(5).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) is a major global public health concern. However, there is a dearth of literature on whether MDR-TB and its medications impact maternal and perinatal outcomes, and when such evidence exists the findings are conflicting.
OBJECTIVES: This systematic review and meta-analysis aimed to examine the impact of MDR-TB and its medications during pregnancy on maternal and perinatal outcomes.
SEARCH STRATEGY: PubMed, Scopus and Web of Science databases were searched from earliest to February 2020.
SELECTION CRITERIA: Records were screened based on pre-defined selection criteria and assessed for quality by two independent reviewers.
DATA COLLECTION AND ANALYSIS: A meta-analysis was performed using the random effects model to calculate pooled prevalence for each outcome.
MAIN RESULTS: Of the 72 records identified, 12 were included in the systematic review and meta-analysis, consisting of 174 pregnant women with MDR-TB and 110 adverse outcomes. Maternal death, pregnancy loss, preterm birth and low birthweight were the most common maternal and perinatal adverse outcomes reported in the studies. The overall pooled prevalence was 7.5% (95% CI 3.2-12.8) for maternal death, 10.6% (95% CI 6.0-16.3) for pregnancy loss, 12.9% (95% CI 0.0-38.0) for preterm birth and 23.7% (95% CI 17.0-31.0) for low birthweight.
CONCLUSIONS: The findings suggest that MDR-TB is associated with a high risk of adverse maternal and perinatal outcomes, but these should be interpreted cautiously because the evidence is largely preliminary. Adequately powered prospective cohort studies are urgently required to corroborate these findings.
TWEETABLE ABSTRACT: Multidrug-resistant tuberculosis may increase the risk of adverse maternal and perinatal outcomes.

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2. Rapid and Simple Detection of Isoniazid-Resistant Mycobacterium tuberculosis Utilizing a DNA Chromatography-Based Technique.

Jpn J Infect Dis. 2021 May 24;74(3):214-219. doi: 10.7883/yoken.JJID.2020.754.

Epub 2020 Oct 30.

Kodera T(1), Yamaguchi T(2), Fukushima Y(2), Kobayashi K(1), Takarada Y(1), Chizimu JY(2)(3), Nakajima C(2)(4), Solo ES(5), Lungu PS(6), Kawase M(1), Suzuki Y(2)(4).

Despite the availability of anti-tuberculosis drugs, the treatment of tuberculosis has been complicated by drug-resistant tuberculosis. The early detection of drug resistance makes early treatment possible. However, the available tools are mainly for rifampicin resistance detection, and the existing isoniazid resistance detection method is expensive, highly technical, and complicated, making it unsustainable for use in developing nations. This study aimed to develop a simple, rapid, and low-cost diagnostic kit for isoniazid-resistant tuberculosis using the single-stranded tag hybridization method to target an isoniazid resistance-conferring mutation. Specificity and sensitivity were assessed using DNA extracted from 49 isoniazid-resistant and 41 isoniazid-susceptible Mycobacterium tuberculosis clinical isolates cultured in mycobacterial growth indicator tubes. Positive signals were observed on mutant and wild-type lines with 100% sensitivity and specificity compared with Sanger sequencing results. In contrast, no positive signal was observed for non-tuberculosis mycobacteria. The detection limit of this method was 103 CFU or less. The STH-PAS system for isoniazid-resistant M. tuberculosis detection developed in this study offers a better alternative to conventional phenotypic isoniazid resistance determination, which will be of both clinical and epidemiological significance in resource-limited nations.

DOI: 10.7883/yoken.JJID.2020.754
PMID: 33132303

3. Fluoroquinolone Resistance Among Isolates of Mycobacterium tuberculosis in Khyber Pakhtunkhwa, Pakistan.

Microb Drug Resist. 2021 Jun;27(6):786-791. doi: 10.1089/mdr.2020.0118. Epub 2020 Oct 30.

Ali S(1)(2), Khan MT(3), Khan AS(4), Abbas Q(5), Irfan M(6).

Fluoroquinolones (FQs) are broad-spectrum second-line antimicrobial drugs commonly used in the treatment of tuberculosis (TB). Data on FQ resistance in the Khyber Pakhtunkhwa (KP) province of Pakistan, a high-burden country, are scarce. This study aimed to analyze the resistance to FQs in this specific geographic area. Samples were collected from 25 districts of KP from 2014 to 2019. Data regarding suspected TB patients were collected from their guardians

or secondary caregivers. All the samples were subjected to decontamination and digestion processing. Drug susceptibility testing (DST) was performed according to the standard minimum inhibitory concentration for ofloxacin (OFX), levofloxacin (LEV), and moxifloxacin (MOX), taken as 2, 1, and 1 µg/mL, respectively. For the 5,759 clinical samples collected from 25 districts, DST was conducted for a total of 3,158 samples. Out of the total DSTs, the OFX profile was available for 2,983, MOX profile for 2,290, and LEV profile for 544 samples. OFX and LEV resistance was found to be evenly distributed and has remained the same for the past few years, whereas MOX resistance increased from 1% in 2017 to 4% in 2019. Among a total of 807 OFX-resistant isolates, 218 (27%) were observed to be monoresistant to OFX, whereas 589 (73%) isolates were resistant to OFX and at least one other anti-TB drug. Drug resistance to OFX was higher in multidrug-resistant TB (MDR-TB), that is, 428 (53%). It was concluded that resistance to MOX has been increasing, whereas OFX resistance is much higher in MDR cases. FQ resistance needs to be continuously monitored to avoid further side effects. This study provides useful information for better management of FQ resistance with reference to the global TB control program 2030.

DOI: 10.1089/mdr.2020.0118
PMID: 33124944

4. 'She is like my mother': Community-based care of drug-resistant tuberculosis in rural Eswatini.

Glob Public Health. 2021 Jun;16(6):911-923. doi: 10.1080/17441692.2020.1808039. Epub 2020 Aug 20.

Burtscher D(1), Juul Bjertrup P(2), Vambe D(3), Dlamini V(2), Mmema N(2), Ngwenya S(2), Rusch B(4), Kerschberger B(2).

Patients with drug-resistant tuberculosis (DR-TB) have received community-based care in Eswatini since 2009. Trained and compensated community treatment supporters (CTSs) provide directly observed therapy (DOT), injectables and psychological support. We examined the acceptability of this model of care among DR-TB patients, including the perspective of family members of DR-TB patients and their CTSs in relation to the patient's experience of care and quality of life. This qualitative research was conducted in rural Eswatini in February 2018. DR-TB patients, CTSs and family members participated in in-depth interviews, paired interviews, focus group discussions and PhotoVoice. Data were thematically analysed and coded, and themes were extracted. Methodological triangulation enhanced the interpretation. All patients and CTSs and most family members considered community-based DR-TB care to be supportive. Positive aspects

were emotional support, trust and dedicated individual care, including enabling practical, financial and social factors. Concerns were related to social and economic problems within the family and fears about infection risks for the family and the CTSs. Community-based DR-TB care was acceptable to patients, family members and CTSs. To reduce family members' fears of TB infection, information and sensitisation within the family and constant follow-up appear crucial.

DOI: 10.1080/17441692.2020.1808039
PMID: 32816634

5. Anti-tuberculosis site-specific oral delivery system that enhances rifampicin bioavailability in a fixed-dose combination with isoniazid.

Drug Deliv Transl Res. 2021 Jun;11(3):894-908. doi: 10.1007/s13346-020-00847-9. Epub 2020 Sep 8.

Luciani-Giacobbe LC(1), Lorenzutti AM(2), Litterio NJ(2), Ramírez-Rigo MV(3)(4), Olivera ME(5).

The in vivo release segregation of rifampicin (RIF) and isoniazid (INH) has been proposed as a strategy to avoid RIF acid degradation, which is known as one of the main factors for reduced RIF bioavailability and can result in drug-resistant tuberculosis. So far, this strategy has been scarcely explored. The aims of this study were to investigate the stability and bioavailability of RIF after combination of a very fast release matrix of RIF with a sustained delivery system of INH. A series of INH-alginic acid complexes (AA-INH) was obtained and characterized. Independent and sequential release profile of AA-INH at biorrelevant media of pH 1.20 and 6.80 was explored. In addition, AA-INH was combined with a RIF-carboxymethylcellulose very fast release complex (CMC-RIF) obtained previously and subjected to acid dissolution assays to evaluate RIF acid stability and determine RIF and INH dissolution efficiencies. Finally, a pharmacokinetic study in dogs was carried out. The AA-INH was easily obtained in solid-state. Their characterization revealed its ionic nature, with a loading capacity of around 30%. The dissolution efficiencies (15 min) confirmed release segregation in acid media with 7.8 and 65.6% for AA-INH and CMC-RIF, respectively. INH release rate from the AA-INH system was slow in acid media and increased in simulated intestinal media. The complete release of INH was achieved after 2 h in simulated intestinal media in the sequential release experiments. The acid degradation of RIF was significantly reduced (36.7%) when both systems were combined and oral administration to dogs revealed a 42% increase in RIF bioavailability. In conclusion, CMC-RIF and AA-INH may be useful for the formulation of a site-specific solid dosage form to overcome some of the

main obstacles in tuberculosis treatment. Graphical abstract.

DOI: 10.1007/s13346-020-00847-9
PMID: 32901368

6. 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.

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

7. Drug resistance, fitness and compensatory mutations in Mycobacterium tuberculosis.

Tuberculosis (Edinb). 2021 May 21;129:102091. doi: 10.1016/j.tube.2021.102091. Online ahead of print.

Alame Emane AK(1), Guo X(1), Takiff HE(2), Liu S(3).

For tuberculosis to be eradicated, the transmission of Multi-Drug-Resistant and eXtensively Drug Resistant strains of Mycobacterium tuberculosis (MDR and XDR-TB) must be considerably reduced. Drug resistant strains were initially thought to have reduced fitness, and the majority of resistant strains may actually have compromised fitness because they are found in only one or a few patients. In contrast, some MDR/XDR-TB strains are highly transmitted and cause large outbreaks. Most antibiotics target essential bacterial functions and the mutations that confer resistance to anti-TB drugs can incur fitness costs manifested as slower growth and reduced viability. The fitness costs vary with different resistance mutations and the bacilli can also accumulate secondary mutations that compensate for the compromised functions and partially or fully restore lost fitness. The compensatory mutations (CM) are different for each antibiotic, as they mitigate the deleterious effects of the specific functions compromised by the resistance mutations. CM are generally more common in strains with resistance mutations incurring the greatest fitness costs, but for RIF resistance, CM are most frequent in strains with the mutation carrying the least fitness cost, Ser450Leu. Here, we review what is known about fitness costs, CM and mechanisms of resistance to the drugs that define a strain as MDR or XDR-TB. The relative fitness costs of the resistance mutations and the mitigating effects of CM largely explain why certain mutations are frequently found in highly transmitted clusters while others are less frequently, rarely or never found in clinical isolates. The CM illustrate how drug resistance affects bacteria and how bacteria evolve to overcome the effects of the antibiotics, and thus a paradigm for how mycobacteria can evolve in response to stress.

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DOI: 10.1016/j.tube.2021.102091
PMID: 34090078

8. Evidence-based Definition for Extensively Drug-resistant Tuberculosis.

Am J Respir Crit Care Med. 2021 Jun 9. doi: 10.1164/rccm.202009-3527OC. Online ahead of print.

Roelens M(1), Battista Migliori G(2), Rozanova L(1), Estill J(1)(3), Campbell JR(4), Cegielski JP(5), Tiberi S(6)(7), Palmero D(8), Fox GJ(9), Guglielmetti L(10)(11), Sotgiu G(12), Brust JCM(13), Bang D(14)(15), Lange C(16)(17)(18),

Menzies D(19), Keiser O(1), Raviglione M(20)(21).

RATIONALE: Until 2020, extensively drug-resistant tuberculosis (XDR-TB) was defined as resistance to rifampicin and isoniazid (multidrug-resistant tuberculosis, MDR-TB), any fluoroquinolone (FQ) and any second-line injectable drug (SLID). In 2019 the World Health Organization issued new recommendations for managing patients with drug-resistant tuberculosis, substantially limiting the role of SLID in MDR-TB treatment and thus putting that XDR-TB definition into question.
OBJECTIVE: To propose an up-to-date definition for XDR-TB.
METHODS: We used a large dataset to assess treatment outcomes for MDR-TB patients exposed to any type of longer regimen. We included patients with bacteriologically confirmed MDR-TB and known FQ and SLID resistance results. We did logistic regression to estimate adjusted odds ratios (aORs) for unfavourable treatment outcome (failure, relapse, death, loss-to-follow-up) by resistance pattern (FQ, SLID) and Group A drug use (moxifloxacin/levofloxacin, linezolid, bedaquiline).
MEASUREMENTS AND MAIN RESULTS: We included 11,666 patients with MDR-TB; 4653 (39.9%) had an unfavourable treatment outcome. Resistance to FQs increased the odds of an unfavourable treatment outcome (aOR 1.91; 95% confidence interval [95%CI] 1.63-2.23). Administration of bedaquiline and/or linezolid improved treatment outcomes regardless of resistance to FQ and/or SLID. Among XDR-TB patients, compared to persons receiving no Group A drug, aORs for unfavourable outcome were 0.37 (95%CI 0.20-0.69) with linezolid only, 0.40 (95%CI 0.21-0.77) with bedaquiline only, and 0.21 (95%CI 0.12-0.38) with both.
CONCLUSIONS: Our study supports a new definition of XDR-TB as MDR plus additional resistance to FQ plus bedaquiline and/or linezolid, and helps assess the adequacy of this definition for surveillance and treatment choice.

DOI: 10.1164/rccm.202009-3527OC
PMID: 34107231

9. 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

10. 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

11. Incidence Density and Predictors of Multidrug-Resistant Tuberculosis Among Individuals With Previous Tuberculosis History: A 15-Year Retrospective Cohort Study.

Front Public Health. 2021 May 28;9:644347. doi: 10.3389/fpubh.2021.644347. eCollection 2021.

Cheng Q(1)(2), Xie L(1), Wang L(1), Lu M(1), Li Q(1), Wu Y(1), Huang Y(1), Jia Q(1), Zhao G(1).

Background: To date, too little attention has been paid to monitoring and estimating the risk of incident multidrug-resistant tuberculosis (MDR-TB) among individuals with a previous tuberculosis history (PTBH). The purpose of this study was to assess the incidence of and risk factors for MDR-TB in those individuals. Methods: Between 2005 and 2020, a large, retrospective, population-based cohort study was performed in Hangzhou, China. A multivariable Cox regression model was used to evaluate independent predictors of incident MDR-TB among individuals with PTBH. Results: The incidence density of MDR-TB was 22.6 per 1,000 person-years (95% confidence level and an interval of 20.9-24.3) for individuals with PTBH. The incidence of MDR-TB increased significantly in individuals who • were under 60 years old. • were male. • had a history of direct contact. • came from low-income families. • worked in high-risk occupations. • lived in rural areas. • had a retreatment TB history. • had an unfavorable outcome in their previous treatment ($P < 0.05$). In addition, we found that the following factors were significantly linked to the MDR-TB risk among individuals with PTBH ($P < 0.05$): • sociodemographic factors such as the 21-30 and 31-40 year age groups, or a history of direct contact. • clinical factors like passive modes of TB case finding (PMTCF), human immunodeficiency virus infection, unfavorable treatment outcomes, retreated TB history, non-standardized treatment regimens of retreatment TB patients, and duration of pulmonary cavities (DPC). • microbiological factors, such as duration of

positive sputum culture. We also found that the 21-30 year age group, low family income, and PMTCF were significantly linked to incident MDR-TB only in males with PTBH, whilst the 41-50 year age group, extended treatment course, and DPC were significantly associated with female MDR-TB only. Conclusion: The incidence of MDR-TB was high, with a higher rate among subjects with a history of direct contact and unfavorable treatment outcomes. There was a gender difference in the incidence density and risk factors of MDR-TB among individuals with PTBH. Long-term monitoring and gender-specific risk-factor modifications should be given to individuals with PTBH.

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DOI: 10.3389/fpubh.2021.644347
PMCID: PMC8193499
PMID: 34123987 [Indexed for MEDLINE]

12. Impact of bedaquiline on treatment outcomes of multidrug-resistant tuberculosis in a high-burden country.

Eur Respir J. 2021 Jun 10;57(6):2002544. doi: 10.1183/13993003.02544-2020. Print 2021 Jun.

Chesov D(1)(2)(3), Heyckendorf J(2)(3)(4), Alexandru S(5), Donica A(5), Chesov E(6)(2), Reimann M(2)(3), Crudu V(5), Botnaru V(6), Lange C(2)(3)(4).

BACKGROUND: Evaluation of novel anti-tuberculosis (TB) drugs for the treatment of multidrug-resistant (MDR)-TB continues to be of high interest on the TB research agenda. We assessed treatment outcomes in patients with pulmonary MDR-TB who received bedaquiline-containing treatment regimens in the Republic of Moldova, a high-burden MDR-TB country.
METHOD: We systematically analysed the SIMETB national electronic TB database and performed a retrospective propensity score-matched comparison of treatment outcomes in a cohort of patients with MDR-TB who started treatment during 2016-2018 with a bedaquiline-containing regimen (bedaquiline cohort) and a cohort of patients treated without bedaquiline (non-bedaquiline cohort).
RESULTS: Following propensity score matching, 114 patients were assigned to each cohort of MDR-TB patients. Patients in the bedaquiline cohort had a higher 6-month sputum culture conversion rate than those in the non-bedaquiline cohort (66.7% versus 40.3%; p<0.001). Patients under bedaquiline-containing regimens had a higher cure rate assessed by both World Health Organization (WHO) and TBnet definitions (55.3% versus 24.6%; p=0.001 and 43.5% versus 19.6%; p=0.004, respectively), as well as a lower mortality rate (8.8% versus 20.2%; p<0.001 and 10.9% versus 25.2%; p=0.01, respectively). In patients who previously failed on

MDR-TB treatment, >40% of patients achieved a cure with a bedaquiline-containing regimen.
CONCLUSIONS: Bedaquiline-based MDR-TB treatment regimens result in better disease resolution when compared with bedaquiline-sparing MDR-TB treatment regimens under programmatic conditions in a country with a high burden of MDR-TB.

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DOI: 10.1183/13993003.02544-2020
PMID: 33334942

13. Highly transmitted M. tuberculosis strains are more likely to evolve MDR/XDR and cause outbreaks, but what makes them highly transmitted?

Tuberculosis (Edinb). 2021 Jun 2;129:102092. doi: 10.1016/j.tube.2021.102092. Online ahead of print.

Alame Emane AK(1), Guo X(2), Takiff HE(3), Liu S(4).

Multi-Drug-Resistant strains of Mycobacterium tuberculosis (MDR-TB) are a serious obstacle to global TB eradication. While most MDR-TB strains are infrequently transmitted, a few cause large transmission clusters that contribute substantially to local MDR-TB burdens. Here we examine whether the known mutations in these strains can explain their success. Drug resistance mutations differ in fitness costs and strains can also acquire compensatory mutations (CM) to restore fitness, but some highly transmitted MDR strains have no CM. The acquisition of resistance mutations that maintain high transmissibility seems to occur by chance and are more likely in strains that are intrinsically highly transmitted and cause many cases. Modern Beijing lineage strains have caused several large outbreaks, but MDR outbreaks are also caused by ancient Beijing and lineage 4 strains, suggesting the lineage is less important than the characteristics of the individual strain. The development of fluoroquinolone resistance appears to represent another level of selection, in which strains must surmount unknown fitness costs of gyrA mutations. The genetic determinants of high transmission are poorly defined but may involve genes encoding proteins involved in molybdenum acquisition and the Esx systems. In addition, strains eliciting lower cytokine responses and producing more caseating granulomas may have advantages for transmission. Successful MDR/XDR strains generally evolve from highly transmitted drug sensitive parent strains due to selection pressures from deficiencies in local TB control programs. Until TB incidence is considerably reduced, there will likely be highly transmitted strains that develop resistance to any new antibiotic.

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DOI: 10.1016/j.tube.2021.102092
PMID: 34102584

14. Prevalence and molecular characteristics of drug-resistant Mycobacterium tuberculosis in Hainan, China: from 2014 to 2019.

BMC Microbiol. 2021 Jun 19;21(1):185. doi: 10.1186/s12866-021-02246-7.

Liu L(#)(1), Zhao X(#)(2), Wu X(1), Li S(1), Liu B(1), Rajaofera MJN(1), Zeng Y(1), Dong S(1), Bei Z(3), Pei H(4), Xia Q(5).

BACKGROUND: The emergence of antimicrobial resistance against Mycobacterium tuberculosis (M. tuberculosis) has become the major concern in global tuberculosis control due to its limited therapy options and high mortality. However, the clinical and molecular characteristics of drug-resistant strains vary in different geographical areas. Hainan Island located in southern China, is a high drug-resistant tuberculosis burden area. This study aimed to determine the dynamic changes of drug-resistance patterns and drug-related gene mutation types of M. tuberculosis in Hainan from 2014 to 2019.
RESULTS: A total of 1484 culture-confirmed M. tuberculosis were included in this study. It was found that the proportions of drug resistance to isoniazid and rifampin were 31.3 and 31.1% respectively. Overall the proportion of multidrug resistant M. tuberculosis was 24.9%. Multivariate logistic regression analysis showed that age and the treatment history were independent influencing factors of drug resistant tuberculosis. The proportions of drug-resistant tuberculosis in retreatment patients were considerably higher than those in new patients. The most common mutation types of isoniazid were Ser315 → Thr (66.3%), and the most common mutation types of rifampin were Ser531 → Leu (41.5%).
CONCLUSIONS: Our data suggests that the prevalence of drug resistant TB remains high in Hainan, and the risks for developing drug resistance with diversified mutation types increased significantly in retreatment patients. These results contribute to the knowledge of the prevalence of drug resistance in Hainan Province and expand the molecular characteristics of drug resistance in China simultaneously.

DOI: 10.1186/s12866-021-02246-7
PMID: 34147065

15. Bedaquiline: Current status and future perspectives.

J Glob Antimicrob Resist. 2021 Jun;25:48-59. doi: 10.1016/j.jgar.2021.02.017. Epub 2021 Mar 5.

Khoshnood S(1), Goudarzi M(2), Taki E(3), Darbandi A(4), Kouhsari E(5), Heidary M(6), Motahar M(7), Moradi M(7), Bazyar H(8).

The development of drug-resistant tuberculosis (TB) is a major threat worldwide. Based on World Health Organization (WHO) reports, it is estimated that more than 500 000 new cases of drug-resistant TB occur annually. In addition, there are alarming reports of increasing multidrug-resistant TB (MDR-TB) and the emergence of extensively drug-resistant TB (XDR-TB) from different countries of the world. Therefore, new options for TB therapy are required. Bedaquiline (BDQ), a novel anti-TB drug, has significant minimum inhibitory concentrations (MICs) both against drug-susceptible and drug-resistant TB. Moreover, BDQ was recently approved for therapy of MDR-TB. The current narrative review summarises the available data on BDQ resistance, describes its antimicrobial properties, and provides new perspectives on clinical use of this novel anti-TB agent.

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DOI: 10.1016/j.jgar.2021.02.017
PMID: 33684606

16. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update.

Eur Respir J. 2021 Jun 4;57(6):2003300. doi: 10.1183/13993003.03300-2020. Print 2021 Jun.

Mirzayev F(1), Viney K(1), Linh NN(1), Gonzalez-Angulo L(1), Gegia M(1), Jaramillo E(1), Zignol M(1), Kasaeva T(1).

Antimicrobial resistance is a major public health problem globally. Likewise, forms of tuberculosis (TB) resistant to first- and second-line TB medicines present a major challenge for patients, healthcare workers and healthcare services. In November 2019, the World Health Organization (WHO) convened an independent international expert panel to review new evidence on the treatment of multidrug- (MDR) and rifampicin-resistant (RR) TB, using the Grading of Recommendations Assessment, Development and Evaluation approach.Updated WHO guidelines emerging from this review, published in June 2020, recommend a shorter treatment regimen for patients with MDR/RR-TB not resistant to fluoroquinolones (of 9-11 months), with the inclusion of bedaquiline instead of

an injectable agent, making the regimen all oral. For patients with MDR-TB and additional fluoroquinolone resistance, a regimen composed of bedaquiline, pretomanid and linezolid may be used under operational research conditions (6-9 months). Depending on the drug-resistance profile, extent of TB disease or disease severity, a longer (18-20 months) all-oral, individualised treatment regimen may be used. In addition, the review of new data in 2019 allowed the WHO to conclude that there are no major safety concerns on the use of bedaquiline for >6 months' duration, the use of delamanid and bedaquiline together and the use of bedaquiline during pregnancy, although formal recommendations were not made on these topics.The 2020 revision has highlighted the ongoing need for high-quality evidence and has reiterated the need for clinical trials and other research studies to contribute to the development of evidence-based policy.

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DOI: 10.1183/13993003.03300-2020
PMCID: PMC8176349
PMID: 33243847

17. Distribution and Clonality of drug-resistant tuberculosis in South Africa.

BMC Microbiol. 2021 May 28;21(1):157. doi: 10.1186/s12866-021-02232-z.

Said H(1)(2), Ratabane J(3), Erasmus L(4), Gardee Y(3), Omar S(3), Dreyer A(5), Ismail F(3)(6), Bhyat Z(3), Lebaka T(4), van der Meulen M(3), Gwala T(3), Adelekan A(6), Diallo K(6), Ismail N(3)(7).

BACKGROUND: Studies have shown that drug-resistant tuberculosis (DR-TB) in South Africa (SA) is clonal and is caused mostly by transmission. Identifying transmission chains is important in controlling DR-TB. This study reports on the sentinel molecular surveillance data of Rifampicin-Resistant (RR) TB in SA, aiming to describe the RR-TB strain population and the estimated transmission of RR-TB cases.
METHOD: RR-TB isolates collected between 2014 and 2018 from eight provinces were genotyped using combination of spoligotyping and 24-loci mycobacterial interspersed repetitive-units-variable-number tandem repeats (MIRU-VNTR) typing.
RESULTS: Of the 3007 isolates genotyped, 301 clusters were identified. Cluster size ranged between 2 and 270 cases. Most of the clusters (247/301; 82.0%) were small in size (< 5 cases), 12.0% (37/301) were medium sized (5-10 cases), 3.3% (10/301) were large (11-25 cases) and 2.3% (7/301) were very large with 26-270 cases. The Beijing genotype was responsible for majority of RR-TB cases in Western and Eastern Cape, while the East-African-Indian-Somalian (EAI1_SOM) genotype accounted for a third of RR-TB cases in Mpumalanga. The overall

proportion of RR-TB cases estimated to be due to transmission was 42%, with the highest transmission-rate in Western Cape (64%) and the lowest in Northern Cape (9%).
CONCLUSION: Large clusters contribute to the burden of RR-TB in specific geographic areas such as Western Cape, Eastern Cape and Mpumalanga, highlighting the need for community-wide interventions. Most of the clusters identified in the study were small, suggesting close contact transmission events, emphasizing the importance of contact investigations and infection control as the primary interventions in SA.

DOI: 10.1186/s12866-021-02232-z
PMCID: PMC8161895
PMID: 34044775

18. 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.

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PMID: 34099204

19. Disputed rpoB Mutations in Mycobacterium tuberculosis and Tuberculosis Treatment Outcomes.

Antimicrob Agents Chemother. 2021 Jun 17;65(7):e0157320. doi: 10.1128/AAC.01573-20. Epub 2021 Jun 17.

Lin WH(1)(2), Lee WT(1)(2), Tsai HY(1)(2), Jou R(1)(2)(3).

Discordant results between genotypic drug susceptibility testing (gDST) and phenotypic DST (pDST) for Mycobacterium tuberculosis isolates with disputed (discordance between gDST and pDST results) mutations affect rifampin (RIF)-resistant (RR) and multidrug-resistant (MDR) tuberculosis (TB) treatments due to a lack of practical clinical guidelines. To investigate the role of disputed rpoB mutations in M. tuberculosis and TB treatment outcomes, initial isolates of 837 clinical RR- or MDR-TB cases confirmed during 2014 to 2018 were retested using agar-based RIF pDST and rpoB gene sequencing. MICs were determined for isolates with disputed rpoB mutations. Disputed rpoB mutations were identified in 77 (9.2%) M. tuberculosis isolates, including 50 (64.9%) and 14 (18.2%) phenotypically RIF- and rifabutin (RFB)-resistant isolates, respectively. The predominant single mutations were those encoding L533P (a change of L to P at position 533) (44.2%) and L511P (20.8%). Most of the isolates harboring mutations encoding L511P (87.5%), H526N (100%), D516Y (70.0%), and L533P (63.6%) had MICs of ≤1 mg/liter, whereas isolates harboring the mutation encoding H526L (75%) had a MIC of >1 mg/liter. Of the 63 cases with treatment outcomes available, 11 (17.5%) cases died, 1 (1.6%) case transferred out, and 51 (81%) cases had favorable outcomes, including 8 and 20 cases treated with standard-dose RIF- and RFB-containing regimens, respectively. Excluding cases that transferred out or received no or 1-day treatment, we observed

statistically significant differences between the outcomes using active and inactive fluoroquinolones (FQs) (P = 0.008, odds ratio = 0.05 [95% confidence interval, 0.01 to 0.38]) in 57 cases (where active means a case susceptible to the drug and inactive means a case resistant to the drug or drug not used). We concluded that disputed rpoB mutations are not rare. Depending on the resources available, sequencing and/or MIC testing is recommended for better management of RR- and MDR-TB cases.

DOI: 10.1128/AAC.01573-20
PMID: 33846134

20. Determinants of Multi-drug resistant Tuberculosis in four treatment centers of Eastern Amhara, Ethiopia: A case-control study.

J Infect Dev Ctries. 2021 May 31;15(5):687-695. doi: 10.3855/jidc.13265.

Oumer N(1), Atnafu DD(2), Worku GT(3), Tsehay AK(3).

INTRODUCTION: Tuberculosis is the major global burden of disease contributing about 2% of the global challenges. Poor tuberculosis treatment increased risk of multi-drug resistance tuberculosis occurence. Thus, we aimed to identify determinants of mult-drug resistant tuberclosis in treatment centers of Eastern Amhara, Ethiopia.
METHODOLOGY: Facility based unmatched case-control study was employed in East Amhara, Ethiopia. Cases were tuberculosis patients confirmed for mult-drug resistant tuberclosis while controls were tuberculosis patients with confirmed tuberculosis but susceptible to first line drugs. Respondents were selected using simple random sampling technique. Bivariable and multivariable analysis was conducted to identify diterminants at level of statistical significance p < 0.05.
RESULTS: We enrolled 450 tuberculosis patients. Rural residents (AOR = 3, 95% CI: 1.4-6.0; p = 0.024), family size greater than five (AOR = 3.7, 95% CI: 1.6-8.6; p = 0.0098), having single room (AOR = 4.1, 95% CI:1.8-9.0; p = 0.027), room without window (AOR = 3.8, 95% CI: 1.6-8.5); p = 0.043), contact history of known mult-drug resistant tuberclosis patient (AOR = 5.1, 95% CI: 2.2-12.0; p = 0.02), history of tuberculosis treatment (AOR = 5.7, 95%CI: 2.6-12.9; p = 0.008), window opening practice (AOR = 3.7, 95% CI: 1.4-9.8; p = 0.005), tuberculosis treatment failure (AOR = 7.3, 95% CI: 5.2-7.8; p = 0.035) and tuberculosis relapse (AOR = 5,95% CI: 1.6-15.2; p = 0.019) were determinants of mult-drug resistant tuberclosis.
CONCLUSIONS: Socio-demographic (residence, family size), environmental (number of rooms, number of windows in a room, opening window practice) and clinical (history of tuberculosis treatment, treatment failure and having contact with

known tuberculosis patient) variables were the identified determinants for increased multi-drug resistance tuberculosis.

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PMID: 34106893

21. Depression, stigma and quality of life in people with drug-susceptible TB and drug-resistant TB in Vietnam.

Int J Tuberc Lung Dis. 2021 Jun 1;25(6):461-467. doi: 10.5588/ijtld.20.0952.

Redwood L(1), Mitchell EMH(2), Viney K(3), Snow K(4), Nguyen TA(5), Dung LAT(5), Nguyen VN(6), Fox GJ(1).

BACKGROUND: Drug resistance poses a major barrier to global control of TB - a leading infectious cause of death. Depression and stigma occur commonly among people with TB. However, the relationship between drug-resistant forms of TB, depression and stigma are not well understood.OBJECTIVE: To compare depression, stigma and health-related quality of life (HRQoL), among people with drug-susceptible TB (DS-TB) and multidrug-resistant TB (MDR-TB).METHODS: A cross-sectional study of people treated for DS-TB and MDR-TB in four provinces of Vietnam. The survey included a stigma scale (Vietnamese Tuberculosis Stigma Scale), depression scale (9-item Patient Health Questionnaire) and HRQoL scale (Functional Assessment of Chronic Illness Therapy - Tuberculosis). Differences between the two populations were compared using linear regression.RESULTS: Eighty-one people with DS-TB and 315 people with MDR-TB participated in the study. People with MDR-TB had a higher prevalence of depression than those with DS-TB (difference 17.8%, χ^2 8.64). The mean depression and stigma scores were higher for people with MDR-TB than those with DS-TB (adjusted difference [AD] 8.6 and 7.6 respectively). People with MDR-TB reported lower HRQoL than those with DS-TB (AD -23.8).CONCLUSION: Depression and stigma are common among people with TB in Vietnam. Strategies to prevent and treat depressive symptoms and stigma in people with TB are critical to a holistic, patient-centred approach to care.

DOI: 10.5588/ijtld.20.0952
PMID: 34049608

22. Pretomanid with bedaquiline and linezolid for drug-resistant TB: a comparison of

prospective cohorts.

Int J Tuberc Lung Dis. 2021 Jun 1;25(6):453-460. doi: 10.5588/ijtld.21.0035.

Oelofse S(1), Esmail A(1), Diacon AH(2), Conradie F(3), Olayanju O(1), Ngubane N(4), Howell P(3), Everitt D(5), Crook AM(6), Mendel CM(5), Wills GH(6), Olugbosi M(7), Del Parigi A(5), Sun E(5), Calatroni A(8), Spigelman M(5), Dheda K(9).

BACKGROUND: There are no data comparing the 6-9 month oral three-drug Nix regimen (bedaquiline, pretomanid and linezolid [BPaL]) to conventional regimens containing bedaquiline (B, BDQ) and linezolid (L, LZD).METHODS: Six-month post end-of-treatment outcomes were compared between Nix-TB (n = 109) and 102 prospectively recruited extensively drug-resistant TB patients who received an ˜18-month BDQ-based regimen (median of 8 drugs). A subset of patients received BDQ and LZD (n = 86), and a subgroup of these (n = 75) served as individually matched controls in a pairwise comparison to determine differences in regimen efficacy.RESULTS: Favourable outcomes (%) were significantly better with BPaL than with the B-L-based combination regimen (98/109, 89.9% vs. 56/86, 65.1%; adjusted relative risk ratio [aRRR] 1.35; P < 0.001) and in the matched pairwise analysis (67/75, 89.3% vs. 48/75, 64.0%; aRRR 1.39; P = 0.001), despite significantly higher baseline bacterial load and prior second-line drug exposure in the BPaL cohort. Time to culture conversion (P < 0.001), time to unfavourable outcome (P < 0.01) and time to death (P < 0.03) were significantly better or lower with BPaL than the B-L-based combinations.CONCLUSION: The BPaL regimen (and hence substitution of multiple other drugs by pretomanid and/or higher starting-dose LZD) may improve outcomes in drug-resistant TB patients with poor prognostic features. However, prospective controlled studies are required to definitively answer this question.

CONTEXTE : Il n'y a pas de données comparant les protocoles oraux de 6–9 mois associant trois médicaments (bédaquiline, prétomanide et linézolide [BPaL]) aux protocoles conventionnels contenant de la bédaquiline (B, BDQ) et du linézolide (L, LZD).
MÉTHODE : On a comparé les résultats 6 mois après la fin du traitement entre Nix-TB (n = 109) et 102 patients TB recrutés prospectivement qui ont reçu un protocole de BDQ d'environ 18 mois (médiane de 8 médicaments). Un sous ensemble de patients a reçu de la BDQ et du LZD (n = 86) et un sous-groupe de ces derniers (n = 75) a servi de témoins appariés individuellement pour des comparaisons par paires afin de déterminer les différences d'efficacité du protocole.
RÉSULTATS : Des résultats favorables (%) ont été significativement meilleurs avec BPaL qu'avec le protocole combiné basé sur B-L (98/109, 89,9% contre 56/86, 65,1% ; rapport de risque relatif ajusté [RRRa] 1,35 ; P < 0,001) et dans

l'analyse par paires (67/75, 89,3% contre 48/75, 64,0% ; RRRa 1,39 ; P = 0,001) malgré une charge bactérienne initiale significativement plus élevée et une exposition préalable aux médicaments de deuxième ligne. Le délai de conversion de la culture (P < 0,001), le délai de résultats défavorables (P < 0,01) et de décès (P < 0,03) ont été significativement meilleurs ou plus bas avec BPaL comparés à la combinaison à base de BL.
CONCLUSION : Le protocole BPaL (et donc la substitution de multiples autres médicaments par le prétomanide et/une dose de départ plus élevée de LZD) pourrait améliorer les résultats des patients TB résistante ayant des facteurs de pronostic négatifs. Des études prospectives contrôlées sont cependant requises pour répondre définitivement à cette question.

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PMCID: PMC8171246
PMID: 34049607

23. Depression and its associated factors among people with multidrug-resistant tuberculosis in Myanmar.

Trop Med Int Health. 2021 Jun 10. doi: 10.1111/tmi.13637. Online ahead of print.

Theingi P(1)(2), Kamiya Y(2), Myat Moe M(1), Cho San C(1), Cox SE(2)(3)(4).

BACKGROUND: Depression is an important potential co-morbidity in persons with tuberculosis (TB), yet data in many settings are scarce.
OBJECTIVES: To estimate the prevalence and risk factors of depression in persons with multidrug-resistant tuberculosis (MDR-TB) in Myanmar.
METHODS: A cross-sectional survey among MDR-TB participants at Aung San MDR-TB treatment center in Yangon during routine clinic follow-up visits. Patients Health Questionnaire-9 (PHQ-9) in the local language was used to screen for depression and structured questionnaires conducted. Univariable and multivariable logistic regression models were performed to identify associations.
RESULTS: Three-hundred twenty-nine participants were enrolled between 19th December 2019 to 31st January 2020; 33% (111/329) in the intensive treatment phase. The prevalence of depressive symptoms (PHQ9 ≥10) was (34/329) 10.33%. Multivariable analysis indicated financial hardship as a result of MDR-TB symptoms/treatment (aOR=2.63, 95%CI: 1.12-6.67), suffering ≥1 respiratory symptoms (aOR=6.72, 95%CI: 2.41-18.76), high education level (aOR=4.26, 95%CI: 1.70-10.70), reported diabetes (aOR=3.05, 95%CI: 1.16-7.99) as associated with depressive symptoms, with weak evidence of an association in females (aOR=2.09, 95%CI: 0.94-4.65).
CONCLUSION: Depressive symptoms are more common in those with

co-morbidities/TB-symptoms. Further research is required to determine effects of interventions to support persons with depressive symptoms identified using simple, standardized validated tools like PHQ-9.

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PMID: 34110669

24. 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.

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PMID: 34044311

25. Risk factors for drug-resistant tuberculosis, the association between comorbidity status and drug-resistant patterns: a retrospective study of previously treated pulmonary tuberculosis in Shandong, China, during 2004-2019.

BMJ Open. 2021 Jun 16;11(6):e044349. doi: 10.1136/bmjopen-2020-044349.

Tao NN(#)(1)(2), Li YF(#)(1)(2), Song WM(1), Liu JY(3), Zhang QY(1), Xu TT(2), Li SJ(1), An QQ(1), Liu SQ(1), Li HC(4)(2)(5).

OBJECTIVE: This study was designed to identify the risk factors for drug-resistant tuberculosis (DR-TB) and the association between comorbidity and drug resistance among retreated pulmonary tuberculosis (PTB).
DESIGN: A retrospective study was conducted among all the 36 monitoring sites in Shandong, China, over a 16-year period. Baseline characteristics were collected from the TB Surveillance System. Categorical variables were compared by Fisher's exact or Pearson's χ2 test. The risk factors for drug resistance were identified using univariable analysis and multivariable logistic models. The influence of comorbidity on different types of drug resistance was evaluated by performing multivariable logistic models with the covariates adjusted by age, sex, body mass index, drinking/smoking history and cavity.
RESULTS: A total of 10 975 patients with PTB were recorded during 2004-2019, and of these 1924 retreated PTB were finally included. Among retreated PTB, 26.2% were DR-TB and 12.5% had comorbidity. Smoking (adjusted OR (aOR): 1.69, 95% CI 1.19 to 2.39), cavity (aOR: 1.55, 95% CI 1.22 to 1.97) and comorbidity (aOR: 1.44, 95% CI 1.02 to 2.02) were risk factors for DR-TB. Of 504 DR-TB, 9.5% had diabetes mellitus, followed by hypertension (2.0%) and chronic obstructive pulmonary disease (1.8%). Patients with retreated PTB with comorbidity were more likely to be older, have more bad habits (smoking, alcohol abuse) and have clinical symptoms (expectoration, haemoptysis, weight loss). Comorbidity was significantly associated with DR-TB (aOR: 1.44, 95% CI 1.02 to 2.02), overall rifampin resistance (aOR: 2.17, 95% CI 1.41 to 3.36), overall streptomycin resistance (aOR: 1.51, 95% CI 1.00 to 2.27) and multidrug resistance (aOR: 1.96, 95% CI 1.17 to 3.27) compared with pan-susceptible patients ($p<0.05$).
CONCLUSION: Smoking, cavity and comorbidity lead to an increased risk of drug resistance among retreated PTB. Strategies to improve the host's health, including smoking cessation, screening and treatment of comorbidity, might contribute to the control of tuberculosis, especially DR-TB, in China.

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PMID: 34135033 [Indexed for MEDLINE]

26. 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 Jun 1:AAC0060821. doi: 10.1128/AAC.00608-21. Online ahead of print.

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 (Mtb) in patient sputa can miss large populations of viable Mtb that are unable to grow either on solid media or in liquid media if not extensively diluted. Because these bacteria can be detected in liquid media after limiting dilution, they have been termed differentially culturable or differentially detectable Mtb (DD Mtb). Treatment with isoniazid, rifampin, pyrazinamide and ethambutol (HRZE) for 1-2 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 in the sputum of 47 subjects, 29 with DS TB and 18 with DR TB, before initiation of their treatment regimens and at 2 weeks and 2 months thereafter. Prior to treatment, DD Mtb represented the majority of Mtb 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 was 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 was detected in the sputum of only 2/15 (13.3%) subjects with DS TB and 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

27. A case series of multidrug-resistant tuberculosis in renal transplant recipients: Challenges in management from a TB endemic country.

Transpl Infect Dis. 2021 May 31:e13659. doi: 10.1111/tid.13659. Online ahead of print.

Babar ZU(1), Nasim A(1), Kumar S(1), Nazmi J(2), Badlani S(1), Nadeem A(3), Aziz T(4).

Multidrug-resistant tuberculosis (MDR-TB) is caused by Mycobacterium tuberculosis that is resistant to isoniazid and rifampicin (Rif). The use of immunosuppressive drugs in solid organ transplant recipients can increase the risk of TB. Management of MDR-TB is quite challenging in the general population with poor compliance owing to lengthy treatment duration and drug toxicities. New drugs as well as shorter regimen have been used to increase the likelihood of adherence. The experience of treating MDR-TB in the transplant recipients is limited. New drugs like bedaquiline, linezolid, clofazimine, and delamanid have rarely been used in transplant recipients. To the best of our knowledge, only 14 cases of MDR-TB in transplant population have been reported in the literature and no case from Pakistan, a high TB burden country. We are reporting our experience of treating 4 renal transplant recipients. We used new drug regimen and found many side effects. Treatment outcome was successful with complete cure in 3 of our patients, however one died of severe drug toxicity. The most worrisome drug interaction was between azathioprine and linezolid, with life-threatening thrombocytopenia. There was no graft dysfunction noted at the end of the therapy. The management of MDR-TB in transplant recipients is challenging; excellent coordination between transplant team and Infectious Diseases Physician for close monitoring and follow-up is needed.

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DOI: 10.1111/tid.13659
PMID: 34057810

28. TB or not TB?: Definitive determination of species within the M. tuberculosis complex in unprocessed sputum from adults with presumed multidrug-resistant tuberculosis.

Trop Med Int Health. 2021 Jun 9. doi: 10.1111/tmi.13638. Online ahead of print.

Mbelele PM(1)(2), Sauli E(2), Mpolya EA(2), Mohamed SY(3), Addo KK(4), Mfinanga SG(5)(6), Heysell SK(3), Mpagama S(1)(2).

OBJECTIVES: Differences among Mycobacterium tuberculosis complex (MTC) species may predict drug-resistance or treatment success. Thus, we optimized and deployed the genotype MTBC assay (gMTBC) to identify MTC to the species level, and then performed comparative genotypic drug-susceptibility testing to anti-tuberculosis drugs from direct sputum of patients with presumed multidrug-resistant tuberculosis (MDR-TB) by the MTBDRplus/sl reference method.
METHODS: Patients with positive Xpert® MTB/RIF (Xpert) results were consented to provide early-morning-sputum for testing by the gMTBC and the reference MTBDRplus/sl. Chi-Square or fisher's exact test compared proportions. Modified-Poisson regression modelled detection of MTC by gMTBC.
RESULTS: Among 73 patients, 53 (73%) were male and a mean age of 43 (95% CI; 40 - 45) years. In total, 34 (47%), 36 (49%) and 38 (55%) had positive gMTBC, Culture and MTBDR respectively. Forty patients (55%) had low quantity MTC by Xpert, including 31 (78%) with a negative culture. gMTBC was more likely to be positive in patients with chest cavity 4.18 (1.31 - 13.32, p = 0.016), high-quantity MTC by Xpert 3.03 (1.35 - 6.82, p = 0.007), and sputum smear positivity 1.93 (1.19 - 3.14, p = 0.008). The accuracy of gMTBC in detecting MTC was 95% (95% CI; 86 - 98; κ = 0.89) compared to MTBDRplus/sl. All M. tuberculosis/canetii identified by gMTB were susceptible to fluoroquinolone and aminoglycosides/capreomycin.
CONCLUSIONS: The concordance between the gMTBC assay and MTBDRplus/sl in detecting MTC was high but lagged behind the yield of Xpert MTB/RIF. All M. tuberculosis/canetti were susceptible to fluoroquinolones, a core drug in MDR-TB treatment regimens.

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DOI: 10.1111/tmi.13638
PMID: 34107112

29. Defining Outcomes of Tuberculosis (Treatment): From the Past to the Future.

Respiration. 2021 May 31:1-10. doi: 10.1159/000516392. Online ahead of print.

Günther G(1)(2), Heyckendorf J(3)(4)(5), Zellweger JP(6), Reimann M(3)(4)(5), Claassens M(2)(7), Chesov D(3)(8), van Leth F(9).

Untreated active tuberculosis (TB) has a very high long-term mortality. Treatment of TB reduces mortality dramatically and should maximize cure, preventing ongoing transmission and TB sequelae. However, predicting the risk of failure and relapse is crucial for the management of individual patients and for the evaluation of effectiveness of programs. Various outcome definitions for

drug-sensitive and drug-resistant TB were developed, implemented, and endorsed since introduction of TB chemotherapy by the World Health Organization (WHO), mostly based on culture and smear results. They should be applicable for individual patient care, surveillance, and research. Definitions with focus on program evaluation differ from definitions to evaluate the efficacy and effectiveness of regimens. Lack of sputum production at the later stage of treatment reduces the easy applicability of current definitions. Definitions of failure and cure are sometimes difficult to apply. Alternative approaches suggest culture positivity at 6 months or more of treatment as an indicator for failure. New definitions for cure including a relapse-free period posttreatment and reduced number of culture and smear results are considered. Increasing variation and individualization of treatment and its duration urgently require new approaches using pathogen- or host-specific biomarkers, which indicate risk of failure and define cure. Such biomarkers are under evaluation but still far from translation in clinical routine practice.

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PMID: 34058739

30. Greenness exposure and all-cause mortality during multi-drug resistant tuberculosis treatment: A population-based cohort study.

Sci Total Environ. 2021 Jun 1;771:145422. doi: 10.1016/j.scitotenv.2021.145422. Epub 2021 Jan 26.

Ge E(1), Gao J(2), Ren Z(3), Liu X(4), Luo M(5), Zhong J(6), Fei F(7), Chen B(8), Wang X(9), Wei X(10), Peng Y(11).

BACKGROUND: Living closer to greenness were thought to benefit various health outcomes. We aimed to assess the association between residential greenness and mortality among patients undergoing multidrug resistant tuberculosis (MDR-TB) treatment.
METHODS: We enrolled all local MDR-TB patients reported in Zhejiang, China from 2009 to 2017 and followed them throughout the treatment. We calculated the contemporaneous normalized difference vegetation index (NDVI) in the 250 and 500 m radius around patient's residence. Cox proportional hazards regression models with time-varying NDVI were used to assess the impact of greenness exposure on all-cause mortality during MDR-TB treatment, adjusting for potential individual and contextual covariates.
RESULTS: We ascertained 1,621 active MDR-TB cases, which contributed 3036 person-years at risk with an average follow-up of 684 days (s.d. 149 days) per

patient. Among them, there were 163 deaths during follow-up, representing a crude mortality rate of 537 deaths per 10,000 person-years. Patients exposed to the second quintile (Q2) of greenness within the 500 m buffer had around 64% reduced mortality risk over the lowest quintile of greenness with hazard ratio (HR) = 0.364 (95% CI: 0.109-1.22). In lower nighttime light (NTL) areas, the hazard ratios (HR) per quintile increase in NDVI within the 500 m buffer were Q2: 0.35 (95% CI: 0.10-1.18), Q3: 0.24 (95% CI: 0.09-0.66), Q4: 0.26 (95% CI: 0.10-0.69), and Q5: 0.26 (95% CI: 0.10-0.71) relevant to the lowest quintile Q1, with a trend of p-value ≤0.01. Patients who were female, younger (<60 years), resided in urban areas, or had high PM2.5 (i.e. particles with diagram ≤2.5 μm) exposure were more likely to benefit from greenness exposure. Associations were neither observed with NDVI in the 250 m buffer nor for patients living in higher NTL areas. There was a non-linear exposure-response relationship between greenness and deaths with p-value ≤0.05.
CONCLUSION: Increasing greenness exposure along with medical treatment reduces all-cause mortality among patients living in lower NTL areas.

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PMID: 33548711 [Indexed for MEDLINE]

31. Rapid detection of multidrug-resistant tuberculosis based on allele-specific recombinase polymerase amplification and colorimetric detection.

PLoS One. 2021 Jun 11;16(6):e0253235. doi: 10.1371/journal.pone.0253235. eCollection 2021.

Singpanomchai N(1), Akeda Y(2), Tomono K(2), Tamaru A(3), Santanirand P(4), Ratthawongjirakul P(5).

Multidrug-resistant tuberculosis (MDR-TB) poses a serious threat to TB control. Early diagnosis and proper treatment are essential factors to limit the spread of the disease. The existing molecular tests for MDR-TB usually require specific instruments, steady power supply, and routine maintenance, which might be obstacles for low-resource settings. This study aimed to develop allele-specific isothermal recombinase polymerase amplification (allele-specific RPA) to simultaneously detect the most common mutations in the rpoB gene at codons 516, 526, and 531, which are associated with rifampicin resistance, and in the katG gene at codon 315, which is related to isoniazid resistance. Allele-specific primers targeting four major mutations, rpoB516, rpoB526, rpoB531, and katG315, were constructed and used in individual RPA reactions. The RPA amplicons were endpoints detected by the naked eye immediately after applying SYBR Green I. The

optimised RPA assay was evaluated with the Mycobacterium tuberculosis wild-type strain H37Rv and 141 clinical M. tuberculosis isolates. The results revealed that allele-specific RPA combined with SYBR Green I detection (AS-RPA/SYBR) detected these four major mutations with 100% sensitivity and specificity relative to DNA sequencing. The limits of detection for these particular mutations with AS-RPA/SYBR were 5 ng. As a result of the outstanding performance of AS-RPA/SYBR, including its easy setup, speed, lack of a specific instrument requirement, and lack of cross-reaction with other bacteria, this technique may be integrated for the molecular diagnosis of MDR-TB, especially in low-resource settings.

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PMID: 34115793

32. Significance of the coexistence of non-codon 315 katG, inhA, and oxyR-ahpC intergenic gene mutations among isoniazid-resistant and multidrug-resistant isolates of Mycobacterium tuberculosis: a report of novel mutations.

Pathog Glob Health. 2021 Jun 4:1-8. doi: 10.1080/20477724.2021.1928870. Online ahead of print.

Norouzi F(1), Moghim S(1), Farzaneh S(1), Fazeli H(1), Salehi M(2), Nasr Esfahani B(1).

Tuberculosis (TB) is a global threat due to the emergence and spread of drug-resistant Mycobacterium tuberculosis (MTB). Isoniazid (INH) is the main antibiotic used for prevention and treatment of TB. Evidence shows that accumulated mutations can produce INH resistant (INHR) strains, resulting in the progression of multidrug-resistant (MDR) TB. Since point mutations in katG gene, inhA gene, and oxyR-ahpC region correlated with the INH resistance, in this study, we aimed to identify mutations in these three genes in INHR and MDR clinical isolates of MTB by Sanger DNA sequencing analysis. Thirty-three out of 438 isolates were resistant, including 66.7% INHR and 30.3% MDR isolates. In the katG gene, 68.2% INHR isolates had non-synonymous point mutations, mainly R463L (63.6%), and non-synonymous point mutation KatG L587P was seen in one of the MDR isolate. A novel silent substitution L649L was identified in the inhA gene of the MDR isolates. The oxyR-ahpC intergenic region g-88a common mutations (63.6%) in INHR and two distinct novel mutations were found at positions -76 and -77 of the oxyR-ahpC intergenic region. The coexistence of katG non-codon 315 with oxyR-ahpC intergenic region mutations was highly frequent in INHR 59.1% and MDR isolates 70%. Since mutations of all three genes 95.5% lead to the detection of INHR, they might be useful for molecular detection. Our results indicated the continuous evolution and region-specific prevalence of INH resistance. Overall,

identification of new mutations in INH resistance can improve the available strategies for diagnosis and control of TB.

DOI: 10.1080/20477724.2021.1928870
PMID: 34086544

33. Microevolution of Mycobacterium tuberculosis Subpopulations and Heteroresistance in a Patient Receiving 27 Years of Tuberculosis Treatment in Germany.

Antimicrob Agents Chemother. 2021 Jun 17;65(7):e0252020. doi: 10.1128/AAC.02520-20. Epub 2021 Jun 17.

Sonnenkalb L(1), Strohe G(2), Dreyer V(1), Andres S(3), Hillemann D(3), Maurer FP(3)(4), Niemann S(#)(1)(5), Merker M(#)(1).

Preexisting and newly emerging resistant pathogen subpopulations (heteroresistance) are potential risk factors for treatment failure of multi/extensively drug resistant (MDR/XDR) tuberculosis (TB). Intrapatient evolutionary dynamics of Mycobacterium tuberculosis complex (Mtbc) strains and their implications on treatment outcomes are still not completely understood. To elucidate how Mtbc strains escape therapy, we analyzed 13 serial isolates from a German patient by whole-genome sequencing. Sequencing data were compared with phenotypic drug susceptibility profiles and the patient's collective 27-year treatment history to further elucidate factors fostering intrapatient resistance evolution. The patient endured five distinct TB episodes, ending in resistance to 16 drugs and a nearly untreatable XDR-TB infection. The first isolate obtained, during the patient's 5th TB episode, presented fixed resistance mutations to 7 anti-TB drugs, including isoniazid, rifampin, streptomycin, pyrazinamide, prothionamide, para-aminosalicylic acid, and cycloserine-terizidone. Over the next 13 years, a dynamic evolution with coexisting, heterogeneous subpopulations was observed in 6 out of 13 sequential bacterial isolates. The emergence of drug-resistant subpopulations coincided with frequent changes in treatment regimens, which often included two or fewer active compounds. This evolutionary arms race between competing subpopulations ultimately resulted in the fixation of a single XDR variant. Our data demonstrate the complex intrapatient microevolution of Mtbc subpopulations during failing MDR/XDR-TB treatment. Designing effective treatment regimens based on rapid detection of (hetero) resistance is key to avoid resistance development and treatment failure.

DOI: 10.1128/AAC.02520-20
PMID: 33903103

34. In vitro potency of 2-(((2-hydroxyphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione against drug-resistant and non-replicating persisters of Mycobacterium tuberculosis.

J Glob Antimicrob Resist. 2021 Jun;25:202-208. doi: 10.1016/j.jgar.2021.03.015. Epub 2021 Mar 28.

Rather MA(1), Bhat ZS(2), Lone AM(3), Maqbool M(1), Bhat BA(3), Ahmad Z(4).

OBJECTIVES: New antituberculosis agents active against drug-resistant and non-replicating tubercle bacilli are required. We evaluated a previously identified hit, 2-(((2-hydroxyphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (PAMCHD), against several clinical Mycobacterium tuberculosis isolates, including multidrug-resistant (MDR) strains and non-replicating drug-tolerant persisters of M. tuberculosis H37Rv.
METHODS: PAMCHD's potential against drug-resistant M. tuberculosis was investigated by broth microdilution. CFU enumeration was performed to determine PAMCHD's activity against five types of dormant bacilli.
RESULTS: No significant differences in MICs of PAMCHD were observed against M. tuberculosis H37Rv (2.5-5 μg/mL) and eight drug-susceptible strains (1.25-5 μg/mL) as well as drug-resistant strains including six isoniazid (INH)-resistant (2.5-10 μg/mL), one INH + ethambutol (EMB)-resistant (5 μg/mL), one rifampicin (RIF) + EMB-resistant (5 μg/mL) and three MDR (2.5-10 μg/mL) strains. Thus, PAMCHD maintains activity against all kinds of clinical strains, especially MDR. Regarding drug-tolerant persisters, INH and RIF killed, respectively, 0.5 and 5.0 log10 CFU of non-replicating persisters developed by hypoxia and 1.5 and 2.5 log10 CFU developed by nutrient starvation at 64 × of their respective MIC against actively dividing cultures. In contrast, PAMCHD sterilised persister cultures developed by hypoxia (killed 6.5 log10 CFU) or starvation (killed 7.5 log10 CFU). PAMCHD sterilised RIF-tolerant (tolerance level up to 100 μg/mL of RIF) 100-day-old static persisters at 64 × MIC, while moxifloxacin killed only 1.0 log10 CFU of these persisters at 64 × MIC.
CONCLUSION: PAMCHD offers significant potential against MDR-TB and exhibits notable potency against non-replicating drug-tolerant M. tuberculosis persisters. These findings warrant further studies of PAMCHD for further anti-TB drug development.

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DOI: 10.1016/j.jgar.2021.03.015
PMID: 33789204

35. In Silico Approach for Phytocompound-Based Drug Designing to Fight Efflux Pump-Mediated Multidrug-Resistant Mycobacterium tuberculosis.

Appl Biochem Biotechnol. 2021 Jun;193(6):1757-1779. doi: 10.1007/s12010-021-03557-1. Epub 2021 Apr 7.

Biswas SS(1), Browne RB(2), Borah VV(2), Roy JD(2).

Tuberculosis (TB), caused by the bacteria Mycobacterium tuberculosis, is one of the principal causes of death in the world despite the existence of a significant number of antibiotics aimed against it. This is mainly due to the drug resistance mechanisms present in the bacterium, which leads to multidrug-resistant tuberculosis (MDR-TB). Additionally, the development of new antibiotics has become limited over the years. Although there are various drug resistance mechanisms present, efflux pumps are of utmost importance because they extrude out several dissimilar antitubercular drugs out of the cell. There are many efflux pump proteins present in Mycobacterium tuberculosis. Therefore, blocking these efflux pumps by inhibitors can raise the efficacy of the existing antibiotics and may also pave the path for the discovery and synthesis of new drugs. Plant compounds can act as a resource for the development of efflux pump inhibitors (EPIs), which may eventually replace or augment the current therapeutic options. This is mainly because plants have been traditionally used for ages for food or treatment and are considered safe with little or no side effects. Various computational tools are available which are used for the virtual screening of a large number of phytocompounds within a short span of time. This review aims to highlight the mechanism and appearance of drug resistance in Mycobacterium tuberculosis with emphasis on efflux pumps along with the significance of phytochemicals as inhibitors of these pumps and their screening strategy by computational approaches.

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PMCID: PMC8024441
PMID: 33826064

36. Acceptability of the Medication Event Reminder Monitor for Promoting Adherence to Multidrug-Resistant Tuberculosis Therapy in Two Indian Cities: Qualitative Study of Patients and Health Care Providers.

J Med Internet Res. 2021 Jun 10;23(6):e23294. doi: 10.2196/23294.

Thomas BE(#)(1), Kumar JV(1), Periyasamy M(1), Khandewale AS(1), Hephzibah Mercy J(1), Raj EM(1), Kokila S(1), Walgude AS(1), Gaurkhede GR(1), Kumbhar JD(1),

Ovung S(1), Paul M(1), Rajkumar BS(1), Subbaraman R(#)(2)(3)(4).

BACKGROUND: Patients with multidrug-resistant tuberculosis (MDR-TB) face challenges adhering to medications, given that treatment is prolonged and has a high rate of adverse effects. The Medication Event Reminder Monitor (MERM) is a digital pillbox that provides pill-taking reminders and facilitates the remote monitoring of medication adherence.
OBJECTIVE: This study aims to assess the MERM's acceptability to patients and health care providers (HCPs) during pilot implementation in India's public sector MDR-TB program.
METHODS: From October 2017 to September 2018, we conducted qualitative interviews with patients who were undergoing MDR-TB therapy and were being monitored with the MERM and HCPs in the government program in Chennai and Mumbai. Interview transcripts were independently coded by 2 researchers and analyzed to identify the emergent themes. We organized findings by using the Unified Theory of Acceptance and Use of Technology (UTAUT), which outlines 4 constructs that predict technology acceptance-performance expectancy, effort expectancy, social influence, and facilitating conditions.
RESULTS: We interviewed 65 patients with MDR-TB and 10 HCPs. In patient interviews, greater acceptance of the MERM was related to perceptions that the audible and visual reminders improved medication adherence and that remote monitoring reduced the frequency of clinic visits (performance expectancy), that the device's organization and labeling of medications made it easier to take them correctly (effort expectancy), that the device facilitated positive family involvement in the patient's care (social influences), and that remote monitoring made patients feel more cared for by the health system (facilitating conditions). Lower patient acceptance was related to problems with the durability of the MERM's cardboard construction and difficulties with portability and storage because of its large size (effort expectancy), concerns regarding stigma and the disclosure of patients' MDR-TB diagnoses (social influences), and the incorrect understanding of the MERM because of suboptimal counseling (facilitating conditions). In their interviews, HCPs reported that MERM implementation resulted in fewer in-person interactions with patients and thus allowed HCPs to dedicate more time to other tasks, which improved job satisfaction.
CONCLUSIONS: Several features of the MERM support its acceptability among patients with MDR-TB and HCPs, and some barriers to patient use could be addressed by improving the design of the device. However, some barriers, such as disease-related stigma, are more difficult to modify and may limit use of the MERM among some patients with MDR-TB. Further research is needed to assess the accuracy of MERM for measuring adherence, its effectiveness for improving treatment outcomes, and patients' sustained use of the device in larger scale implementation.

©Beena E Thomas, J Vignesh Kumar, Murugesan Periyasamy, Amit Subhash Khandewale, J Hephzibah Mercy, E Michael Raj, S Kokila, Apurva Shashikant Walgude, Gunjan Rahul Gaurkhede, Jagannath Dattatraya Kumbhar, Senthanro Ovung, Mariyamma Paul, B Sathyan Rajkumar, Ramnath Subbaraman. Originally published in the Journal of Medical Internet Research (https://www.jmir.org), 10.06.2021.

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PMID: 34110300

37. Situational analysis of the 10 high drug resistant tuberculosis burden countries two years post-UNHLM declaration: progress and setbacks in a changing landscape.

Int J Infect Dis. 2021 Jun 14:S1201-9712(21)00511-7. doi: 10.1016/j.ijid.2021.06.022. Online ahead of print.

Monedero-Recuero I(1), Gegia M(2), Wares DF(3), S Chadha S(4), Mirzayev F(4).

OBJECTIVES: Drug-resistant tuberculosis (DR-TB) is the leading cause of death globally related to antimicrobial resistance, affecting 500,000 emergent cases annually. In 2018, the first United Nations high level meeting (UNHLM) on tuberculosis, declared DR-TB a global public health priority. Bold country targets were established for 2018-2022. This study reviews the DR-TB situation in 2018 and the UNHLM targets accomplishments in the 10 world high burden countries (HBCs).
METHODS: Ecological descriptive analysis of the 10 DR-TB HBCs (Bangladesh, China, India, Indonesia, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, and South Africa) that share 70% of the global DR-TB burden; complemented by a cascade of care analysis and a survey gathering additional information on key advances and setbacks 2 years post the UNHLM declaration.
RESULTS: Most countries are showing historical advances and being on track for the 2018 and 2019 targets. However, according to the cascade of care, no country is capable of providing effective care for 50% of the estimated patients. Increasing levels of fluoroquinolone resistance and access to timely susceptibility testing can jeopardize ongoing adoption of shorter, all-oral treatment regimens. The programmatic management of DR-TB in children remains minimal. Achievements for 2020 and beyond might be significantly affected by the COVID-19 pandemic.
CONCLUSION: Triggered by the COVID-19 pandemic, there is a global risk of recoil in DR-TB care with long-term consequences in terms of deaths, suffering and wider antimicrobial resistant transmission. Investment to support DR-TB services is more important now than ever to meet the aspirations of the UNHLM declaration.

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PMID: 34139370

38. Population Pharmacokinetics and Bayesian Dose Adjustment to Advance TDM of Anti-TB Drugs.

Clin Pharmacokinet. 2021 Jun;60(6):685-710. doi: 10.1007/s40262-021-00997-0. Epub 2021 Mar 6.

Sturkenboom MGG(1), Märtson AG(1), Svensson EM(2)(3), Sloan DJ(4)(5)(6), Dooley KE(7), van den Elsen SHJ(1)(8), Denti P(9), Peloquin CA(10), Aarnoutse RE(3), Alffenaar JC(11)(12)(13)(14).

Tuberculosis (TB) is still the number one cause of death due to an infectious disease. Pharmacokinetics and pharmacodynamics of anti-TB drugs are key in the optimization of TB treatment and help to prevent slow response to treatment, acquired drug resistance, and adverse drug effects. The aim of this review was to provide an update on the pharmacokinetics and pharmacodynamics of anti-TB drugs and to show how population pharmacokinetics and Bayesian dose adjustment can be used to optimize treatment. We cover aspects on preclinical, clinical, and population pharmacokinetics of different drugs used for drug-susceptible TB and multidrug-resistant TB. Moreover, we include available data to support therapeutic drug monitoring of these drugs and known pharmacokinetic and pharmacodynamic targets that can be used for optimization of therapy. We have identified a wide range of population pharmacokinetic models for first- and second-line drugs used for TB, which included models built on NONMEM, Pmetrics, ADAPT, MWPharm, Monolix, Phoenix, and NPEM2 software. The first population models were built for isoniazid and rifampicin; however, in recent years, more data have emerged for both new anti-TB drugs, but also for defining targets of older anti-TB drugs. Since the introduction of therapeutic drug monitoring for TB over 3 decades ago, further development of therapeutic drug monitoring in TB next steps will again depend on academic and clinical initiatives. We recommend close collaboration between researchers and the World Health Organization to provide important guideline updates regarding therapeutic drug monitoring and pharmacokinetics/pharmacodynamics.

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PMCID: PMC7935699
PMID: 33674941

39. Trends of Drug Resistance Tuberculosis from 2014 to 2018, Bale Zone, Oromia Region, Ethiopia.

Infect Drug Resist. 2021 Jun 3;14:2073-2078. doi: 10.2147/IDR.S300723.
eCollection 2021.

Bedaso MH(1), Kalil FS(2).

PURPOSE: Multidrug-resistant tuberculosis threatens global tuberculosis care and prevention and remains a major public health concern in many countries. In 2016, there were an estimated 490,000 cases of MDR and 110,000 more cases resistant to rifampicin (RR TB). Ethiopia is among the highest MDR TB burden countries according to the WHO. This study aims to describe the magnitude, trends, and geographical distribution of the drug-resistant TB in Bale Zone during study period.
MATERIALS AND METHODS: A descriptive study was conducted. We reviewed secondary data of MDR and RR TB cases from July 2014 to June 2018. Data were extracted from the Bale zone health management information system database, checked for completeness, and then analyzed for trends over time.
RESULTS: A total of 43 cases (67.4% female) of drug-resistant TB were reviewed, with 30.2% MDR and 69.8% RR TB. The prevalence of drug-resistant tuberculosis cases declined from 0.81% to 0.62% (trend χ 2=2.18; P=0.14) during study period. Among drug-resistant TB cases, RR TB increased from 52.6% to 81% (trend χ 2=6.5; P=0.01).
CONCLUSION: Drug-resistant TB decreased over the period studied, although the trend did not reach statistical significance. These trends may reflect the efficacy of TB control programs to reduce drug-resistant TB transmission, as well as improved RR TB detection due to increased use of molecular diagnostic platforms like GeneXpert MTB/RIF.

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PMCID: PMC8184147
PMID: 34113133

40. Treatment Interruption Among Drug-Susceptible Pulmonary Tuberculosis Patients in Southern Ethiopia.

Patient Prefer Adherence. 2021 May 26;15:1143-1151. doi: 10.2147/PPA.S307091.
eCollection 2021.

Workie MG(1), Aycheh MW(2), Birhanu MY(2), Tsegaye TB(2).

BACKGROUND: Tuberculosis treatment interruption is a failure of attending two scheduled appointments to collect the drugs in either phase of tuberculosis treatment. Even if TB treatment is crucial to achieve a cure and avoid the emergence of drug resistance, treatment interruption is the most testing and deterring factor for successful tuberculosis treatment and one of the problems leading to the development of drug-resistant tuberculosis. TB treatment interruption is the precursor for loss to follow-up and treatment failure, but the magnitude of this problem is unknown in Ethiopia. Thus, this study was intended to identify determinants of treatment interruption among drug-susceptible pulmonary tuberculosis patients in South Ari district, Southern Ethiopia.
METHODS: An institution-based unmatched case control study was conducted from February through April 2020 using 255 samples with a ratio of 2:1 (controls to cases). Data were entered into Epi data version 4.2 and exported for analysis using STATA 14.0 statistical software. The variables having a p-value of less than 0.25 in the bivariable analysis were subjected to multivariable logistic regression analysis. In multivariable logistic regression analysis, AORs, 95% CIs, and p-values of <0.05 were used to identify significant variables.
RESULTS: The median age was 34 (IQR: 18) years in cases and 29 (IQR: 16) years in control groups. Significant factors that were associated with treatment interruption were alcohol consumption (AOR = 2.99, 95% CI; 1.41-6.36); smoking habits (AOR = 2.82, 95% CI; 1.14-6.94); use of traditional medicine (AOR = 2.35, 95% CI 1.05-5.24); co-infected with HIV (AOR=1.58, 95% CI; 1.85-4.29), and waiting time at the health facility ≥30 minutes (AOR = 2.98, 95% CI; 1.31-6.80).
CONCLUSION: Alcohol consumption, waiting time at the health facility ≥30 minutes, smoking habits, used traditional medicine, and HIV co-infected were potential determinants. Enhancing public health education, designing strategies that emphasize patients with HIV co-infection, and reducing waiting times are recommended.

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PMID: 34079235

41. 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.

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PMID: 34039674

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

mSphere. 2021 May 28:e0024521. doi: 10.1128/mSphere.00245-21. Online ahead of print.

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

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

Biopharm Drug Dispos. 2021 Jun 11. doi: 10.1002/bdd.2294. Online ahead of print.

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.

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PMID: 34117648

44. Comprehensive review on mechanism of action, resistance and evolution of antimycobacterial drugs.

Life Sci. 2021 Jun 1;274:119301. doi: 10.1016/j.lfs.2021.119301. Epub 2021 Mar 3.

Chauhan A(1), Kumar M(2), Kumar A(3), Kanchan K(4).

Tuberculosis is one of the deadliest infectious diseases existing in the world since ancient times and still possesses serious threat across the globe. Each

year the number of cases increases due to high drug resistance shown by Mycobacterium tuberculosis (Mtb). Available antimycobacterial drugs have been classified as First line, Second line and Third line antibiotics depending on the time of their discoveries and their effectiveness in the treatment. These antibiotics have a broad range of targets ranging from cell wall to metabolic processes and their non-judicious and uncontrolled usage in the treatment for years has created a significant problem called multi-drug resistant (MDR) tuberculosis. In this review, we have summarized the mechanism of action of all the classified antibiotics currently in use along with the resistance mechanisms acquired by Mtb. We have focused on the new drug candidates/repurposed drugs, and drug in combinations, which are in clinical trials for either treating the MDR tuberculosis more effectively or involved in reducing the time required for the chemotherapy of drug sensitive TB. This information is not discussed very adequately on a single platform. Additionally, we have discussed the recent technologies that are being used to discover novel resistance mechanisms acquired by Mtb and for exploring novel drugs. The story of intrinsic resistance mechanisms and evolution in Mtb is far from complete. Therefore, we have also discussed intrinsic resistance mechanisms of Mtb and their evolution with time, emphasizing the hope for the development of novel antimycobacterial drugs for effective therapy of tuberculosis.

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

Nat Med. 2021 May 24. doi: 10.1038/s41591-021-01358-x. Online ahead of print.

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

46. Monocarbonyl curcuminoids as antituberculosis agents with their moderate in-vitro metabolic stability on human liver microsomes.

J Biochem Mol Toxicol. 2021 Jun;35(6):1-10. doi: 10.1002/jbt.22754. Epub 2021 Mar 10.

Gagandeep(1), Singh M(2), Kidawi S(2), Das US(3), Velpandian T(3), Singh R(2), Rawat DS(1).

Tuberculosis, an airborne infectious disease, results in a high morbidity and mortality rate. The continuous emergence of TB resistance strains including MDR (multidrug-resistant tuberculosis), XDR (extensive drug-resistant tuberculosis), and especially TDR (totally drug-resistant tuberculosis) is a major public health threat and has intensified the need to develop new antitubercular agents. A natural product, curcumin, possesses diverse biological activities but suffers due to a lack of water solubility and bioavailability. To overcome these limitations, a series of 17 water-soluble monocarbonyl curcuminoids was synthesized and evaluated for antimycobacterial activity. All compounds exhibited good to moderate anti-TB activity with MIC99 in the range of 3.12-25.0 µM, out of which 7c and 7p were found the most potent compounds with MIC99 in the range of 3.12-6.25 µM. Furthermore, these compounds were observed to be nonhaemolytic, nontoxic, and stable under both physiological as well as reducing conditions. In-vitro metabolic stability data of the representative compound 7p with the human liver microsome revealed that these compounds possess a moderate metabolism with a half-life of 1.2 h and an intrinsic clearance of 1.12 ml/h/mg.

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DOI: 10.1002/jbt.22754
PMID: 33751730

47. The Tuberculosis-Depression Syndemic and Evolution of Pharmaceutical Therapeutics: From Ancient Times to the Future.

Front Psychiatry. 2021 Jun 1;12:617751. doi: 10.3389/fpsyt.2021.617751. eCollection 2021.

Van Der Walt M(1), Keddy KH(1).

The interplay between tuberculosis and depression has been problematic since the humoralists. Over the centuries similarities in disease management have transpired. With the advent of isoniazid chemotherapy, transformation of tuberculosis patients from morbidly depressive to euphoric was noted. Isoniazid was thereafter widely prescribed for depression: hepatotoxicity ending its use as an antidepressant in 1961. Isoniazid monotherapy led to the emergence of drug resistant tuberculosis, stimulating new drug development. Vastly increased investment into antidepressants ensued thereafter while investment in new drugs for tuberculosis lagged. In the 21st century, both diseases independently contribute significantly to global disease burdens: renewed convergence and the resultant syndemic is detrimental to both patient groups. Ending the global tuberculosis epidemic and decreasing the burden of depression and will require multidisciplinary, patient-centered approaches that consider this combined co-morbidity. The emerging era of big data for health, digital interventions and novel and repurposed compounds promise new ways to treat both diseases and manage the syndemic, but absence of clinical structures to support these innovations may derail the treatment programs for both. New policies are urgently required optimizing use of the current advances in healthcare available in the digital era, to ensure that patient-centered care takes cognizance of both diseases.

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DOI: 10.3389/fpsyt.2021.617751
PMCID: PMC8203803
PMID: 34140898

48. Tuberculosis of the spine in children - Does drug resistance affect surgical outcomes?

Spine J. 2021 Jun 8:S1529-9430(21)00722-1. doi: 10.1016/j.spinee.2021.06.001. Online ahead of print.

Pinto D(1), Dhawale DA(2), Shah I(3), Rokade S(4), Shah A(5), Chaudhary K(6),

Aroojis A(7), Mehta R(8), Nene A(9).

BACKGROUND CONTEXT: The emergence of drug resistance has complicated the management of spinal tuberculosis (TB). While it is well known that the medical management of drug-resistant spinal TB is more difficult, the surgical outcomes of the same have not been studied sufficiently, particularly in children.
PURPOSE: To analyze the surgical outcomes in a cohort of children treated for spinal TB, and to thus assess whether drug resistant (DR) disease is associated with poorer surgical outcomes.
STUDY DESIGN/SETTING: Retrospective observational study.
PATIENT SAMPLE: All children diagnosed and treated for tuberculous spondylodiscitis at a single center between January 2014 and June 2017.
OUTCOME MEASURES: Surgical outcomes in terms of neurological status and kyphosis angle at final follow-up, and complication rates.
METHODS: Radiographic and clinical data of children treated for spinal TB with minimum two-year follow-up were retrospectively analyzed. Data gathered included age, gender, level of spine affected, number of vertebrae involved, neurology (Frankel grade), microbiological reports, duration and type of anti-tuberculous therapy (ATT), details of Orthopaedic management and complications during treatment. In DR cases, the time from presentation to starting of second-line ATT was also assessed. Radiographs were reviewed to note the pre- and post-operative degree of kyphosis as well as the angle at final follow-up. Patients that developed major complications were compared statistically with those that did not.
RESULTS: Forty-one consecutive children (mean age 8.5±4.2 years, 20 boys, 21 girls) were treated for spinal TB with a mean follow-up of 31.2±6.4 months. Fifteen were managed conservatively, of which only one had DR-TB. Of the 26 managed surgically, 13 were managed with first-line ATT and 13 required second-line ATT. Of this latter group, eight had microbiologically proven drug resistance, whereas five were switched to second-line therapy presumptively because of failure to show an adequate response to first-line regimen. At last follow-up, all children had completed the prescribed course of ATT and had been declared cured. Neurological improvement was seen in all but one patient; and at last follow-up, 18 children were Frankel E, seven were Frankel D, and one was Frankel B. The immediate post-operative Kyphosis angle averaged 24.38° ± 15.21°. However, six children showed a subsequent worsening of kyphosis, and the Kyphosis angle at last follow-up averaged 30.96° ± 23.92°. Five children had major complications requiring revision surgery; complications included wound dehiscence, vertebral collapse, screw pull-out and implant breakage. Significantly higher number of patients in the group with complications had required second-line ATT ($p<0.05$).
CONCLUSIONS: In a cohort of children treated surgically for spinal tuberculosis, a higher complication rate, and thus poor surgical outcomes, were found to be associated with drug resistant disease.

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DOI: 10.1016/j.spinee.2021.06.001
PMID: 34116216

49. Assessment of the GenoType MTBDRsl VER 2.0 compared to the phenotypic drug susceptibility testing and whole genome sequencing for the rapid detection of resistance to fluoroquinolone and second-line injectable drugs among rifampicin-resistant Mycobacterium tuberculosis isolates.

Arch Microbiol. 2021 May 25. doi: 10.1007/s00203-021-02387-3. Online ahead of print.

Kardan-Yamchi J(1)(2), Amini S(3), Hamzelou G(3), Rahimi Foroushani A(4), Ghodousi A(5), Cirillo DM(5), Feizabadi MM(6)(7).

Molecular techniques have considerable advantages for rapid detection, a reduction of infectiousness, prevention of further resistance development and surveillance of drug-resistant TB. MTBDRsl VER 2.0 was used to detect resistance to second-line anti-tuberculosis drugs on 35 rifampicin-resistant M. tuberculosis (RR-MTB) isolates compared to the minimum inhibitory concentrations (MICs) and whole genome sequencing (WGS). The MTBDRsl VER 2.0 (Hain Life Science, Nehren, Germany) and WGS (San Diego, CA, USA) were performed for tracing mutations in resistant-related genes involved in resistance to fluoroquinolone (FLQ) and second-line injectable drugs. The broth microdilution method using 7H9 Middlebrook media supplemented with OADC was used to determine the MICs. The MTBDRsl VER 2.0 correctly detected 5/6 (83.3%) of FLQ-resistant strains. The MUT1 A1401G (seven strains) and MUT2 G1484T (one strain) mutations in rrs gene were detected in eight AMK/KAN/CAP-resistant strains. Four low-level KAN-resistant strains with the G-10A/C-12T (three strains) and eis C-14T (one strain) mutations in eis gene was diagnosed using MTBDRsl VER 2.0. Five errors were found in detecting resistance to kanamycin and capreomycin compared to the phenotypic drug susceptibility testing and WGS. Failling wild-type bands without improved mutant bands did not indicate a reliable resistance. WGS could efficiently resolve the discrepancies of the results. MTBDRsl showed better performance in detecting XDR strains than pre-XDR.

DOI: 10.1007/s00203-021-02387-3
PMID: 34032874

50. Discontinuation of tuberculosis treatment among children in the Kampala Capital

City Authority health facilities: a mixed-methods study.

BMC Infect Dis. 2021 Jun 1;21(1):511. doi: 10.1186/s12879-021-06244-y.

Kibirige L(1), Izudi J(1)(2), Okoboi S(3)(4).

INTRODUCTION: Discontinuation of tuberculosis treatment (DTT) among children in sub-Saharan Africa is a major obstacle to effective tuberculosis (TB) control and has the potential to worsen the emergence of multi-drug resistant TB and death. DTT in children is understudied in Uganda. We examined the level and factors associated with DTT among children at four large health facilities in Kampala Capital City Authority and documented the reasons for DTT from treatment supporters and healthcare provider perspectives.
METHODS: We conducted a retrospective analysis of records for children < 15 years diagnosed and treated for TB between January 2018 and December 2019. We held focus group discussions with treatment supporters and key informant interviews with healthcare providers. We defined DTT as the stoppage of TB treatment for 30 or more consecutive days. We used a stepwise generalized linear model to assess factors independently associated with DTT and content analysis for the qualitative data reported using sub-themes.
RESULTS: Of 312 participants enrolled, 35 (11.2%) had discontinued TB treatment. The reasons for DTT included lack of privacy at healthcare facilities for children with TB and their treatment supporters, the disappearance of TB symptoms following treatment initiation, poor implementation of the community-based directly observed therapy short-course (CB-DOTS) strategy, insufficient funding to the TB program, and frequent stock-outs of TB drugs. DTT was more likely during the continuation phase of TB treatment compared to the intensive phase (Adjusted odds ratio (aOR), 5.22; 95% Confidence Interval (CI), 1.76-17.52) and when the treatment supporter was employed compared to when the treatment supporter was unemployed (aOR, 3.60; 95% CI, 1.34-11.38).
CONCLUSION: Many children with TB discontinue TB treatment and this might exacerbate TB morbidity and mortality. To mitigate DTT, healthcare providers should ensure children with TB and their treatment supporters are accorded privacy during service provision and provide more information about TB symptom resolution and treatment duration versus the need to complete treatment. The district and national TB control programs should address gaps in funding to TB care, the supply of TB drugs, and the implementation of the CB-DOTS strategy.

DOI: 10.1186/s12879-021-06244-y
PMCID: PMC8167996
PMID: 34074268 [Indexed for MEDLINE]

51. The impact of immigration on tuberculosis and HIV burden between Colombia and

Venezuela and across frontier regions.

Cad Saude Publica. 2021 May 28;37(5):e00078820. doi: 10.1590/0102-311X00078820. eCollection 2021.

Arenas-Suarez NE(1)(2), Cuervo LI(1), Avila EF(2), Duitama-Leal A(3), Pineda-Peña AC(4)(5).

Historically, human migrations have determined the spread of many infectious diseases by promoting the emergence of temporal outbreaks between populations. We aimed to analyze health indicators, expenditure, and disability caused by tuberculosis (TB) and HIV/AIDS burden under the Colombian-Venezuelan migration flow focusing on the Northeastern border. A retrospective study was conducted using TB and HIV/AIDS data since 2009. We consolidated a database using official reports from the Colombian Surveillance System, World Health Organization, Indexmundi, the Global Health Observatory, IHME HIV atlas, and Joint United Nations Programme on HIV/AIDS (UNAIDS). Disability metrics regarding DALYs (disability adjusted life years) and YLDs (years lived with disability), were compared between countries. Mapping was performed on ArcGIS using official migration data of Venezuelan citizens. Our results indicate that TB profiles from Colombia and Venezuela are identical in terms of disease burden, except for an increase in TB incidence in the Colombian-Venezuelan border departments in recent years, concomitantly with the massive Venezuelan immigration since 2005. We identified a four-fold underfunding for the TB program in Venezuela, which might explain the low-testing rates for cases of multidrug-resistant TB (67%) and HIV/AIDS (60%), as well as extended hospital stays (150 days). We found a significant increase in DALYs of HIV/AIDS patients in Venezuela, specifically, 362.35 compared to 265.37 observed in Colombia during 2017. This study suggests that the Venezuelan massive migration and program underfunding might exacerbate the dual burden of TB and HIV in Colombia, especially towards the Colombian-Venezuelan border.

DOI: 10.1590/0102-311X00078820
PMID: 34076096 [Indexed for MEDLINE]

52. An Automated Approach to Differentiate Drug Resistant Tuberculosis in Chest X-ray Images Using Projection Profiling and Mediastinal Features.

Stud Health Technol Inform. 2021 May 27;281:512-513. doi: 10.3233/SHTI210220.

Tulo SK(1), Ramu P(2), Swaminathan R(1).

In this study, an attempt has been made to differentiate Drug Resistant

Tuberculosis (DR-TB) in chest X-rays using projection profiling and mediastinal features. DR-TB is a condition which is non-responsive to at least one of anti-TB drugs. Mediastinum variations can be considered as significant image biomarkers for detection of DR-TB. Images are obtained from a public database and are contrast enhanced using coherence filtering. Projection profiling is used to obtain the feature lines from which the mediastinal and thoracic indices are computed. Classification of Drug Sensitive (DS-TB) and DR-TB is performed using three classifiers. Results show that the mediastinal features are found to be statistically significant. Support vector machine with quadratic kernel is able to provide better classification performance values of greater than 93%. Hence, the automated analysis of mediastinum could be clinically significant in differentiation of DR-TB.

DOI: 10.3233/SHTI210220
PMID: 34042626 [Indexed for MEDLINE]

53. Nanoparticle-mediated macrophage targeting-a new inhalation therapy tackling tuberculosis.

Drug Deliv Transl Res. 2021 Jun;11(3):1037-1055. doi: 10.1007/s13346-020-00815-3.

Makled S(1), Boraie N(1), Nafee N(2)(3).

Despite the potent clinical efficacy of linezolid (LNZ) against drug-resistant tuberculosis, its safety and tolerability remain of major concern. Our objective is to develop antitubercular inhalable LNZ nano-embedded microparticles. In this context, LNZ incorporated in non-structured lipid carriers (NLCs) was characterized in terms of colloidal, morphological, thermal, and release profiles. The potential of LNZ-NLCs to cross mucosal barriers and invade alveolar macrophages (AM, MH-S cells) was appraised. In vivo proof of concept was accomplished via orotracheal administration to mice. Respirable microparticles prepared by spray drying NLCs with diluents were assessed for their size, shape, flowability, aerosolization performance, and lung deposition pattern. NLCs (809-827 nm in size, zeta potential - 37.4 to - 58.9 mV) ensued 19% LNZ loading and pH-independent sustained release. Penetration studies revealed 73% LNZ crossing mucus within 1 h. Meanwhile, viability assay on A549 cells ensured an IC50 of 1.2 and 0.32 mg/mL for plain and LNZ-NLCs, respectively. CLSM confirmed phagocytosis of NLCs by MH-S macrophages, while H&E staining demonstrated NLC accumulation in murine AM in vivo with no signs of histopathological/biochemical changes. Bronchoalveolar lavage showed significantly low levels of LDH and total proteins (TP) for LNZ-NLCs highlighting their superior safety. Respirable microparticles embedding LNZ-NLCs

ensured excellent aerosolization (MMAD 2 µm, FPF 93%) denoting perfect alveolar deposition. The developed inhalation therapy provided sustained LNZ release, mucus penetrability, potential safety in therapeutic doses, in vitro and in vivo macrophage targetability, and preferential deposition in the deep lung. Overall positive outcomes rely on reduced dose, dosing frequency, and per se superior safety circumventing systemic-associated life-threatening side effects.
Graphical abstract.

DOI: 10.1007/s13346-020-00815-3
PMID: 32617866

54. Performance of the MeltPro MTB Assays in the Diagnosis of Drug-Resistant Tuberculosis Using Formalin-Fixed, Paraffin-Embedded Tissues.

Am J Clin Pathol. 2021 Jun 17;156(1):34-41. doi: 10.1093/ajcp/aqaa203.

Mu J(1)(2), Liu Z(2), Zhang C(2), Wang C(2), Du W(2), Lin H(2), Li K(2), Song J(2), Che N(2), Liu H(1).

OBJECTIVES: The MeltPro MTB assays for detection of resistance to antituberculosis (TB) drugs perform well in genotypic drug susceptibility testing (DST) of clinical samples, but their effectiveness with formalin-fixed, paraffin-embedded (FFPE) tissues is unknown.
METHODS: FFPE tissues were obtained from 334 patients with TB. Susceptibility to rifampicin (RIF), isoniazid (INH), and fluoroquinolones was examined using the MeltPro MTB assays, with Xpert MTB/RIF (Xpert) and/or phenotypic DST (pDST) results as references. Samples with discordant results were analyzed by multiplex polymerase chain reaction-targeted amplicon sequencing (MTA-seq).
RESULTS: With pDST as the reference, the MeltPro MTB assays sensitivity for RIF, INH, levofloxacin (LVX), and moxifloxacin (MXF) was 95.00%, 96.00%, 100%, and 100%, respectively, and the specificity was 95.15%, 95.92%, 94.69%, and 89.92%, respectively. Concordance was 99.08% between the MeltPro MTB and Xpert (κ = 0.956) for RIF and 95.12% (κ = 0.834), 95.93% (κ = 0.880), 95.12% (κ = 0.744), and 90.24% (κ = 0.367) between the MeltPro MTB and pDST for RIF, INH, LVX, and MXF, respectively. MTA-seq confirmed the discordancy between the MeltPro MTB and pDST for 26 (89.66%) of 29 samples.
CONCLUSIONS: The MeltPro MTB assays rapidly and efficiently predict Mycobacterium tuberculosis resistance to the main first- and second-line anti-TB drugs in FFPE tissues.

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DOI: 10.1093/ajcp/aqaa203
PMID: 33438007

55. Isoniazid-monoresistant tuberculosis in France: Risk factors, treatment outcomes and adverse events.

Int J Infect Dis. 2021 Jun;107:86-91. doi: 10.1016/j.ijid.2021.03.093. Epub 2021 Apr 3.

Bachir M(1), Guglielmetti L(2), Tunesi S(3), Billard-Pomares T(4), Chiesi S(5), Jaffré J(6), Langris H(7), Pourcher V(8), Schramm F(9), Lemaître N(10), Robert J(2); Isoniazid Resistance Group.

OBJECTIVES: Isoniazid-monoresistant tuberculosis (HR-TB) is the most prevalent form of drug-resistant TB worldwide and in France and is associated with poorer treatment outcomes compared with drug-susceptible TB (DS-TB). The objective of this study was to determine the characteristics of HR-TB patients in France and to compare outcomes and safety of treatment for HR-TB and DS-TB.
METHODS: We performed a case-control multicenter study to identify risk factors associated with HR-TB and compare treatment outcomes and safety between HR-TB patients and DS-TB patients.
RESULTS: Characteristics of 99 HR-TB patients diagnosed and treated in the university hospitals of Paris, Lille, Caen and Strasbourg were compared with 99 DS-TB patients. Female sex (OR = 2.2; 1.0-4.7), birth in the West-Pacific World Health Organization region (OR = 4.6; 1.1-18.7) and resistance to streptomycin (OR = 77.5; 10.1-594.4) were found to be independently associated with HR-TB. Rates of treatment success did not differ significantly between HR-TB and DS-TB.
CONCLUSIONS: Factors associated with HR-TB are not significant enough to efficiently screen TB patients at risk of HR-TB. The systematic implementation of rapid molecular testing on clinical samples remains the only effective way to make the early diagnosis of HR-TB and adapt treatment.

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DOI: 10.1016/j.ijid.2021.03.093
PMID: 33823278

56. The burden of drug resistance tuberculosis in Ghana; results of the First National Survey.

PLoS One. 2021 Jun 10;16(6):e0252819. doi: 10.1371/journal.pone.0252819. eCollection 2021.

Sylverken AA(1)(2), Kwarteng A(2)(3), Twumasi-Ankrah S(2)(4), Owusu M(5), Arthur RA(2), Dumevi RM(2), Adu-Amoah L(2), Addofoh N(2), Okyere PB(2), Dzata F(6), Bonsu F(6), Adusi-Poku Y(6), Kranzer K(7), Siroka A(8), Gemert WV(8), Dean A(8), Owusu-Dabo E(2)(9).

Resistance to Tuberculosis drugs has become a major threat to the control of tuberculosis (TB) globally. We conducted the first nation-wide drug resistance survey to investigate the level and pattern of resistance to first-line TB drugs among newly and previously treated sputum smear-positive TB cases. We also evaluated associations between potential risk factors and TB drug resistance. Using the World Health Organization (WHO) guidelines on conducting national TB surveys, we selected study participants from 33 health facilities from across the country, grouped into 29 clusters, and included them into the survey. Between April 2016 and June 2017, a total of 927 patients (859 new and 68 previously treated) were enrolled in the survey. Mycobacterium tuberculosis complex (MTBC) isolates were successfully cultured from 598 (65.5%) patient samples and underwent DST, 550 from newly diagnosed and 48 from previously treated patients. The proportion of patients who showed resistance to any of the TB drugs tested was 25.2% (95% CI; 21.8-28.9). The most frequent resistance was to Streptomycin (STR) (12.3%), followed by Isoniazid (INH) (10.4%), with Rifampicin (RIF), showing the least resistance of 2.4%. Resistance to Isoniazid and Rifampicin (multi-drug resistance) was found in 19 (3.2%; 95% CI: 1.9-4.9) isolates. Prevalence of multidrug resistance was 7 (1.3%; 95% CI: 0.5-2.6) among newly diagnosed and 12 (25.0%; 95% CI: 13.6-39.6) among previously treated patients. At both univariate and multivariate analysis, MDR-TB was positively associated with previous history of TB treatment (OR = 5.09, 95% CI: 1.75-14.75, p = 0.003); (OR = 5.41, 95% CI: 1.69-17.30, p = 0.004). The higher levels of MDR-TB and overall resistance to any TB drug among previously treated patients raises concerns about adherence to treatment. This calls for strengthening existing TB programme measures to ensure a system for adequately testing and monitoring TB drug resistance.

DOI: 10.1371/journal.pone.0252819
PMCID: PMC8191906
PMID: 34111159

57. Clinical implications of high-risk mutations in drug resistant tuberculosis (DR-TB): An observational cohort study.

Indian J Med Microbiol. 2021 Jun 11:S0255-0857(21)04122-0. doi: 10.1016/j.ijmmb.2021.05.020. Online ahead of print.

Thampy A(1), Ninan MM(2), Michael JS(3), James P(4), Rupali P(5).

Genotype MTBDRsl [SL-LPA] was endorsed as a tool for early diagnosis of fluoroquinolones (FQ) and injectable second-line TB drugs (SLID) resistance in DR-TB. Correlation between specific genetic mutations using this tool and clinical outcome has not hitherto been studied in India. We conducted a observational cohort study to evaluate the predictive value of specific mutations for bad outcome. Our study identified 15 different types of gyrA mutations, commonest being A90V and D94G. Poor outcome was associated with mutations D94G and D94N/D94Y.Most XDR-TB patients harbored the high risk mutation of A1401G. Hence information of specific mutations using SL-LPA can help prognosticate and design appropriate treatment regimens.

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DOI: 10.1016/j.ijmmb.2021.05.020
PMID: 34127320

58. All-oral longer regimens are effective for the management of multidrug resistant tuberculosis in high burden settings.

Eur Respir J. 2021 Jun 17:2004345. doi: 10.1183/13993003.04345-2020. Online ahead of print.

Khan PY(1)(2)(3), Franke MF(4)(5)(3), Hewison C(6), Seung KJ(4)(7), Huerga H(8), Atwood S(7), Ahmed S(9), Khan M(10), Sultana T(11), Manzur-Ul-Alam M(11), Vo LNQ(12)(13), Lecca L(14), Yae K(15), Kozhabekov S(16), Tamirat M(17), Gelin A(18), Vilbrun SC(19), Kikvidze M(20), Faqirzai J(21), Kadyrov A(22), Skrahina A(23), Mesic A(24), Avagyan N(6), Bastard M(8), Rich ML(4)(7), Khan U(12)(3), Mitnick CD(4)(5)(3).

BACKGROUND: Recent World Health Organisation guidance on drug-resistant tuberculosis treatment de-prioritised injectable agents, in use for decades, and endorsed all-oral longer regimens. However, questions remain about the role of the injectable agent, particularly in the context of regimens using new and repurposed drugs. We compared the effectiveness of an injectable-containing regimen to that of an all-oral regimen among patients with drug-resistant tuberculosis who received bedaquiline- and/or delamanid as part of their multidrug regimen.
METHODS: Patients with a positive baseline culture were included. Six-month culture conversion was defined as two consecutive negative cultures collected >15 days apart. We derived predicted probabilities of culture conversion and

relative risk using marginal standardisation methods.
RESULTS: Culture conversion was observed in 83.8% (526/628) of patients receiving an all-oral regimen and 85.5% (425/497) of those receiving an injectable-containing regimen. The adjusted relative risk comparing injectable-containing regimens to all-oral regimens was 0.96 (95%CI: 0.88-1.04). We found very weak evidence of effect modification by HIV status: among patients living with HIV, there was a small increase in the frequency of conversion among those receiving an injectable-containing regimen, relative to an all-oral regimen, which was not apparent in HIV-negative patients.
CONCLUSIONS: Among individuals receiving bedaquiline and/or delamanid as part of a multidrug regimen for drug-resistant tuberculosis, there was no significant difference between those who received an injectable and those who did not regarding culture conversion within 6 months. The potential contribution of injectable agents in the treatment of drug-resistant tuberculosis among those who were HIV positive requires further study.

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DOI: 10.1183/13993003.04345-2020
PMID: 34140298

59. Extracellular matrix-inspired inhalable aerogels for rapid clearance of pulmonary tuberculosis.

Biomaterials. 2021 Jun;273:120848. doi: 10.1016/j.biomaterials.2021.120848. Epub 2021 Apr 22.

Simonson AW(1), Umstead TM(2), Lawanprasert A(1), Klein B(1), Almarzooqi S(1), Halstead ES(2), Medina SH(3).

Tuberculosis (TB) remains a leading cause of death from a single infectious agent, and limiting the spread of multidrug-resistant TB (MDR-TB) is now an urgent global health priority. Essential to the persistence of this disease is the ability of Mycobacterium tuberculosis (Mtb) to circumvent host defenses by infecting lung macrophages to create a cellular niche for its survival and proliferation. This has urged the development of new therapeutic strategies that act through mechanisms distinct from conventional antibiotics, and thus are effective against MDR bacteria, while being able to efficiently kill persister Mtb cells in infected host macrophages. Here, we report a new class of gel-like microparticle aerosols, or 'aerogels', designed to exploit metabolic vulnerabilities of Mtb pathogens and TB-infected macrophages to enable preferential delivery of synergistic peptide-antibiotic combinations for potent

and rapid antitubercular therapy. This is achieved by formulating aerogels through the supramolecular assembly of a de novo designed anti-TB peptide and the extracellular matrix (ECM)-derived polysaccharide, hyaluronic acid (HA). Importantly, HA serves as a nutrient source for Mtb cells during tissue invasion and proliferation, and is recognized by CD44 receptors highly expressed on lung macrophages during TB infection. By exploiting this metabolic substrate for pathogen targeting, HA aerogels are shown to avidly bind and kill both drug-sensitive and drug-resistant mycobacteria, while being efficiently internalized into macrophage host cells in vitro and in vivo to clear Mtb persisters. This multifaceted bioactivity suggests aerogels may serve as a versatile inhalable platform upon which novel biomaterials-enabled therapeutics can be developed to rapidly clear pulmonary MDR-TB.

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DOI: 10.1016/j.biomaterials.2021.120848
PMID: 33915409 [Indexed for MEDLINE]

60. The Mur Enzymes Chink in the Armour of Mycobacterium tuberculosis cell wall.

Eur J Med Chem. 2021 Jun 2;222:113568. doi: 10.1016/j.ejmech.2021.113568. Online ahead of print.

Shinde Y(1), Ahmad I(1), Surana S(1), Patel H(2).

TUBERCULOSIS: (TB) transmitted by Mycobacterium tuberculosis (Mtb) is one of the top 10 causes of death globally. Currently, the widespread occurrence of resistance toward Mtb strains is becoming a significant concern to public health. This scenario exaggerated the need for the discovery of novel targets and their inhibitors. Targeting the "Mtb cell wall peptidoglycan synthesis" is an attractive strategy to overcome drug resistance. Mur enzymes (MurA-MurF) play essential roles in the peptidoglycan synthesis by catalyzing the ligation of key amino acid residues to the stem peptide. These enzymes are unique and confined to the eubacteria and are absent in humans, representing potential targets for anti-tubercular drug discovery. Mtb Mur ligases with the same catalytic mechanism share conserved amino acid regions and structural features that can conceivably exploit for the designing of the inhibitors, which can simultaneously target more than one isoforms (MurC-MurF) of the enzyme. In light of these findings in the current review, we have discussed the recent advances in medicinal chemistry of Mtb Mur enzymes (MurA-MurF) and their inhibitors, offering attractive multi-targeted strategies to combat the problem of drug-resistant in M. tuberculosis.

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DOI: 10.1016/j.ejmech.2021.113568
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61. Outbreak of pre- and extensively drug-resistant tuberculosis in northern italy: urgency of cross-border, multidimensional, surveillance systems.

Eur Respir J. 2021 Jun 3:2100839. doi: 10.1183/13993003.00839-2021. Online ahead of print.

Villa S(1)(2), Tagliani E(3)(2), Borroni E(3), Castellotti PF(4), Ferrarese M(4), Ghodousi A(3), Lamberti A(5), Senatore S(5), Faccini M(5)(6), Cirillo DM(7), Codecasa LR(8)(6).

DOI: 10.1183/13993003.00839-2021
PMID: 34049944

62. Prediction of Human Pharmacokinetic Profiles of the Anti-tuberculosis Drug Delamanid from Nonclinical Data: Potential Therapeutic Value Against Extrapulmonary Tuberculosis.

Antimicrob Agents Chemother. 2021 Jun 7:AAC0257120. doi: 10.1128/AAC.02571-20. Online ahead of print.

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

63. An overview of zinc oxide nanoparticles produced by plant extracts for anti-tuberculosis treatments.

Curr Med Chem. 2021 Jun 14. doi: 10.2174/0929867328666210614122109. Online ahead of print.

Behzad F(1), Sefidgar E(2), Samadi A(3), Lin W(4), Pouladi I(5), Pi J(4).

Tuberculosis (TB), induced by Mycobacterium tuberculosis (MTB), is a fatal infectious disease that kills millions of lives worldwide. The emergence of drug-resistant and multidrug-resistant cases is regarded as one of the most challenging threats to TB control due to the low cure rate. Therefore, TB and drug-resistant TB epidemics urge us to explore more effective therapies. The increasing knowledge of nanotechnology has extended to some nanomedicines for disease treatment in the clinic, which also provides novel possibilities for nano-based medicines for TB treatment. Zinc oxide nanoparticles (ZnO NPs) have gained increasing attention for anti-bacterial uses based on their strong ability to induce reactive oxidative species (ROS) and release bactericidal Zinc ions (Zn2+), which are expected to act as novel strategies for TB and drug-resistant TB treatment. Some active herbal medicines from plant extracts have been widely reported to show attractive anti-bacterial activity for infectious treatment, including TB. Here, we summarize the synthesis of ZnO NPs using plant extracts (green synthesized ZnO NPs) and further discuss their potentials for anti-TB treatments. This is the first review article discussing the anti-TB activity of ZnO NPs produced using plant extracts, which might contribute to the further applications of green synthesized ZnO NPs for anti-TB and drug-resistant TB treatment.

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PMID: 34126883

64. The largest prison outbreak of TB in Western Europe investigated using whole-genome sequencing.

Int J Tuberc Lung Dis. 2021 Jun 1;25(6):491-497. doi: 10.5588/ijtld.21.0033.

Roycroft E(1), Fitzgibbon MM(1), Kelly DM(2), Scully M(2), McLaughlin AM(3), Flanagan PR(1), Gordon SV(4), Rogers TR(1), Keane J(3), O Meara M(2).

BACKGROUND: In March 2011, the Department of Public Health East in Ireland were notified of two cases of TB in two prisoners sharing a cell. We define the resulting outbreak and highlight the role of public health and laboratory-based molecular epidemiology in mapping and control of a prison outbreak.METHODS: Cases were identified through clinical presentation, contact tracing, case-finding exercise or enhanced laboratory surveillance. Mycobacterium tuberculosis isolates were genotyped and underwent whole-genome sequencing (WGS).RESULTS: Of the 34 cases of TB linked to the outbreak, 27 were prisoners (79%), 4 prison officers (12%) and 3 community cases (9%). M. tuberculosis was isolated from 31 cases (culture positivity: 91%). A maximum of six single-nucleotide polymorphisms separated the isolates, with 22 being identical, suggestive of a highly infectious 'super-spreader´ within the prison. Isolates belonged to the Beijing sub-lineage, and were susceptible to first-line anti-TB agents. A case-finding exercise incidentally detected a prisoner with multidrug-resistant TB. Of the 143 prison officers screened, 52% had latent TB infection. Litigation costs exceeded five million euros.CONCLUSION: This constitutes the largest prison outbreak of TB in Western Europe investigated using WGS. A robust prison entry TB screening and education programme is required to effect better TB control, and prevent future outbreaks and attendant litigation.

DOI: 10.5588/ijtld.21.0033
PMID: 34049612

65. Validation of a host blood transcriptomic biomarker for pulmonary tuberculosis in people living with HIV: a prospective diagnostic and prognostic accuracy study.

Lancet Glob Health. 2021 Jun;9(6):e841-e853. doi: 10.1016/S2214-109X(21)00045-0. Epub 2021 Apr 13.

Mendelsohn SC(1), Fiore-Gartland A(2), Penn-Nicholson A(1), Mulenga H(1), Mbandi SK(1), Borate B(2), Hadley K(1), Hikuam C(1), Musvosvi M(1), Bilek N(1), Erasmus M(1), Jaxa L(1), Raphela R(1), Nombida O(1), Kaskar M(1), Sumner T(3), White RG(3), Innes C(4), Brumskine W(4), Hiemstra A(5), Malherbe ST(5), Hassan-Moosa R(6), Tameris M(1), Walzl G(5), Naidoo K(6), Churchyard G(7), Scriba TJ(1), Hatherill M(8); CORTIS-HR Study Team.

BACKGROUND: A rapid, blood-based triage test that allows targeted investigation for tuberculosis at the point of care could shorten the time to tuberculosis treatment and reduce mortality. We aimed to test the performance of a host blood transcriptomic signature (RISK11) in diagnosing tuberculosis and predicting progression to active pulmonary disease (prognosis) in people with HIV in a community setting.
METHODS: In this prospective diagnostic and prognostic accuracy study, adults (aged 18-59 years) with HIV were recruited from five communities in South Africa. Individuals with a history of tuberculosis or household exposure to multidrug-resistant tuberculosis within the past 3 years, comorbid risk factors for tuberculosis, or any condition that would interfere with the study were excluded. RISK11 status was assessed at baseline by real-time PCR; participants and study staff were masked to the result. Participants underwent active surveillance for microbiologically confirmed tuberculosis by providing spontaneously expectorated sputum samples at baseline, if symptomatic during 15 months of follow-up, and at 15 months (the end of the study). The coprimary outcomes were the prevalence and cumulative incidence of tuberculosis disease confirmed by a positive Xpert MTB/RIF, Xpert Ultra, or Mycobacteria Growth Indicator Tube culture, or a combination of such, on at least two separate sputum samples collected within any 30-day period.
FINDINGS: Between March 22, 2017, and May 15, 2018, 963 participants were assessed for eligibility and 861 were enrolled. Among 820 participants with valid RISK11 results, eight (1%) had prevalent tuberculosis at baseline: seven (2·5%; 95% CI 1·2-5·0) of 285 RISK11-positive participants and one (0·2%; 0·0-1·1) of 535 RISK11-negative participants. The relative risk (RR) of prevalent tuberculosis was 13·1 times (95% CI 2·1-81·6) greater in RISK11-positive participants than in RISK11-negative participants. RISK11 had a diagnostic area under the receiver operating characteristic curve (AUC) of 88·2% (95% CI 77·6-96·7), and a sensitivity of 87·5% (58·3-100·0) and specificity of 65·8% (62·5-69·0) at a predefined score threshold (60%). Of those with RISK11 results, eight had primary endpoint incident tuberculosis during 15 months of follow-up. Tuberculosis incidence was 2·5 per 100 person-years (95% CI 0·7-4·4) in the RISK11-positive group and 0·2 per 100 person-years (0·0-0·5) in the RISK11-negative group. The probability of primary endpoint incident tuberculosis was greater in the RISK11-positive group than in the RISK11-negative group (cumulative incidence ratio 16·0 [95% CI 2·0-129·5]). RISK11 had a prognostic

AUC of 80·0% (95% CI 70·6-86·9), and a sensitivity of 88·6% (43·5-98·7) and a specificity of 68·9% (65·3-72·3) for incident tuberculosis at the 60% threshold. INTERPRETATION: RISK11 identified prevalent tuberculosis and predicted risk of progression to incident tuberculosis within 15 months in ambulant people living with HIV. RISK11's performance approached, but did not meet, WHO's target product profile benchmarks for screening and prognostic tests for tuberculosis. FUNDING: Bill & Melinda Gates Foundation and the South African Medical Research Council.

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PMID: 33862012

66. Diagnostic Procedures, Diagnoses, and Treatment Outcomes of Patients with Presumptive Tuberculosis Pleural Effusion in Uzbekistan.

Int J Environ Res Public Health. 2021 May 27;18(11):5769. doi: 10.3390/ijerph18115769.

Abdugapparov F(1), Grigoryan R(2), Parpieva N(3), Massavirov S(1), Riskiyev A(3), Gadoev J(4), Buziashvili M(5), Tukvadze N(5), Hovhannesyan A(6), Dadu A(6).

Tuberculosis (TB) pleural effusion (TPE) is the second most common manifestation of extrapulmonary TB (EPTB), which remains a great diagnostic challenge worldwide. In Uzbekistan, there has been no formal evaluation of the actual practices of diagnosing and treating TPE. Our cohort study therefore aimed to describe the frequency and types of different diagnostic procedures of TPE during 2017-2018 and assess the association of baseline characteristics and establish diagnostic methods with TB treatment outcomes. In total, 187 patients with presumptive TPE were assessed, and 149 had a confirmed diagnosis of TPE (other diagnoses included cancer n = 8, pneumonia n = 17, and 13 cases were unspecified). TB was bacteriologically confirmed in 22 (14.8%), cytologically confirmed in 64 (43.0%), and histologically confirmed in 16 (10.7%) patients. Hepatitis was the only co-morbidity significantly associated with unsuccessful treatment outcomes (RR 4.8; 95%CI: 1.44-15.98, p value 0.011). Multivariable regression analysis showed that drug-resistant TB was independently associated with unsuccessful TB treatment outcome. (RR 3.83; 95%CI: 1.05-14.02, p value 0.04). Multidisciplinary approaches are required to maximize the diagnostic

accuracy of TPE and minimize the chances of misdiagnosis. TPE patients with co-infections and those with drug resistance should be more closely monitored to try and ensure successful TB treatment outcomes.

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PMCID: PMC8198680
PMID: 34072161

67. Early COVID-19 pandemic's toll on tuberculosis services, WHO European Region, January to June 2020.

Euro Surveill. 2021 Jun;26(24). doi: 10.2807/1560-7917.ES.2021.26.24.2100231.

Dara M(1), Kuchukhidze G(1), Yedilbayev A(1), Perehinets I(1), Schmidt T(1), Van Grinsven WL(1), Boeree MJ(2).

BackgroundEssential health services, including for tuberculosis (TB), are being affected by public health and social measures (PHSM) introduced to control COVID-19. In many settings, TB resources, facilities and equipment are being redirected towards COVID-19 response.AimWe sought to assess the COVID-19 pandemic's impact on TB services in the World Health Organization (WHO) European Region.MethodsThe fifty-three European Region Member States were asked to report qualitative and quantitative data in quarter one and two (Q1 and Q2) 2020. TB notifications were triangulated with the severity score on domestic movement restrictions to assess how they may have influenced TB detection.ResultsTwenty-nine countries reported monthly TB notifications for the first half of 2019 and 2020. TB notifications decreased by 35.5% during Q2 2020 compared with Q2 2019, which is six-fold more than the average annual decrease of 5.1% documented during 2015-2019. The number of patients enrolled in rifampicin-resistant/multidrug-resistant TB treatment also decreased dramatically in Q2 2020, by 33.5%. The highest movement restriction severity score was observed between April and May 2020, which coincided with the highest observed decrease in TB notifications.ConclusionA decrease in TB detection and enrolment to treatment may cause increases in TB burden and threatens the Region's ability to reach the TB targets of the 2030 Sustainable Development Goals, still this might be mitigated with rapid restoration of TB services and the implementation of targeted interventions during periods with severe PHSM in place, such as those introduced in response to the COVID-19 pandemic.

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PMID: 34142649

68. Identification of novel benzothiopyranones with ester and amide motifs derived from active metabolite as promising leads against Mycobacterium tuberculosis.

Eur J Med Chem. 2021 Jun 5;222:113603. doi: 10.1016/j.ejmech.2021.113603. Online ahead of print.

Li P(1), Wang B(2), Fu L(2), Guo K(3), Ma C(3), Wang B(3), Lin Z(1), Li G(4), Huang H(5), Lu Y(6).

We reported three distinct series of novel benzothiopyranones, derived from an active metabolite (M-1) of anti-TB agent 6b. These small molecules were evaluated for their biological activities against a range of Mycobacterium tuberculosis (M. tuberculosis) strains. Preliminary druggability evaluation demonstrated that M-1 showed good aqueous solubility and hepatocyte stability. Benzothiopyranones with acyl, sulfonyl and phosphoryl groups exhibited potent in vitro inhibitory activity against M. tuberculosis H37Rv and low cytotoxicity. In particular, compound 3d, containing a benzoate fragment, displayed marked metabolic stability and potent in vitro activity against drug-resistant tuberculosis clinical strains. Further druggability evaluation based on the identified compounds 3d, 4e and 5b is ongoing for the discovery of promising anti-TB agents.

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PMID: 34126456

69. A decade of drug-resistant tuberculous meningitis: A wake-up call for patient-centric therapy.

Indian J Med Microbiol. 2021 Jun 2:S0255-0857(21)04115-3. doi: 10.1016/j.ijmmb.2021.05.013. Online ahead of print.

Sharma K(1), Sharma M(2), Modi M(3), Goyal M(3), Sharma A(4), Ray P(5).

On analyzing the drug susceptibility profile of 151 clinical isolates collected from patients of tuberculous meningitis (TBM) over 10 years, we reflect on few lessons learnt from the trend of susceptibility profile - drug resistance was not uncommon, fluoroquinolone resistance was observed even among otherwise susceptible isolates and hetero-resistance was observed against rifampicin, isoniazid and also fluoroquinolones. In the midst of widening gap between incidence of drug resistant TBM and availability of effective drugs, our data suggests that universal testing for drug resistance, careful choice of drugs

having optimal penetration and individualized therapy should form important pillars of TBM management.

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PMID: 34090744

70. Challenges and opportunities to end tuberculosis in the COVID-19 era.

Lancet Respir Med. 2021 Jun;9(6):556-558. doi: 10.1016/S2213-2600(21)00161-2. Epub 2021 Mar 24.

Wingfield T(1), Karmadwala F(2), MacPherson P(3), Millington KA(2), Walker NF(4), Cuevas LE(5), Squire SB(4).

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PMCID: PMC7988354
PMID: 33773121 [Indexed for MEDLINE]

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71. Shortening MDR-TB treatment: is treating more patients with fewer drugs better?

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Akkerman OW(1), Tiberi S(2), Alffenaar JW(3).

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PMID: 34049601