Literature

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

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

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

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

2. **Multidrug-resistant tuberculosis in Sierra Leone.**

Lancet Glob Health. 2022 Apr;10(4):e459-e460. doi: 10.1016/S2214-109X(22)00045-6.

Lakoh S(1), Yendewa GA(2).

Comment in
Lancet Glob Health. 2022 Apr;10(4):e543-e554.

DOI: 10.1016/S2214-109X(22)00045-6
PMCID: PMC8923690
PMID: 35303445 [Indexed for MEDLINE]

3. **Investigation of Clofazimine Resistance and Genetic Mutations in Drug-Resistant Mycobacterium tuberculosis Isolates.**

J Clin Med. 2022 Mar 30;11(7):1927. doi: 10.3390/jcm11071927.

Park S(1), Jung J(1), Kim J(1), Han SB(2), Ryoo S(1).

Recently, as clofazimine (CFZ) showed a good therapeutic effect in treating multi-drug-resistant tuberculosis (MDR-TB), the anti-tuberculosis activity and resistance were re-focused. Here, we investigated the CFZ resistance and genetic mutations of drug-resistant Mycobacterium tuberculosis (DR-Mtb) isolates to improve the diagnosis and treatment of drug-resistant TB patients. The minimal

inhibitory concentration (MIC) of CFZ was examined by resazurin microtiter assay (REMA) with two reference strains and 122 clinical isolates from Korea. The cause of CFZ resistance was investigated in relation to the therapeutic history of patients. Mutations of Rv0678, Rv1979c and pepQ of CFZ resistant isolates were analyzed by PCR and DNA sequencing. The rate of CFZ resistance with MIC > 1 mg/L was 4.1% in drug-resistant Mtb isolates. The cause of CFZ resistance was not related to treatment with CFZ or bedaquiline. A CFZ susceptibility test should be conducted regardless of dugs use history. The four novel mutation sites were identified in the Rv0678 and pepQ genes related to CFZ resistance in this study.

DOI: 10.3390/jcm11071927
PMCID: PMC9000149
PMID: 35407536

4. **Drug resistant TB - latest developments in epidemiology, diagnostics and management.**

Int J Infect Dis. 2022 Mar 25:S1201-9712(22)00165-5. doi: 10.1016/j.ijid.2022.03.026. Online ahead of print.

Tiberi S(1), Utjesanovic N(2), Galvin J(3), Centis R(4), D'Ambrosio L(5), van den Boom M(6), Zumla A(7), Migliori GB(4).

AIM: The aim of this review is to inform the reader on the latest developments in epidemiology, diagnostics and management.
EPIDEMIOLOGY: Drug-resistant Tuberculosis (DR-TB) continues to be a current global health threat, and is defined by higher morbidity and mortality, sequelae, higher cost and complexity. The WHO classifies drug-resistant TB into 5 categories: isoniazid-resistant TB, rifampicin resistant (RR)-TB and MDR-TB, (TB resistant to isoniazid and rifampicin), pre-extensively drug-resistant TB (pre-XDR-TB) which is MDR-TB with resistance to a fluoroquinolone and finally XDR-TB that is TB resistant to rifampicin, plus any fluoroquinolone, plus at least one further priority A drug (bedaquiline or linezolid). Of 500,000 estimated new cases of RR-TB in 2020, only 157 903 cases are notified. Only about a third of cases are detected and treated annually.
DIAGNOSTICS: Recently newer rapid diagnostic methods like the GeneXpert, whole genome sequencing and Myc-TB offer solutions for rapid detection of resistance.
TREATMENT: The availability of new TB drugs and shorter treatment regimens have been recommended for the management of DR-TB.
CONCLUSION: Despite advances in diagnostics and treatments we still have to find and treat two thirds of the drug resistant cases that go undetected and therefore go untreated each year. Control of TB and elimination will only occur

if cases are detected, diagnosed and treated promptly.

DOI: 10.1016/j.ijid.2022.03.026
PMID: 35342000

5. **Drug resistant tuberculosis: Current scenario and impending challenges.**

Indian J Tuberc. 2022 Apr;69(2):227-233. doi: 10.1016/j.ijtb.2021.04.008. Epub 2021 Apr 20.

Singh Dewhare S(1).

Tuberculosis is still one of the ten leading causes for death worldwide. In spite of the latest medical and health advance gained over a period of time, tuberculosis effectively evades the successful targeting by drugs. The persistence abilities demonstrated by the mycobacteria had surprised the global community, since its discovery and pathogenesis in humans. Emergence and detection of drug resistant mycobacteria (MDR-TB, XDR-TB) had further complicated the treatment regime. Under the aegis of WHO, there is a concerted understanding and effort by the global community to eradicate TB. Towards this goal, novel drug molecules, new vaccine and treatment regime are being developed. Here, our current understanding pertaining to mode of action, molecular mechanisms of novel as well as traditional drug molecules and possible drug resistance mechanism in M. Tuberculosis is reviewed. Recent advances on new vaccination regime are also reviewed as it demonstrated huge potential in containing TB. This knowledge is essential for the development of more effective drug molecules, vaccines and may help in devising new strategy for containing and eradicating TB.

DOI: 10.1016/j.ijtb.2021.04.008
PMID: 35379406 [Indexed for MEDLINE]

6. **First outbreak of multidrug-resistant tuberculosis (MDR-TB) in Denmark involving six Danish-born cases.**

Int J Infect Dis. 2022 Apr;117:258-263. doi: 10.1016/j.ijid.2022.02.017. Epub 2022 Feb 11.

Suppli CH(1), Norman A(1), Folkvardsen DB(1), Gissel TN(2), Weinreich UM(3), Koch A(4), Wejse C(5), Lillebaek T(6).

BACKGROUND: Denmark is a low-incidence country for tuberculosis (TB) and multidrug-resistant (MDR) TB at 5 and 0.05 cases per 100,000 population, respectively. Until 2018, the transmission of MDR-TB was nonexistent except for a few pairwise related family cases. In this study, we describe the first MDR-TB outbreak in Denmark.
METHODS: On the basis of genotyping of all Mycobacterium tuberculosis (Mtb) culture-positive cases in Denmark spanning 3 decades, 6 molecular- and epidemiologically linked Danish-born cases were identified as the first cluster of an MDR-TB in Denmark. The primary case was diagnosed posthumously in 2010 followed by 5 epidemiologically linked cases from 2018 to 2019.
RESULTS AND CONCLUSION: Through a combination of routine Mtb genotyping and clinical epidemiological surveillance data, we identified the first Danish MDR-TB outbreak spanning 10 years and were able to disclose the specific transmission pathways in detail, which helped guide the outbreak investigations. The occurrence of an MDR-TB outbreak in a resource-rich low TB incidence setting such as Denmark highlights the importance of a collaborative control system combining classic contact tracing; timely identification of drug-resistant TB through rapid diagnostics; and a close collaboration between clinicians and classical- and molecular epidemiologists for the benefit of TB control.

DOI: 10.1016/j.ijid.2022.02.017
PMID: 35158061 [Indexed for MEDLINE]

7. **A multidrug-resistant tuberculosis outbreak among immigrants in Tokyo, Japan, 2019-2021.**

Jpn J Infect Dis. 2022 Mar 31. doi: 10.7883/yoken.JJID.2021.643. Online ahead of print.

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

In mid-September 2019, a teenage Chinese male student and part time waiter in Tokyo was diagnosed with multidrug-resistant (MDR) sputum smear-positive pulmonary tuberculosis (TB). This study describes the outbreak investigation of his friends and colleagues at the restaurant. We investigated six friends and 15 colleagues, of whom five friends and 13 colleagues underwent interferon-ã

release assay (IGRA). Of these, three friends (60.0%) and four colleagues (30.8%) were IGRA-positive. Each one of the friends and colleagues was found to have MDR-TB (20% and 7.7%, respectively). Challenges during the investigation were the unavailability of regimens for latent TB infection (LTBI) for contacts with MDR-TB, budgetary constraints concerning implementing computed tomography (CT) scans for the contacts, frequent address changes of foreign-born patients and contacts, investigation during the coronavirus disease pandemic, and variations of alphabetical expression of the names of the patients and contacts, particularly for those from China. It is recommended that the national government officially adopt prophylaxis regimens for LTBI with MDR-TB, address the budgetary constraints regarding CT-scans, and deploy liaison officer(s) for coordinating investigations involving many foreign-born patients and contacts scattered in multiple municipalities. The names of foreign-born persons could more accurately be identified using both the alphabet and Chinese characters.

DOI: 10.7883/yoken.JJID.2021.643
PMID: 35354703

8. **Concise Clinical Review of Hematologic Toxicity of Linezolid in Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: Role of Mitochondria.**

Tuberc Respir Dis (Seoul). 2022 Apr;85(2):111-121. doi: 10.4046/trd.2021.0122. Epub 2022 Jan 20.

Oehadian A(1), Santoso P(1), Menzies D(2), Ruslami R(3)(4).

Multidrug-resistant tuberculosis (MDR-TB) is caused by an organism that is resistant to both rifampicin and isoniazid. Extensively drug-resistant TB, a rare type of MDR-TB, is caused by an organism that is resistant to quinolone and one of group A TB drugs (i.e., linezolid and bedaquiline). In 2018, the World Health Organization revised the groupings of TB medicines and reclassified linezolid as a group A drug for the treatment of MDR-TB. Linezolid is a synthetic antimicrobial agent in the oxazolidinone class. Although linezolid has a good efficacy, it can cause substantial adverse events, especially hematologic toxicity. In both TB infection and linezolid mechanism of action, mitochondrial dysfunction plays an important role. In this concise review, characteristics of linezolid as an anti-TB drug are summarized, including its efficacy, pathogenesis of hematologic toxicity highlighting mitochondrial dysfunction, and the monitoring and management of hematologic toxicity.

DOI: 10.4046/trd.2021.0122
PMCID: PMC8987663

PMID: 35045688

9. **Cycloserine did not increase depression incidence or severity at standard dosing for multidrug-resistant tuberculosis.**

Eur Respir J. 2022 Mar 24;59(3):2102511. doi: 10.1183/13993003.02511-2021. Print 2022 Mar.

Tornheim JA(1), Udwadia ZF(2), Arora PR(3), Gajjar I(3), Gupte N(1)(4), Sharma S(3), Karane M(3), Sawant N(3), Kharat N(3), Blum AJ(5), Shivakumar SVBY(4), Mullerpattan JB(6), Pinto LM(6), Ashavaid TF(3), Gupta A(1)(7), Rodrigues C(8).

In a longitudinal cohort of MDR-TB patients receiving individualised, DST-based treatment, neither the inclusion of cycloserine in a multidrug regimen nor the dose used (up to 750 mg daily) significantly increased incidence of depression during treatment https://bit.ly/3GtQmOH

In 2018 cycloserine was elevated to World Health Organization (WHO) group B status for multidrug-resistant tuberculosis (MDR-TB), and is recommended in longer MDR-TB treatment regimens [1]. Inclusion of cycloserine is associated with improved MDR-TB treatment success and reduced mortality, but is limited by treatment-associated depression, psychosis and neuropathy, forcing 9% of patients to stop therapy [1–3]. Cycloserine also demonstrates wide interindividual pharmacokinetic variation, with significant food and drug interactions, leaving nearly half of patients with inappropriate drug levels [4, 5]. Optimal dosing is unknown [6], but modelling studies suggest doses from 250 mg to 750 mg twice daily, with 500 mg twice daily for paucibacillary disease and 750 mg twice daily for cavitary pulmonary disease [7]. Therefore, clinicians must balance the known benefits of cycloserine with the dearth of susceptibility- and drug-monitoring capacity and the spectre of treatment-limiting side-effects. To evaluate the impact of cycloserine prescription and dose on incident depression during MDR-TB treatment, we analysed longitudinal cohort data from India.

DOI: 10.1183/13993003.02511-2021
PMCID: PMC8943271
PMID: 34949698 [Indexed for MEDLINE]

10. **Delamanid or pretomanid? A Solomonic judgement!**

J Antimicrob Chemother. 2022 Mar 31;77(4):880-902. doi: 10.1093/jac/dkab505.

Mudde SE(1), Upton AM(2), Lenaerts A(3), Bax HI(1)(4), De Steenwinkel JEM(1).

Given the low treatment success rates of drug-resistant tuberculosis (TB), novel TB drugs are urgently needed. The landscape of TB treatment has changed considerably over the last decade with the approval of three new compounds: bedaquiline, delamanid and pretomanid. Of these, delamanid and pretomanid belong to the same class of drugs, the nitroimidazoles. In order to close the knowledge gap on how delamanid and pretomanid compare with each other, we summarize the main findings from preclinical research on these two compounds. We discuss the compound identification, mechanism of action, drug resistance, in vitro activity, in vivo pharmacokinetic profiles, and preclinical in vivo activity and efficacy. Although delamanid and pretomanid share many similarities, several differences could be identified. One finding of particular interest is that certain Mycobacterium tuberculosis isolates have been described that are resistant to either delamanid or pretomanid, but with preserved susceptibility to the other compound. This might imply that delamanid and pretomanid could replace one another in certain regimens. Regarding bactericidal activity, based on in vitro and preclinical in vivo activity, delamanid has lower MICs and higher mycobacterial load reductions at lower drug concentrations and doses compared with pretomanid. However, when comparing in vivo preclinical bactericidal activity at dose levels equivalent to currently approved clinical doses based on drug exposure, this difference in activity between the two compounds fades. However, it is important to interpret these comparative results with caution knowing the variability inherent in preclinical in vitro and in vivo models.

DOI: 10.1093/jac/dkab505
PMCID: PMC8969540
PMID: 35089314 [Indexed for MEDLINE]

11. **Linezolid toxicity in patients with drug-resistant tuberculosis: a prospective cohort study.**

J Antimicrob Chemother. 2022 Mar 31;77(4):1146-1154. doi: 10.1093/jac/dkac019.

Wasserman S(1)(2), Brust JCM(3), Abdelwahab MT(4), Little F(5), Denti P(4), Wiesner L(4), Gandhi NR(6)(7), Meintjes G(1)(8), Maartens G(1)(4).

BACKGROUND: Linezolid is recommended for treating drug-resistant TB. Adverse events are a concern to prescribers but have not been systematically studied at

the standard dose, and the relationship between linezolid exposure and clinical toxicity is not completely elucidated.
PATIENTS AND METHODS: We conducted an observational cohort study to describe the incidence and determinants of linezolid toxicity, and to determine a drug exposure threshold for toxicity, among patients with rifampicin-resistant TB in South Africa. Linezolid exposures were estimated from a population pharmacokinetic model. Mixed-effects modelling was used to analyse toxicity outcomes.
RESULTS: One hundred and fifty-one participants, 63% HIV positive, were enrolled and followed for a median of 86 weeks. Linezolid was permanently discontinued for toxicity in 32 (21%) participants. Grade 3 or 4 linezolid-associated adverse events occurred in 21 (14%) participants. Mean haemoglobin concentrations increased with time on treatment (0.03 g/dL per week; 95% CI 0.02-0.03). Linezolid trough concentration, male sex and age (but not HIV positivity) were independently associated with a decrease in haemoglobin >2 g/dL. Trough linezolid concentration of 2.5 mg/L or higher resulted in optimal model performance to describe changing haemoglobin and treatment-emergent anaemia (adjusted OR 2.9; 95% CI 1.3-6.8). SNPs 2706A > G and 3010G > A in mitochondrial DNA were not associated with linezolid toxicity.
CONCLUSIONS: Permanent discontinuation of linezolid was common, but linezolid-containing therapy was associated with average improvement in toxicity measures. HIV co-infection was not independently associated with linezolid toxicity. Linezolid trough concentration of 2.5 mg/L should be evaluated as a target for therapeutic drug monitoring.

DOI: 10.1093/jac/dkac019
PMCID: PMC7612559
PMID: 35134182 [Indexed for MEDLINE]

12. **Prospects of contezolid (MRX-I) against multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis.**

Drug Discov Ther. 2022 Apr 12. doi: 10.5582/ddt.2022.01025. Online ahead of print.

Yang M(1), Zhan S(1), Fu L(1), Wang Y(1), Zhang P(1), Deng G(1).

Tuberculosis has become a great global public health threat. Compared with drug-susceptible tuberculosis (TB), the treatment regimens for

multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) involve more severe adverse events and poorer treatment outcomes. Linezolid (LZD) is the first oxazolidinones used for TB. Thanks to its potent activity against Mycobacterium tuberculosis, LZD has become one of the key agents in the regimens against MDR/XDR-TB. However, this drug may cause intolerability and other adverse events. Contezolid, another novel oxazolidinone, can also inhibit M. tuberculosis, still with fewer adverse effects compared with LZD. This paper is to prospect the potentials of contezolid in the treatment of MDR/XDR-TB, with focus on its efficacy and possible adverse effects.

DOI: 10.5582/ddt.2022.01025
PMID: 35418550

13. **A Scoping Review of the Clinical Pharmacokinetics of Bedaquiline.**

Clin Pharmacokinet. 2022 Apr;61(4):481-488. doi: 10.1007/s40262-022-01107-4. Epub 2022 Jan 27.

Wilby KJ(1).

Tuberculosis continues to be a major infectious disease burden worldwide. Increasing drug resistance to first-line agents is making treatment more difficult. Bedaquiline is an orally administered drug active against Mycobacterium tuberculosis and is indicated for patients with confirmed multi-drug-resistant tuberculosis. This review aims to identify published literature reporting on the pharmacokinetics of bedaquiline, with a focus on key factors and drug interactions that may affect its use. Findings identified multiple areas for future study. First, exposure-response relationships should be further developed to determine the best ways to monitor both efficacy and safety. Second, dosing may be optimized through greater understanding of specific factors that may influence observed concentrations, including patient demographics and comorbidities. Finally, firm guidance for co-administration of bedaquiline with other drugs known to induce or inhibit cytochrome P450 enzymes is urgently required.

DOI: 10.1007/s40262-022-01107-4
PMID: 35083732 [Indexed for MEDLINE]

14. **Social and health factors associated with adverse treatment outcomes among people with multidrug-resistant tuberculosis in Sierra Leone: a national, retrospective cohort study.**

Lancet Glob Health. 2022 Apr;10(4):e543-e554. doi: 10.1016/S2214-109X(22)00004-3.

Kamara RF(1), Saunders MJ(2), Sahr F(3), Losa-Garcia JE(4), Foray L(5), Davies G(6), Wingfield T(7).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) is a global health emergency. We aimed to evaluate treatment outcomes among people with MDR-TB in Sierra Leone and investigate social and health factors associated with adverse treatment outcomes.
METHODS: This national, retrospective cohort study recruited all people notified with MDR-TB to the Sierra Leone National TB Programme, admitted to Lakka hospital (Lakka, Western Area Rural District, Freetown, Sierra Leone) between April, 2017, and September, 2019. Participants were followed up to May, 2021. People who were eligible but had no social or health data available, or were subsequently found to have been misdiagnosed, were excluded from participation. MDR-TB treatment was with the 2017 WHO-recommended short (9-11 month) or long (18-24 month) aminoglycoside-containing regimens. Multivariable logistic regression models examined associations of programmatic social and health data with WHO-defined adverse treatment outcomes (death, treatment failure, loss to follow-up).
FINDINGS: Of 370 notified MDR-TB cases, 365 (99%) were eligible for study participation (five participants were excluded due to lack of social or health data or misdiagnosis). Treatment was started by 341 (93%) of 365 participants (317 received the short regimen, 24 received the long regimen, and 24 received no treatment). Median age was 35 years (IQR 26-45), 263 (72%) of 365 were male and 102 (28%) were female, 71 (19%) were HIV-positive, and 127 (35%) were severely underweight (body-mass index <16·5 kg/m2). Overall, 267 (73%) of 365 participants had treatment success, 95 (26%) had an adverse outcome, and three (1%) were still on treatment in May, 2021. Age 45-64 years (adjusted odds ratio [aOR] 2·4, 95% CI 1·2-5·0), severe underweight (aOR 4·2, 1·9-9·3), untreated HIV (aOR 10, 2·6-40·0), chronic lung disease (aOR 2·0, 1·0-4·2), previously unsuccessful drug-sensitive tuberculosis retreatment (aOR 4·3, 1·0-19), and a long regimen (aOR 6·5, 2·3-18·0) were associated with adverse outcomes. A sensitivity analysis showed that prothionamide resistance (aOR 3·1, 95% CI 1·5-10·0) and aminoglycoside-related complete deafness (aOR 6·6, 1·3-35) were independently associated with adverse outcomes.
INTERPRETATION: MDR-TB treatment success in Sierra Leone approached WHO targets and the short regimen was associated with higher success. The social and health factors associated with adverse outcomes in this study suggest a role for

integrated tuberculosis, HIV, and non-communicable disease services alongside nutritional and socioeconomic support for people with MDR-TB and emphasise the urgent need to scale up coverage of all-oral aminoglycoside-sparing regimens.
FUNDING: Wellcome Trust, Joint Global Health Trials.

DOI: 10.1016/S2214-109X(22)00004-3
PMCID: PMC8938764
PMID: 35303463

15. **Chest X-ray findings in drug-sensitive and drug-resistant pulmonary tuberculosis patients in Uganda.**

J Clin Tuberc Other Mycobact Dis. 2022 Mar 25;27:100312. doi: 10.1016/j.jctube.2022.100312. eCollection 2022 May.

Oriekot A(1), Sereke SG(1), Bongomin F(2), Bugeza S(1), Muyinda Z(3).

BACKGROUND: Tuberculosis (TB) is one of the leading causes of death worldwide. Radiology has an important role in the diagnosis of both drug-sensitive (DS) and rifampicin-resistant (RR) pulmonary TB (PTB). This study aimed to compare the chest x-ray (CXR) patterns of microbiologically confirmed DS and RR PTB cases stratified by HIV serostatus in Uganda.
METHODS: We conducted a hospital-based retrospective study at the Mulago National Referral Hospital (MNRH) TB wards. All participants had a microbiologically confirmed diagnosis of PTB. CXR findings extracted included infiltrates, consolidation, cavity, fibrosis, bronchiectasis, atelectasis, and other non-lung parenchymal findings. All films were examined by two independent radiologists blinded to the clinical diagnosis.
RESULTS: We analyzed CXR findings of 165 participants: 139 DS- and 26 RR-TB cases. The majority (n = 118, 71.7%) of the participants were seronegative for HIV. Overall, 5/165 (3%) participants had normal CXR. There was no statistically significant difference in the proportion of participants with consolidations (74.8% versus 88.5%; p = 0.203), bronchopneumonic opacities (56.1% versus 42.3%, p = 0.207) and cavities (38.1% versus 46.2%, p = 0.514), across drug susceptibility status (DS versus RR TB). Among HIV-infected participants, consolidations were predominantly in the middle lung zone in the DS TB group and in the lower lung zone in the RR TB group (42.5% versus 12.8%, p = 0.66). HIV-infected participants with RR TB had statistically significantly larger cavity sizes compared to their HIV uninfected counterparts with RR TB

(7.7 ± 6.8 cm versus 4.2 ± 1.3 cm, p = 0.004).
CONCLUSIONS: We observed that a vast majority of participants had similar CXR changes, irrespective of drug susceptibility status. However, HIV-infected RR PTB had larger cavities.The diagnostic utility of cavity sizes for the differentiation of HIV-infected and non-infected RR TB could be investigated further.

DOI: 10.1016/j.jctube.2022.100312
PMCID: PMC8958542
PMID: 35355939

16. **Molecular characterisation of second-line drug resistance among drug resistant tuberculosis patients tested in Uganda: a two and a half-year's review.**

BMC Infect Dis. 2022 Apr 11;22(1):363. doi: 10.1186/s12879-022-07339-w.

Mujuni D(1)(2), Kasemire DL(2), Ibanda I(3), Kabugo J(2), Nsawotebba A(2)(4), Phelan JE(5), Majwala RK(6), Tugumisirize D(2)(7), Nyombi A(2)(7), Orena B(2), Turyahabwe I(8), Byabajungu H(2), Nadunga D(2), Musisi K(2), Joloba ML(2)(9), Ssengooba W(10)(11).

BACKGROUND: Second-line drug resistance (SLD) among tuberculosis (TB) patients is a serious emerging challenge towards global control of the disease. We characterized SLD-resistance conferring-mutations among TB patients with rifampicin and/or isoniazid (RIF and/or INH) drug-resistance tested at the Uganda National TB Reference Laboratory (NTRL) between June 2017 and December 2019.
METHODS: This was a descriptive cross-sectional secondary data analysis of 20,508 M. tuberculosis isolates of new and previously treated patients' resistant to RIF and/or INH. DNA strips with valid results to characterise the SLD resistance using the commercial Line Probe Assay Genotype MTBDRsl Version 2.0 Assay (Hain Life Science, Nehren, Germany) were reviewed. Data were analysed with STATAv15 using cross-tabulation for frequency and proportions of known resistance-conferring mutations to injectable agents (IA) and fluoroquinolones (FQ).
RESULTS: Among the eligible participants, 12,993/20,508 (63.4%) were male and median (IQR) age 32 (24-43). A total of 576/20,508 (2.8%) of the M. tuberculosis isolates from participants had resistance to RIF and/or INH. These included; 102/576 (17.7%) single drug-resistant and 474/576 (82.3%) multidrug-resistant (MDR) strains. Only 102 patients had test results for FQ of whom 70/102 (68.6%) and 01/102 (0.98%) had resistance-conferring mutations in

the gyrA locus and gyrB locus respectively. Among patients with FQ resistance, gyrAD94G 42.6% (30.0-55.9) and gyrA A90V 41.1% (28.6-54.3) mutations were most observed. Only one mutation, E540D was detected in the gyrB locus. A total of 26 patients had resistance-conferring mutations to IA in whom, 20/26 77.0% (56.4-91.0) had A1401G mutation in the rrs gene locus.
CONCLUSIONS: Our study reveals a high proportion of mutations known to confer high-level fluoroquinolone drug-resistance among patients with rifampicin and/or isoniazid drug resistance. Utilizing routinely generated laboratory data from existing molecular diagnostic methods may aid real-time surveillance of emerging tuberculosis drug-resistance in resource-limited settings.

DOI: 10.1186/s12879-022-07339-w
PMCID: PMC9003953
PMID: 35410160 [Indexed for MEDLINE]

17. **Can the GeneXpert MTB/XDR deliver on the promise of expanded, near-patient tuberculosis drug-susceptibility testing?**

Lancet Infect Dis. 2022 Apr;22(4):e121-e127. doi: 10.1016/S1473-3099(21)00613-7. Epub 2022 Feb 25.

Naidoo K(1), Dookie N(2).

Early diagnosis, including universal drug-susceptibility testing for all patients with tuberculosis, remains a key priority for tuberculosis elimination by 2035. The drug-resistant tuberculosis care cascade remains persistently challenged by substantial gaps in timely diagnosis and treatment of drug-resistant tuberculosis. Current diagnostics for drug-resistant tuberculosis are limited with respect to accuracy, time to results, affordability, suitability for resource-poor endemic settings, and accessibility for use at the point of care. WHO endorsement of the novel Xpert MTB/XDR assay holds notable promise for expanding access to testing and rapid diagnosis of tuberculosis drug resistance. The Xpert MTB/XDR assay detects resistance to isoniazid, ethionamide, fluoroquinolones, and second-line injectables, and is indicated for testing in patients with confirmed pulmonary tuberculosis. However, this iteration of the Xpert MTB/XDR cartridge might have less of an effect than expected, as WHO has since downgraded the role of second-line injectable agents in treating drug-resistant tuberculosis, and has revised case definitions of drug-resistant tuberculosis to incorporate resistance to new drugs. This Personal View explores the strengths and limitations of the Xpert MTB/XDR assay in the detection of drug resistance, the assay's ability to inform appropriate

drug-resistant tuberculosis drug selection, and the optimal placement of the Xpert XDR assay in the laboratory diagnostic workflow.

DOI: 10.1016/S1473-3099(21)00613-7
PMID: 35227392 [Indexed for MEDLINE]

18. **In vivo microevolution of Mycobacterium tuberculosis and transient emergence of atpE_Ala63Pro mutation during treatment in a pre-XDR TB patient.**

Eur Respir J. 2022 Mar 24;59(3):2102102. doi: 10.1183/13993003.02102-2021. Print 2022 Mar.

Ghodousi A(1)(2), Hussain Rizvi A(3), Khanzada FM(3), Akhtar N(4)(5), Ghafoor A(4), Trovato A(2), Cirillo DM(1)(2), Tahseen S(6).

Comment in
doi: 10.1183/13993003.00149-2022.

This letter describes microevolution of a pre-XDR MTB strain isolated from a pulmonary TB patient over an 18-month exposure to BDQ. MDR-TB therapies with BDQ require a functional background regimen to prevent emergence of additional resistance. https://bit.ly/3D05qT9

Bedaquiline is a novel anti-tuberculosis drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) recommended by the World Health Organization (WHO) [1] and recently upgraded to the group A classification of TB drugs as one of the three key drugs, along with linezolid and fluoroquinolones, to be included in all MDR-TB treatment regimens. Based on this grouping of second-line drugs, extensively drug-resistant tuberculosis (XDR-TB) is redefined as MDR- or rifampicin-resistant-TB that is resistant to a fluoroquinolone and to either bedaquiline or linezolid or both. Moreover, bedaquiline, in combination with pretomanid and linezolid, is a part of BPaL regimen recommended for treating adult pulmonary TB patients having pre-XDR-TB or MDR-TB which is either non-responsive or intolerant to recommended standard treatment [2]. However, globally emerging resistance to bedaquiline threatens the effectiveness of novel treatment regimens for drug-resistant TB.

DOI: 10.1183/13993003.02102-2021
PMCID: PMC8943273
PMID: 34795042 [Indexed for MEDLINE]

19. **QT prolongation in the STREAM Stage 1 Trial.**

Int J Tuberc Lung Dis. 2022 Apr 1;26(4):334-340. doi: 10.5588/ijtld.21.0403.

Hughes G(1), Bern H(1), Chiang CY(2), Goodall RL(1), Nunn AJ(1), Rusen ID(3), Meredith SK(1).

BACKGROUND: STREAM (Standardized Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB) Stage 1 demonstrated non-inferior efficacy of a shortened regimen (the Short regimen) for rifampicin-resistant TB (RR-TB) compared to the contemporaneous WHO-recommended regimen. This regimen included moxifloxacin and clofazimine, known to cause QT prolongation, and severe prolongation was more common on the Short regimen. Here we investigate risk factors for QT prolongation with the Short regimen.METHODS: Data from patients prescribed the Short regimen (n = 282) were analysed to identify risk factors for severe QT prolongation (QT/QTcF ≥500 ms or ≥60 ms increase in QTcF from baseline).RESULTS: Of the 282 patients on the Short regimen, 94 (33.3%) developed severe QT prolongation: 31 QT/QTcF ≥500 ms; 92 experienced ≥60 ms QTcF increase from baseline. The median time to QT/QTcF ≥500 ms was 20 weeks (IQR 8-28), and the time to ≥60 ms increase from baseline was 18 weeks (IQR 8-28). Prolongation ≥500 ms was most frequent in patients from Mongolia (10/22, 45.5%) compared with 3.5-11.9% at other sites, P < 0.001. Higher baseline QTcF increased risk of prolongation to ≥500 ms (QTcF ≥400 ms: OR 5.99, 95% CI 2.04-17.62).CONCLUSION: One third of patients on the Short regimen developed severe QT prolongation. QT/QTcF ≥500 ms was more common in patients from Mongolia and in those with a higher baseline QTcF, which may have implications for implementation of treatment.

DOI: 10.5588/ijtld.21.0403
PMCID: PMC8982645
PMID: 35351238 [Indexed for MEDLINE]

20. **Emergence of bedaquiline resistance in a high tuberculosis burden country.**

Eur Respir J. 2022 Mar 24;59(3):2100621. doi: 10.1183/13993003.00621-2021. Print 2022 Mar.

Chesov E(1)(2)(3)(4)(5), Chesov D(1)(3)(4)(5), Maurer FP(6)(7), Andres S(6), Utpatel C(8), Barilar I(8), Donica A(2), Reimann M(3)(4)(9), Niemann S(3)(6)(8), Lange C(2)(3)(9)(10)(11), Crudu V(2), Heyckendorf J(3)(4)(9)(5), Merker M(12)(8)(13)(5).

Comment in
doi: 10.1183/13993003.00149-2022.

RATIONALE: Bedaquiline has been classified as a group A drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) by the World Health Organization; however, globally emerging resistance threatens the effectivity of novel MDR-TB treatment regimens.
OBJECTIVES: We analysed pre-existing and emerging bedaquiline resistance in bedaquiline-based MDR-TB therapies, and risk factors associated with treatment failure and death.
METHODS: In a cross-sectional cohort study, we employed patient data, whole-genome sequencing (WGS) and phenotyping of Mycobacterium tuberculosis complex (MTBC) isolates. We could retrieve baseline isolates from 30.5% (62 out of 203) of all MDR-TB patients who received bedaquiline between 2016 and 2018 in the Republic of Moldova. This includes 26 patients for whom we could also retrieve a follow-up isolate.
MEASUREMENTS AND MAIN RESULTS: At baseline, all MTBC isolates were susceptible to bedaquiline. Among 26 patients with available baseline and follow-up isolates, four (15.3%) patients harboured strains which acquired bedaquiline resistance under therapy, while one (3.8%) patient was re-infected with a second bedaquiline-resistant strain. Treatment failure and death were associated with cavitary disease (p=0.011), and any additional drug prescribed in the bedaquiline-containing regimen with WGS-predicted resistance at baseline (OR 1.92 per unit increase, 95% CI 1.15-3.21; p=0.012).
CONCLUSIONS: MDR-TB treatments based on bedaquiline require a functional background regimen to achieve high cure rates and to prevent the evolution of bedaquiline resistance. Novel MDR-TB therapies with bedaquiline require timely and comprehensive drug resistance monitoring.

DOI: 10.1183/13993003.00621-2021
PMCID: PMC8943268
PMID: 34503982 [Indexed for MEDLINE]

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

Ann Pharmacother. 2022 Apr;56(4):441-462. doi: 10.1177/10600280211031390. Epub 2021 Jul 14.

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

OBJECTIVE: To review the spectrum of activity, efficacy, safety, and role in

therapy of all antibiotics and related biologics approved by the Food and Drug Administration (FDA) in the last decade.
DATA SOURCES: A literature search was performed using PubMed and Google Scholar (2010 to end May 2021) with the search terms' name of the antibiotic or the biologic. Data were also obtained from the prescribing information, FDA, and ClinicalTrials.gov websites.
STUDY SELECTION: All relevant English-language, late phase clinical trials assessing the safety and efficacy of the identified drugs were included. Review articles and references of retrieved articles were evaluated for relevant data.
DATA SYNTHESIS: Antibiotic resistance is a public health crisis, and antibiotic development is imperative to outpace the ability of bacteria to develop resistance. Only 17 new systemic antibiotics and 1 related biologic have been approved by the FDA since 2010. Among these drugs, 14 were approved for common bacterial infections, 1 was approved for Clostridioides difficile infection (CDI), 1 was licensed to prevent CDI recurrence, and 2 were approved for drug-resistant tuberculosis. Very few antibiotics are in clinical development.
RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE: The arrival of these new antibiotics was welcomed with great enthusiasm, particularly when they met previously unmet medical needs. Unfortunately, the majority of them represent modifications to existing chemical structures rather than new drug classes. Despite the availability of these antibiotics, managing patients with deep-seated infections and those with extensively resistant gram-negative organisms remains challenging.
CONCLUSIONS: The number of new antibiotics and their indications are not keeping up with resistance and the needs of the patients.

DOI: 10.1177/10600280211031390
PMID: 34259076 [Indexed for MEDLINE]

22. **Evaluation of TBMDR® and XDRA® for the detection of multidrug resistant and pre-extensively drug resistant tuberculosis.**

J Clin Tuberc Other Mycobact Dis. 2022 Feb 9;27:100303. doi: 10.1016/j.jctube.2022.100303. eCollection 2022 May.

Cho E(1), Lee SJ(2), Lim J(2), Kim DS(2), Kim N(2), Park HO(2), Lee JI(1), Son E(1), Cho SN(1), Aung WW(3), Seok Lee J(1).

This study evaluated the diagnostic performance of the AccuPower® TB&MDR Real-Time PCR (TBMDR®) and AccuPower® XDR-TB Real-Time PCR Kit-A (XDRA®) to detect multidrug-resistant (MDR-TB) and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) in comparison with phenotypic drug susceptibility testing (DST) using MGIT 960 on 234 clinical Mycobacterium tuberculosis

isolates. Discrepant results were confirmed by direct-sequencing. Sensitivity and specificity of TBMDR and XDRA for cultured isolates were 81.2% and 95.8% for isoniazid (INH) resistance, 95.7% and 95.7% for rifampicin (RIF) resistance, 84.1% and 99.1% for fluoroquinolone (FQ) resistance, and 67.4% and 100% for second-line injectables resistance. The sensitivities of each drug were equivalent to other molecular DST methods. High concordance was observed when compared to direct-sequencing. We also found that TBMDR and XDRA assays can detect INH, RIF and FQ resistance in isolates with low level resistance-associated mutations which were missed by phenotypic DST. Our study showed TBMDR and XDRA assays could be the useful tools to detect MDR-TB and pre-XDR-TB.

DOI: 10.1016/j.jctube.2022.100303
PMCID: PMC8857659
PMID: 35243010

23. **Bedaquiline can act as core drug in a standardised treatment regimen for fluoroquinolone-resistant rifampicin-resistant tuberculosis.**

Eur Respir J. 2022 Mar 24;59(3):2102124. doi: 10.1183/13993003.02124-2021. Print 2022 Mar.

Decroo T(1), Aung KJM(2), Hossain MA(2), Gumusboga M(3), Ortuno-Gutierrez N(4), De Jong BC(3), Van Deun A(5).

Comment in
doi: 10.1183/13993003.00149-2022.

In the original short treatment regimen for rifampicin-resistant tuberculosis, bedaquiline proved an adequate core drug for fluoroquinolone resistance, ensuring early conversion and relapse-free cure. Use of linezolid did not have the same early effect. https://bit.ly/3gWuf9z

In Bangladesh, a standardised short treatment regimen (STR) was highly effective in patients diagnosed with rifampicin-resistant tuberculosis (RR-TB), without proof of initial resistance to fluoroquinolone, and no prior treatment for RR-TB [1]. The STR relied on a fluoroquinolone, either gatifloxacin, levofloxacin or moxifloxacin, as core drug, with gatifloxacin being most effective in assuring relapse-free cure [2]. A second-line injectable was used during at least the first four months to prevent the selection of fluoroquinolone-resistant (sub)populations [3]. Other drugs served as companion drugs.

DOI: 10.1183/13993003.02124-2021
PMCID: PMC8943272
PMID: 34561288 [Indexed for MEDLINE]

24. **Low BMI increases all-cause mortality rates in patients with drug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Apr 1;26(4):326-333. doi: 10.5588/ijtld.21.0450.

Adamashvili N(1), Baliashvili D(2), Kuchukhidze G(1), Salindri AD(3), Kempker RR(4), Blumberg HM(5), Lomtadze N(6), Avaliani Z(6), Magee MJ(7).

BACKGROUND: Loss to follow-up (LTFU) is common among patients with drug-resistant TB (DR-TB) receiving second-line TB treatment; however, little is known about outcomes after LTFU, including mortality.OBJECTIVE: To determine rates of and factors associated with all-cause mortality among patients with DR-TB who were LTFU.METHODS: Retrospective cohort study of adult patients with DR-TB in Georgia who initiated second-line TB treatment during 2011-2014 and were LTFU. Survival analyses were used to estimate all-cause mortality rates and adjusted hazard ratios (aHR).RESULTS: During 2011-2014, 2,437 second-line treatment episodes occurred and 695 patients were LTFU. Among 695 LTFU patients, 143 (21%) died during 2,686 person-years (PY) post-LTFU (all-cause mortality rate 5.1%, 95% CI 4.3-6.0 per 100 PY). In multivariable analysis, low weight (BMI < 18.5 kg/m^2) at treatment initiation (aHR 3.2, 95% CI 2.2-4.7), return to treatment after LTFU (aHR 3.1, 95% CI 2.2-4.4), <12 months of treatment (aHR 2.4, 95% CI 1.4-4.1) and a pre-LTFU positive culture (aHR 3.3, 95% CI 2.2-4.9) were associated with all-cause mortality.CONCLUSION: High all-cause mortality occurred among patients with DR-TB after LTFU despite a low HIV prevalence. Providing additional assistance for patients during DR-TB treatment to prevent LTFU and use of new and shorter treatment regimens may reduce mortality among LTFU.

DOI: 10.5588/ijtld.21.0450
PMID: 35351237

25. **Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review.**

JAC Antimicrob Resist. 2022 Mar 29;4(2):dlac029. doi: 10.1093/jacamr/dlac029. eCollection 2022 Apr.

Mallick JS(1), Nair P(1), Abbew ET(1)(2), Van Deun A(3), Decroo T(1).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is considered to be a public health threat and is difficult to cure, requiring a lengthy treatment with potent, potentially toxic drugs. The novel antimicrobial agent bedaquiline has shown promising results for patients with DR-TB, improving the rate of culture conversion and reducing TB-related mortality. However, increasing numbers of cases with acquired bedaquiline resistance (ABR) have been reported in recent years.
METHODS: This systematic review aimed to assess the frequency of ABR and characteristics of patients acquiring it. Studies showing data on sequential bedaquiline drug-susceptibility testing in patients treated with a bedaquiline-containing regimen were included. The databases CENTRAL, PubMed and Embase were manually searched, and 866 unique records identified, eventually leading to the inclusion of 13 studies. Phenotypic ABR was assessed based on predefined MIC thresholds and genotypic ABR based on the emergence of resistance-associated variants.
RESULTS: The median (IQR) frequency of phenotypic ABR was 2.2% (1.1%-4.6%) and 4.4% (1.8%-5.8%) for genotypic ABR. Among the studies reporting individual data of patients with ABR, the median number of likely effective drugs in a treatment regimen was five, in accordance with WHO recommendations. In regard to the utilization of important companion drugs with high and early bactericidal activity, linezolid was included in the regimen of most ABR patients, whereas the usage of other group A (fluoroquinolones) and former group B drugs (second-line injectable drugs) was rare.
CONCLUSIONS: Our findings suggest a relevant frequency of ABR, urging for a better protection against it. Therefore, treatment regimens should include drugs with high resistance-preventing capacity through high and early bactericidal activity.

DOI: 10.1093/jacamr/dlac029
PMCID: PMC8963286
PMID: 35356403

26. **Feasibility of a "Salvage Regimen" Using Home-based Intravenous Meropenem Therapy With a Delamanid/Bedaquilline Containing Regimen in the Management of MDR/XDR Pediatric Tuberculosis.**

Pediatr Infect Dis J. 2022 May 1;41(5):401-404. doi: 10.1097/INF.0000000000003486.

Shah I(1), Antony S(1), Jaiswal A(1), Bodhanwala M(2), Shah D(3), Tipre P(3), Salve J(4), Parmar M(4)(5), Sachdeva KS(6).

INTRODUCTION: The prevalence of multidrug resistant (MDR) tuberculosis (TB) with additional resistance to fluoroquinolones or second-line injectables (MDRFQ/SLI)/extensively drug-resistant TB (XDR-TB) in children is high in Mumbai. There are limited therapeutic options available in management of such children. Carbapenems, although approved for this indication, requires 2 to 3 daily injections, which are cumbersome. Bedaquilline (Bdq) and Delamanid (Dlm), the new antitubercular drugs still remain inaccessible to this subset of patients caused by conditional approvals. Hence, newer strategies to combat MDRFQ/SLI/XDR-TB needs to be explored.
OBJECTIVES: To study feasibility and interim outcomes of a "salvage regimen" using home-based carbapenem therapy through peripherally inserted central catheter as part of a longer (18-20 months) optimized background regimen including Dlm or Bdq or both in pediatric MDRFQ/SLI/XDR-TB patients who failed a standard MDR-TB regimen under the National Tuberculosis Elimination Programme in Mumbai, India.
DESIGN AND METHODS: Retrospective descriptive analysis study. National Tuberculosis Elimination Programme medical records of all MDRFQ/SLI/XDR-TB patients enrolled at the pediatric TB clinic at BJ Wadia Hospital for Children, Mumbai who were initiated on such "salvage regimen" during the period between April 2018 and December 2020 were retrospectively studied. Treatment outcomes and adverse events were described.
RESULTS: Of the 15 patients enrolled, mean age of the patient population was 12.53 ± 2.47 years and the female:male ratio was 13:2. Seven patients had XDR-TB while 8 patients had MDRFQ/SLI. Most common adverse event noted was dyselectrolytemia (3 patients). Catheter-related complications were reported in 5 patients and included catheter blockage, leak, and thrombosis. Sputum culture conversion was reported in all of the patients. One child mortality was reported and 2 patients were lost to follow up during study period.
CONCLUSIONS: Home-based meropenem therapy using peripherally inserted central catheter is feasible with few adverse effects. This can be a promising strategy in the management of MDRFQ/SLI/XDR-TB when an effective oral regimen cannot be otherwise constituted and needs to be explored further.

DOI: 10.1097/INF.0000000000003486
PMID: 35153288 [Indexed for MEDLINE]

27. **Updating the approaches to define susceptibility and resistance to anti-tuberculosis agents: implications for diagnosis and treatment.**

Eur Respir J. 2022 Apr 14;59(4):2200166. doi: 10.1183/13993003.00166-2022. Print 2022 Apr.

Antimycobacterial Susceptibility Testing Group; Antimycobacterial Susceptibility Testing Group:.

DOI: 10.1183/13993003.00166-2022
PMID: 35422426 [Indexed for MEDLINE]

28. **A 10-year Review of TB Notifications and Mortality Trends Using a Joint Point Analysis in Zambia - a High TB burden country: Invited article - IJID World TB Day Series 2022.**

Int J Infect Dis. 2022 Mar 29:S1201-9712(22)00188-6. doi: 10.1016/j.ijid.2022.03.046. Online ahead of print.

Lungu P(1), Kasapo C(2), Mihova R(3), Chimzizi R(4), Sikazwe L(5), Banda I(6), Mucheleng'anga LA(7), Chanda-Kapata P(8), Kapata N(9), Zumla A(10), Mwaba P(11).

BACKGROUND: Zambia is one of the TB high-burden countries. It is important to track the progress being made towards enhancing case finding and reducing mortality. We reviewed routine TB notifications and mortality trends, over a decade from all facilities in Zambia.
METHODS: A 10-year retrospective study of TB notifications and mortality trends was performed using a Joint Point Analysis version 4.9.0.0, NCI. We extracted the annual national TB program data for the period under review.
RESULTS: There was a decline in annual point average for notification between 2010 and 2020 in both males and females, but the females notification rates had a higher rate of decline (AAPC = -6.7, 95%CI:-8.3 to -5.0), p<0.001) compared to the decline in males notification rate (AAPC = -4.1, 95%CI:-4.1 to -5.1, P<0.001). We found a significant growth rate in the proportion of TB patients that were bacteriologically confirmed (AAPC = 6.1, 95% CI: 3.6 to 8.7, p< 0.001), while the proportion of clinically diagnosed patients declined (AAPC= -0.1, 95%CI: -2.3 to 2.1, p<0.001). Notification of drug-resistant TB increased exponentially (AAPC=27.3, 95% CI: 13 to 41), p< 0.001) while mortality rate declined from 21.3 in 2011 to 12.7 in 2019 per 100,000 population (AAP=-5.6, 95%CI: -9.6 to -1.5, p=0.008).
CONCLUSIONS: This study has illustrated the importance of reviewing and analyzing routinely collected TB data by national programs. The study revealed areas of improvement in terms of TB control and underscores the need for increased and sustained investment in case detection and diagnostics.

DOI: 10.1016/j.ijid.2022.03.046
PMID: 35364287

29. **Programme costs of longer and shorter tuberculosis drug regimens and drug import: a modelling study for Karakalpakstan, Uzbekistan.**

ERJ Open Res. 2022 Mar 21;8(1):00622-2021. doi: 10.1183/23120541.00622-2021. eCollection 2022 Jan.

Kohler S(1)(2), Sitali N(3), Achar J(4), Paul N(2).

BACKGROUND: The introduction of new and often shorter tuberculosis (TB) drug regimens affects the cost of TB programmes.
METHODS: We modelled drug purchase and import costs for 20-month, 9-month and 4- to 6-month TB drug regimens based on 2016-2020 treatment numbers from a TB programme in Karakalpakstan, Uzbekistan, and 2021 Global Drug Facility prices.
RESULTS: On average, 2225±374 (±sd) people per year started TB treatment, 30±2.1% of whom were diagnosed with drug-resistant forms of TB. Transitioning from a 6-month to a 4-month drug-susceptible (DS)-TB drug regimen increased the TB programme's annual DS-TB drug cost from USD 65±10 K to USD 357±56 K ($p<0.001$) and its drug import cost from USD 6.4±1.0 K to USD 9.3±1.4 K ($p=0.008$). Transitioning from a 20-month all-oral multidrug-resistant (MDR)-TB drug regimen to a 9-month MDR-TB drug regimen with an injectable antibiotic decreased the TB programme's annual MDR-TB drug cost from USD 1336±265 K to USD 266±53 K ($p<0.001$) and had no significant effect on the drug import cost (USD 28±5.5 K versus USD 27±5.4 K; $p=0.88$). Purchasing (USD 577±114 K) and importing (USD 3.0±0.59 K) the 6-month all-oral MDR-TB drug regimen cost more than procuring the 9-month MDR-TB drug regimen but less than the 20-month all-oral MDR-TB drug regimen (both $p<0.01$).
CONCLUSION: Introducing new and shorter TB drug regimens could increase the cost of TB programmes with low drug resistance rates and decrease the cost of TB programmes with high drug resistance rates.

DOI: 10.1183/23120541.00622-2021
PMCID: PMC8943289
PMID: 35350276

30. **Rapid Identification of Drug-Resistant Tuberculosis Genes Using Direct PCR**

Amplification and Oxford Nanopore Technology Sequencing.

Can J Infect Dis Med Microbiol. 2022 Mar 28;2022:7588033. doi: 10.1155/2022/7588033. eCollection 2022.

Zhao K(1), Tu C(1), Chen W(2), Liang H(2), Zhang W(1), Wang Y(1), Jin Y(2), Hu J(2), Sun Y(3), Xu J(3), Yu Y(1).

Mycobacterium tuberculosis antimicrobial resistance has been continually reported and is a major public health issue worldwide. Rapid prediction of drug resistance is important for selecting appropriate antibiotic treatments, which significantly increases cure rates. Gene sequencing technology has proven to be a powerful strategy for identifying relevant drug resistance information. This study established a sequencing method and bioinformatics pipeline for resistance gene analysis using an Oxford Nanopore Technologies sequencer. The pipeline was validated by Sanger sequencing and exhibited 100% concordance with the identified variants. Turnaround time for the nanopore sequencing workflow was approximately 12 h, facilitating drug resistance prediction several weeks earlier than that of traditional phenotype drug susceptibility testing. This study produced a customized gene panel assay for rapid bacterial identification via nanopore sequencing, which improves the timeliness of tuberculosis diagnoses and provides a reliable method that may have clinical application.

DOI: 10.1155/2022/7588033
PMCID: PMC8979720
PMID: 35386470

31. **Modeling treatment effect modification in multidrug-resistant tuberculosis in an individual patientdata meta-analysis.**

Stat Methods Med Res. 2022 Apr;31(4):689-705. doi: 10.1177/09622802211046383. Epub 2021 Dec 13.

Liu Y(1), Schnitzer ME(2)(3), Wang G(1), Kennedy E(4), Viiklepp P(5), Vargas MH(6), Sotgiu G(7), Menzies D(8)(9), Benedetti A(1)(8)(10).

Effect modification occurs while the effect of the treatment is not homogeneous across the different strata of patient characteristics. When the effect of treatment may vary from individual to individual, precision medicine can be improved by identifying patient covariates to estimate the size and direction of the effect at the individual level. However, this task is statistically

challenging and typically requires large amounts of data. Investigators may be interested in using the individual patient data from multiple studies to estimate these treatment effect models. Our data arise from a systematic review of observational studies contrasting different treatments for multidrug-resistant tuberculosis, where multiple antimicrobial agents are taken concurrently to cure the infection. We propose a marginal structural model for effect modification by different patient characteristics and co-medications in a meta-analysis of observational individual patient data. We develop, evaluate, and apply a targeted maximum likelihood estimator for the doubly robust estimation of the parameters of the proposed marginal structural model in this context. In particular, we allow for differential availability of treatments across studies, measured confounding within and across studies, and random effects by study.

DOI: 10.1177/09622802211046383
PMCID: PMC8961254
PMID: 34903098 [Indexed for MEDLINE]

32. **Chrysomycin A inhibits the topoisomerase I of Mycobacterium tuberculosis.**

J Antibiot (Tokyo). 2022 Apr;75(4):226-235. doi: 10.1038/s41429-022-00503-z. Epub 2022 Feb 8.

Muralikrishnan B(1), Edison LK(1), Dusthackeer A(2), Jijimole GR(1), Ramachandran R(1), Madhavan A(1), Kumar RA(3).

Novel anti-tuberculosis drugs are essential to manage drug-resistant tuberculosis, caused by Mycobacterium tuberculosis. We recently reported the antimycobacterial activity of chrysomycin A in vitro and in infected macrophages. In this study, we report that it inhibits the growth of drug-resistant clinical strains of M. tuberculosis and acts in synergy with anti-TB drugs such as ethambutol, ciprofloxacin, and novobiocin. In pursuit of its mechanism of action, it was found that chrysomycin A is bactericidal and exerts this activity by interacting with DNA at specific sequences and by inhibiting the topoisomerase I activity of M. tuberculosis. It also exhibits weak inhibition of the DNA gyrase enzyme of the pathogen.

DOI: 10.1038/s41429-022-00503-z
PMID: 35136191

33. **Prediction of different interventions on the burden of drug-resistant tuberculosis in China: a dynamic modeling study.**

J Glob Antimicrob Resist. 2022 Mar 26:S2213-7165(22)00073-X. doi: 10.1016/j.jgar.2022.03.018. Online ahead of print.

Xu A(1), Wen ZX(1), Wang Y(1), Wang WB(2).

BACKGROUND: Tuberculosis (TB) is one of the top ten causes of death worldwide. The World Health Organization adopted the "End TB Strategy" to end the global TB epidemic by 2035. However, achieving this goal will be difficult using current measures.
METHODS: A Susceptible-Exposed-Infectious-Recovered (SEIR) model that distinguishes drug-sensitive (DS) and drug-resistant (DR) TB in the entire Chinese population was established. Goodness-of-fit tests and sensitivity analyses were used to assess model performance. Predictive analysis was performed to assess the effect of different prevention and control strategies on DR-TB.
RESULTS: We used parameter fitting to determine the basic reproduction number of the model as R0 =0.6993. The predictive analysis led to two major projections that can achieve the goal by 2035. First, if the progression rate of latently infected people reaches 10%, there will be 92.2% fewer cases than in 2015. Second, if the cure rate of DR-TB increases to 40%, there will be 91.5% fewer cases than in 2015. A combination of five interventions could lead to earlier achievement of the 2035 target.
CONCLUSION: We found that reducing the probability of transmission and the rate of disease progression in patients with DR-TB, improving treatment compliance and the cure rate of patients with DR-TB can contribute to attaining the goal of the End TB Strategy.

DOI: 10.1016/j.jgar.2022.03.018
PMID: 35351676

34. **Treatments of Multidrug-Resistant Tuberculosis: Light at the End of the Tunnel.**

Am J Respir Crit Care Med. 2022 Mar 23. doi: 10.1164/rccm.202202-0393ED. Online ahead of print.

Lange C(1), Barry Iii CE(2), Horsburgh CR Jr(3).

DOI: 10.1164/rccm.202202-0393ED
PMID: 35320062

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

HIV Med. 2022 Mar 25. doi: 10.1111/hiv.13268. Online ahead of print.

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

BACKGROUND: The European AIDS Clinical Society (EACS) Guidelines were revised in 2021 for the 17th time with updates on all aspects of HIV care.
KEY POINTS OF THE GUIDELINES UPDATE: Version 11.0 of the Guidelines recommend six first-line treatment options for antiretroviral treatment (ART)-naïve adults: tenofovir-based backbone plus an unboosted integrase inhibitor or plus doravirine; abacavir/lamivudine plus dolutegravir; or dual therapy with lamivudine or emtricitabine plus dolutegravir. Recommendations on preferred and alternative first-line combinations from birth to adolescence were included in the new paediatric section made with Penta. Long-acting cabotegravir plus rilpivirine was included as a switch option and, along with fostemsavir, was added to all drug-drug interaction (DDI) tables. Four new DDI tables for anti-tuberculosis drugs, anxiolytics, hormone replacement therapy and COVID-19 therapies were introduced, as well as guidance on screening and management of anxiety disorders, transgender health, sexual health for women and menopause. The sections on frailty, obesity and cancer were expanded, and recommendations for the management of people with diabetes and cardiovascular disease risk were revised extensively. Treatment of recently acquired hepatitis C is recommended with ongoing risk behaviour to reduce transmission. Bulevirtide was included as a treatment option for the hepatitis Delta virus. Drug-resistant tuberculosis guidance was adjusted in accordance with the 2020 World Health Organization recommendations. Finally, there is new guidance on COVID-19 management with a focus on continuance of HIV care.
CONCLUSIONS: In 2021, the EACS Guidelines were updated extensively and broadened to include new sections. The recommendations are available as a free app, in interactive web format and as an online pdf.

DOI: 10.1111/hiv.13268
PMID: 35338549

36. **Molecular Epidemiology and Polymorphism Analysis in Drug-Resistant Genes in M. tuberculosis Clinical Isolates from Western and Northern India.**

Infect Drug Resist. 2022 Apr 8;15:1717-1732. doi: 10.2147/IDR.S345855.
eCollection 2022.

Rana V(1), Singh N(1), Nikam C(2), Kambli P(2), Singh PK(3), Singh U(3), Jain A(3), Rodrigues C(2), Sharma C(1).

INTRODUCTION: The mechanistic details of first line drug (FLD) resistance have been thoroughly explored but the genetic resistance mechanisms of second line injectables, which form the backbone of the combinatorial drug resistant tuberculosis therapy, are partially identified. This study aims to highlight the genetic and spoligotypic differences in the second line drug (SLD) resistant and sensitive Mycobacterium tuberculosis (Mtb) clinical isolates from Mumbai (Western India) and Lucknow (Northern India).
METHODS: The rrs, eis, whiB7, tlyA, gyrA and gyrB target loci were screened in 126 isolates and spoligotyped.
RESULTS: The novel mutations were observed in whiB7 loci (A43T, C44A, C47A, G48T, G59A and T152G in 5'-UTR; A42C, C253T and T270G in gene), tlyA (+CG200, G165A, C415G, and +G543) and gyrB (+G1359 and +A1429). Altogether, the rrs, eis, and whiB7 loci harbored mutations in ~86% and ~47% kanamycin resistant isolates from Mumbai and Lucknow, respectively. Mumbai strains displayed higher prevalence of mutations in gyrA (~85%) and gyrB loci (~13%) as compared to those from Lucknow (~69% and ~3.0%, respectively). Further, spoligotyping revealed that Beijing lineage is distributed equally amongst the drug resistant strains of Mumbai and Lucknow, but EAI-5 is existed at a higher level only in Mumbai. The lineages Manu2, CAS1-Delhi and T1 are more prevalent in Lucknow.
CONCLUSION: Besides identifying novel mutations in whiB7, tlyA and gyrB target loci, our analyses unveiled a potential polymorphic and phylogeographical demarcation among two distinct regions.

DOI: 10.2147/IDR.S345855
PMCID: PMC9005233
PMID: 35422638

37. **Multidrug-resistant tuberculosis control in Rwanda overcomes a successful clone**

that causes most disease over a quarter century.

J Clin Tuberc Other Mycobact Dis. 2022 Jan 24;27:100299. doi: 10.1016/j.jctube.2022.100299. eCollection 2022 May.

Ngabonziza JCS(1)(2)(3), Rigouts L(2)(4), Torrea G(2), Decroo T(5)(6), Kamanzi E(1), Lempens P(2)(4), Rucogoza A(1), Habimana YM(7), Laenen L(8), Niyigena BE(1), Uwizeye C(2), Ushizimpumu B(1), Mulders W(2), Ivan E(1), Tzfadia O(2), Muvunyi CM(3), Migambi P(6), Andre E(2)(8)(9), Mazarati JB(10), Affolabi D(11), Umubyeyi AN(12), Nsanzimana S(13), Portaels F(2), Gasana M(7), de Jong BC(2), Meehan CJ(2)(14).

SUMMARY BACKGROUND: Multidrug-resistant (MDR) tuberculosis (TB) poses an important challenge in TB management and control. Rifampicin resistance (RR) is a solid surrogate marker of MDR-TB. We investigated the RR-TB clustering rates, bacterial population dynamics to infer transmission dynamics, and the impact of changes to patient management on these dynamics over 27 years in Rwanda.
METHODS: We analysed whole genome sequences of a longitudinal collection of nationwide RR-TB isolates. The collection covered three important periods: before programmatic management of MDR-TB (PMDT; 1991-2005), the early PMDT phase (2006-2013), in which rifampicin drug-susceptibility testing (DST) was offered to retreatment patients only, and the consolidated phase (2014-2018), in which all bacteriologically confirmed TB patients had rifampicin DST done mostly via Xpert MTB/RIF assay. We constructed clusters based on a 5 SNP cut-off and resistance conferring SNPs. We used Bayesian modelling for dating and population size estimations, TransPhylo to estimate the number of secondary cases infected by each patient, and multivariable logistic regression to assess predictors of being infected by the dominant clone.
RESULTS: Of 308 baseline RR-TB isolates considered for transmission analysis, the clustering analysis grouped 259 (84.1%) isolates into 13 clusters. Within these clusters, a single dominant clone was discovered containing 213 isolates (82.2% of clustered and 69.1% of all RR-TB), which we named the "Rwanda Rifampicin-Resistant clone" (R3clone). R3clone isolates belonged to Ugandan sub-lineage 4.6.1.2 and its rifampicin and isoniazid resistance were conferred by the Ser450Leu mutation in rpoB and Ser315Thr in katG genes, respectively. All R3clone isolates had Pro481Thr, a putative compensatory mutation in the rpoC gene that likely restored its fitness. The R3clone was estimated to first arise in 1987 and its population size increased exponentially through the 1990s', reaching maximum size (∼84%) in early 2000 s', with a declining trend since 2014. Indeed, the highest proportion of R3clone (129/157; 82·2%, 95%CI: 75·3-87·8%) occurred between 2000 and 13, declining to 64·4% (95%CI: 55·1-73·0%) from 2014 onward. We showed that patients with R3clone detected after an unsuccessful category 2 treatment were more likely to generate secondary cases than patients with R3clone detected after an unsuccessful category 1 treatment

regimen.
CONCLUSIONS: RR-TB in Rwanda is largely transmitted. Xpert MTB/RIF assay as first diagnostic test avoids unnecessary rounds of rifampicin-based TB treatment, thus preventing ongoing transmission of the dominant R3clone. As PMDT was intensified and all TB patients accessed rifampicin-resistance testing, the nationwide R3clone burden declined. To our knowledge, our findings provide the first evidence supporting the impact of universal DST on the transmission of RR-TB.

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PMCID: PMC8802117
PMID: 35146133

38. **Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study.**

Lancet Infect Dis. 2022 Apr;22(4):496-506. doi: 10.1016/S1473-3099(21)00470-9. Epub 2021 Nov 12.

Ismail NA(1), Omar SV(2), Moultrie H(3), Bhyat Z(3), Conradie F(4), Enwerem M(5), Ferreira H(6), Hughes J(7), Joseph L(3), Kock Y(8), Letsaolo V(3), Maartens G(9), Meintjes G(9), Ngcamu D(3), Okozi N(3), Padanilam X(10), Reuter A(11), Romero R(12), Schaaf S(7), Te Riele J(13), Variava E(14), van der Meulen M(3), Ismail F(15), Ndjeka N(8).

Comment in
Lancet Infect Dis. 2022 Feb;22(2):166-167.
Lancet Infect Dis. 2022 Feb;22(2):166.

Comment on
Lancet Infect Dis. 2022 Apr;22(4):432-433.

BACKGROUND: Bedaquiline improves outcomes of patients with rifampicin-resistant and multidrug-resistant (MDR) tuberculosis; however, emerging resistance threatens this success. We did a cross-sectional and longitudinal analysis evaluating the epidemiology, genetic basis, and treatment outcomes associated with bedaquiline resistance, using data from South Africa (2015-19).
METHODS: Patients with drug-resistant tuberculosis starting bedaquiline-based treatment had surveillance samples submitted at baseline, month 2, and month 6, along with demographic information. Culture-positive baseline and post-baseline

isolates had phenotypic resistance determined. Eligible patients were aged 12 years or older with a positive culture sample at baseline or, if the sample was invalid or negative, a sample within 30 days of the baseline sample submitted for bedaquiline drug susceptibility testing. For the longitudinal study, the first surveillance sample had to be phenotypically susceptible to bedaquiline for inclusion. Whole-genome sequencing was done on bedaquiline-resistant isolates and a subset of bedaquiline-susceptible isolates. The National Institute for Communicable Diseases tuberculosis reference laboratory, and national tuberculosis surveillance databases were matched to the Electronic Drug-Resistant Tuberculosis Register. We assessed baseline resistance prevalence, mutations, transmission, cumulative resistance incidence, and odds ratios (ORs) associating risk factors for resistance with patient outcomes.
FINDINGS: Between Jan 1, 2015, and July 31, 2019, 8041 patients had surveillance samples submitted, of whom 2023 were included in the cross-sectional analysis and 695 in the longitudinal analysis. Baseline bedaquiline resistance prevalence was 3·8% (76 of 2023 patients; 95% CI 2·9-4·6), and it was associated with previous exposure to bedaquiline or clofazimine (OR 7·1, 95% CI 2·3-21·9) and with rifampicin-resistant or MDR tuberculosis with additional resistance to either fluoroquinolones or injectable drugs (pre-extensively-drug resistant [XDR] tuberculosis: 4·2, 1·7-10·5) or to both (XDR tuberculosis: 4·8, 2·0-11·7). Rv0678 mutations were the sole genetic basis of phenotypic resistance. Baseline resistance could be attributed to previous bedaquiline or clofazimine exposure in four (5·3%) of 76 patients and to primary transmission in six (7·9%). Odds of successful treatment outcomes were lower in patients with baseline bedaquiline resistance (0·5, 0·3-1). Resistance during treatment developed in 16 (2·3%) of 695 patients, at a median of 90 days (IQR 62-195), with 12 of these 16 having pre-XDR or XDR.
INTERPRETATION: Bedaquiline resistance was associated with poorer treatment outcomes. Rapid assessment of bedaquiline resistance, especially when patients were previously exposed to bedaquiline or clofazimine, should be prioritised at baseline or if patients remain culture-positive after 2 months of treatment. Preventing resistance by use of novel combination therapies, current treatment optimisation, and patient support is essential.
FUNDING: National Institute for Communicable Diseases of South Africa.

DOI: 10.1016/S1473-3099(21)00470-9
PMID: 34780706 [Indexed for MEDLINE]

39. **Drug exposure and susceptibility of second-line drugs correlate with treatment response in patients with multidrug-resistant tuberculosis: a multicentre prospective cohort study in China.**

Eur Respir J. 2022 Mar 24;59(3):2101925. doi: 10.1183/13993003.01925-2021. Print 2022 Mar.

Zheng X(1), Davies Forsman L(2)(3), Bao Z(4), Xie Y(5), Ning Z(5), Schön T(6)(7), Bruchfeld J(2)(3), Xu B(1), Alffenaar JW(8)(9)(10)(11), Hu Y(12)(11).

Comment in
doi: 10.1183/13993003.00149-2022.

BACKGROUND: Understanding the impact of drug exposure and susceptibility on treatment response of multidrug-resistant tuberculosis (MDR-TB) will help to optimise treatment. This study aimed to investigate the association between drug exposure, susceptibility and response to MDR-TB treatment.
METHODS: Drug exposure and susceptibility for second-line drugs were measured for patients with MDR-TB. Multivariate analysis was applied to investigate the impact of drug exposure and susceptibility on sputum culture conversion and treatment outcome. Probability of target attainment was evaluated. Random Forest and CART (Classification and Regression Tree) analysis was used to identify key predictors and their clinical targets among patients on World Health Organization-recommended regimens.
RESULTS: Drug exposure and corresponding susceptibility were available for 197 patients with MDR-TB. The probability of target attainment was highly variable, ranging from 0% for ethambutol to 97% for linezolid, while patients with fluoroquinolones above targets had a higher probability of 2-month culture conversion (56.3% versus 28.6%; adjusted OR 2.91, 95% CI 1.42-5.94) and favourable outcome (88.8% versus 68.8%; adjusted OR 2.89, 95% CI 1.16-7.17). Higher exposure values of fluoroquinolones, linezolid and pyrazinamide were associated with earlier sputum culture conversion. CART analysis selected moxifloxacin area under the drug concentration-time curve/minimum inhibitory concentration (AUC0-24h/MIC) of 231 and linezolid AUC0-24h/MIC of 287 as best predictors for 6-month culture conversion in patients receiving identical Group A-based regimens. These associations were confirmed in multivariate analysis.
CONCLUSIONS: Our findings indicate that target attainment of TB drugs is associated with response to treatment. The CART-derived thresholds may serve as targets for early dose adjustment in a future randomised controlled study to improve MDR-TB treatment outcome.

DOI: 10.1183/13993003.01925-2021
PMCID: PMC8943270
PMID: 34737224 [Indexed for MEDLINE]

40. **Analysis of efficacy and safety of linezolid-based chemotherapeutic regimens for patients with postoperative multidrug-resistant spinal tuberculosis.**

Int J Infect Dis. 2022 Mar 24;118:264-269. doi: 10.1016/j.ijid.2022.03.020.
Online ahead of print.

Qiao J(1), Yang L(2), Feng J(2), Dai X(3), Xu F(3), Xia P(4).

OBJECTIVES: The study aimed to explore the efficacy and safety of linezolid-based chemotherapeutic regimens for patients with postoperative multidrug-resistant spinal tuberculosis.
METHODS: The randomized controlled study included 50 Mycobacterium tuberculosis culture or pathological-confirmed multidrug resistant tuberculosis patients who received spinal surgery from January 2018 to February 2020. Twenty-five patients were assigned to the control group and the study group, respectively. Random number method was used for patient allocation and they were treated with levofloxacin, pyrazinamide, thioisonicotinamide enteric-coated tablet, amikacin sulfate injection, and sodium p-amino salicylate injection, accompanied by linezolid or not.
RESULTS: The overall effective rate of the study group was higher than that of the control group (88.00% vs 64.00%, P<0.05). The severity of pain at 3 and 6 months postoperatively was lower in the study group than that in the control group (P<0.05). Postoperatively, the study group had higher bone graft fusion rate, shorter mean bone graft fusion time, and higher paraspinal cyst absorption rate than the control group (P<0.05). Postoperatively, the study group had lower levels of PCT, ESR, and CRP than the control group (P <0.05). All patients had normal hepatic and renal function, and no statistical difference of adverse effects between 2 groups were found.
CONCLUSIONS: Linezolid-based chemotherapeutic regimens can effectively treat patients with postoperative multidrug-resistant spinal tuberculosis but have higher rates of adverse reactions.

DOI: 10.1016/j.ijid.2022.03.020
PMID: 35339715

41. **Adherence measured using electronic dose monitoring is associated with emergent antiretroviral resistance and poor outcomes in patients co-infected with HIV/AIDS and multidrug-resistant tuberculosis.**

Clin Infect Dis. 2022 Mar 30:ciac232. doi: 10.1093/cid/ciac232. Online ahead of

print.

Bateman M(1), Wolf A(2), Chimukangara B(3)(4), Brust JCM(5), Lessells R(6), Amico R(7), Boodhram R(4), Singh N(8), Orrell C(9), Friedland G(10), Naidoo K(4), Padayatchi N(4), O'Donnell MR(2)(11)(4).

BACKGROUND: Medication adherence is known to challenge treatment of HIV/AIDS and multidrug-resistant tuberculosis (MDR-TB). We hypothesized that electronic dose adherence monitoring (EDM) would identify an ART adherence threshold for emergent ART resistance and predict treatment outcomes in patients with MDR-TB and HIV on ART and bedaquiline-containing TB regimens.
METHODS: A prospective cohort of adults with MDR-TB and HIV, on ART and initiating MDR-TB treatment with bedaquiline, were enrolled at a public TB referral hospital in KwaZulu-Natal, South Africa (PRAXIS Study, Clinicaltrials.gov NCT03162107). Participants received separate EDM devices measuring adherence to bedaquiline and ART (nevirapine or lopinavir/ritonavir). Adherence was calculated cumulatively over six months. Participants were followed through completion of MDR-TB treatment. HIV genome sequencing was performed at baseline, 2 and 6 months on samples with HIV RNA ≥1000 copies/mL.
FINDINGS: From November 2016 through February 2018, 198 MDR-TB and HIV co-infected participants were enrolled and followed (median 17.2 months, IQR 12.2 - 19.6). Eleven percent had baseline ART resistance mutations, and 7.5% developed emergent ART resistance at 6 months. ART adherence was independently associated with both emergent ART resistance and mortality. Modeling identified a significant ($p<0.001$), but linear association between ART adherence and emergent resistance, suggesting a strong association without a specific threshold.
INTERPRETATION: Our findings highlight the need for ART resistance testing, especially in MDR-TB HIV co-infected patients, which is currently not standard of care in resource-limited settings. Despite short follow-up duration, reduced ART adherence was significantly associated with emergent resistance and increased mortality.

DOI: 10.1093/cid/ciac232
PMID: 35352097

42. **Supporting tuberculosis program in active contact tracing: a case study from Pakistan.**

Infect Dis Poverty. 2022 Apr 9;11(1):42. doi: 10.1186/s40249-022-00965-1.

Shaikh BT(1), Laghari AK(2), Durrani S(2), Chaudhry A(2), Ali N(2).

Tuberculosis (TB) is on the rise in Pakistan and there could be multiple reasons including poverty, difficulty in access to TB treatment services, non-compliance with treatment, social stigma etc. According to the TB program managers, limited treatment and testing sites for tuberculosis and lack of trained human resources play a major role in compromising TB management. A major lacuna in the TB control program is the absence of active contact tracing strategy. This is essential for a disease where positive cases are known to be able to infect a further 10–15 individuals in a year. Tackling tuberculosis in Pakistan has been beleaguered by funding challenges and other systems' bottlenecks such as lack of skilled human resources and insufficient supply of medicines, despite the fact that disease burden is one of the highest in the world. Although it is a notifiable disease, active case finding, contact tracing and reporting is notoriously low throughout the country. Access to diagnostics and treatment facilities has been limited and stigma attached to the disease remains deeply entrenched among the communities. Researchers have shown that enhanced and active approaches to contact investigation effectively identifies additional patients with TB among household contacts at a relatively modest cost. USAID's Integrated Health Systems Strengthening and Service Delivery Activity extended support to the Health Departments of Sindh and Khyber Pakhtunkhwa provinces. In collaboration with the two provincial TB programs, community based active contact tracing was conducted on 17,696 individuals, based on the index cases. Among the contacts traced, 243 cases were diagnosed as drug sensitive or drug resistant TB. Awareness sessions were conducted to sensitize people on the various aspects of disease and importance of getting tested. The project also supported establishing three satellite Programmatic Management of Drug Resistant Tuberculosis (PMDT) sites for drug resistant TB treatment, enhancing the programs' diagnostic and testing capacity.

DOI: 10.1186/s40249-022-00965-1
PMCID: PMC8994270
PMID: 35397556 [Indexed for MEDLINE]

43. **Intra-urban variation in tuberculosis and community socioeconomic deprivation in Lisbon metropolitan area: a Bayesian approach.**

Infect Dis Poverty. 2022 Mar 24;11(1):24. doi: 10.1186/s40249-022-00949-1.

Oliveira O(1)(2)(3), Ribeiro AI(4)(5)(6), Duarte R(4)(7), Correia-Neves M(8)(9)(10), Rito T(11)(12).

BACKGROUND: Multidrug resistant tuberculosis (MDR-TB) is a recognized threat to global efforts to TB control and remains a priority of the National Tuberculosis Programs. Additionally, social determinants and socioeconomic deprivation have since long been associated with worse health and perceived as important risk factors for TB. This study aimed to analyze the spatial distribution of non-MDR-TB and MDR-TB across parishes of the Lisbon metropolitan area of Portugal and to estimate the association between non-MDR-TB and MDR-TB and socioeconomic deprivation.
METHODS: In this study, we used hierarchical Bayesian spatial models to analyze the spatial distribution of notification of non-MDR-TB and MDR-TB cases for the period from 2000 to 2016 across 127 parishes of the seven municipalities of the Lisbon metropolitan area (Almada, Amadora, Lisboa, Loures, Odivelas, Oeiras, Sintra), using the Portuguese TB Surveillance System (SVIG-TB). In order to characterise the populations, we used the European Deprivation Index for Portugal (EDI-PT) as an indicator of poverty and estimated the association between non-MDR-TB and MDR-TB and socioeconomic deprivation.
RESULTS: The notification rates per 10,000 population of non-MDR TB ranged from 18.95 to 217.49 notifications and that of MDR TB ranged from 0.83 to 3.70. We identified 54 high-risk areas for non-MDR-TB and 13 high-risk areas for MDR-TB. Parishes in the third [relative risk (RR) = 1.281, 95% credible interval (CrI): 1.021-1.606], fourth (RR = 1.786, 95% CrI: 1.420-2.241) and fifth (RR = 1.935, 95% CrI: 1.536-2.438) quintile of socioeconomic deprivation presented higher non-MDR-TB notifications rates. Parishes in the fourth (RR = 2.246, 95% CrI: 1.374-3.684) and fifth (RR = 1.828, 95% CrI: 1.049-3.155) quintile of socioeconomic deprivation also presented higher MDR-TB notifications rates.
CONCLUSIONS: We demonstrated significant heterogeneity in the spatial distribution of both non-MDR-TB and MDR-TB at the parish level and we found that socioeconomically disadvantaged parishes are disproportionally affected by both non-MDR-TB and MDR-TB. Our findings suggest that the emergence of MDR-TB and transmission are specific from each location and often different from the non-MDR-TB settings. We identified priority areas for intervention for a more efficient plan of control and prevention of non-MDR-TB and MDR-TB.

DOI: 10.1186/s40249-022-00949-1
PMCID: PMC8942608
PMID: 35321758 [Indexed for MEDLINE]

44. **'Personalizing' shorter regimens: Need of the hour.**

Indian J Tuberc. 2022 Apr;69(2):242-245. doi: 10.1016/j.ijtb.2021.07.013. Epub 2021 Jul 28.

Garg K(1), Kaur K(2), Gupta A(2), Chopra V(2), Kumari S(2).

INTRODUCTION: The launch of injectable shorter regimens under Programmatic Management of Drug Resistant Tuberculosis (PMDT) guidelines 2017 under Revised National Tuberculosis Control Program (RNTCP) was a welcome step as it decreased the duration of treatment significantly in Drug Resistant Tuberculosis (DRTB) patients. The objective of the present study was to evaluate the treatment outcomes of patients started on injectable shorter regimens from March 2018 to May, 2019.
METHODS: Retrospective study which scrutinized medical records of 85 patients started on injectable shorter regimen was conducted. Necessary information on possible patient and disease related predicting factors like age, gender, weight, HIV status, presence of diabetes mellitus (DM), anemia, gap between diagnosis and initiation of treatment, duration of intensive phase (IP) and time of sputum conversion was retrieved, and analyzed for possible association with treatment outcomes.
RESULTS: 56.5% had successful treatment outcomes. Age, gender, BMI, diabetic/anemic status and gap between diagnosis and initiation of treatment had no statistically significant relationship with the final outcomes. Duration of IP, sputum conversion and time of outcome during the course of illness emerged as significant factors in successful outcomes.
CONCLUSION: The injectable shorter regimens were suitable for a variety of population irrespective of demographic disparities. Patients need to be followed closely as microbiological parameters serve as early indicators of unsuccessful outcomes. These regimens can serve as an alternate choice in patients not tolerating the all oral shorter Bedaquiline containing shorter regimen. Similar such options with combinations of different drugs for individualizing treatment regimens is the need of the hour.

DOI: 10.1016/j.ijtb.2021.07.013
PMID: 35379409 [Indexed for MEDLINE]

45. **Establishment and evaluation of an overlap extension polymerase chain reaction technique for rapid and efficient detection of drug-resistance in Mycobacterium tuberculosis.**

Infect Dis Poverty. 2022 Mar 24;11(1):31. doi: 10.1186/s40249-022-00953-5.

Li J(#)(1), Ouyang J(#)(2), Yuan J(3), Li T(1), Luo M(1), Wang J(1), Chen Y(4)(5)(6).

BACKGROUND: Rapid and accurate detection of drug resistance in Mycobacterium tuberculosis is critical for effective control of tuberculosis (TB). Herein, we established a novel, low cost strategy having high accuracy and speed for the detection of M. tuberculosis drug resistance, using gene splicing by overlap extension PCR (SOE PCR).
METHODS: The SOE PCR assay and Sanger sequencing are designed and constructed to detect mutations of rpoB, embB, katG, and inhA promoter, which have been considered as the major contributors to rifampicin (RFP), isoniazid (INH), and ethambutol (EMB) resistance in M. tuberculosis. One hundred and eight M. tuberculosis isolates came from mycobacterial cultures of TB cases at Chongqing Public Health Medical Center in China from December 2018 to April 2019, of which 56 isolates were tested with the GeneXpert MTB/RIF assay. Performance evaluation of the SOE PCR technique was compared with traditional mycobacterial culture and drug susceptibility testing (DST) or GeneXpert MTB/RIF among these isolates. Kappa identity test was used to analyze the consistency of the different diagnostic methods.
RESULTS: We found that the mutations of S531L, S315T and M306V were most prevalent for RFP, INH and EMB resistance, respectively, in the 108 M. tuberculosis isolates. Compared with phenotypic DST, the sensitivity and specificity of the SOE PCR assay for resistance detection were 100.00% and 88.00% for RFP, 94.64% and 94.23% for INH, and 68.97% and 79.75% for EMB, respectively. Compared with the GeneXpert MTB/RIF, the SOE PCR method was completely consistent with results of the GeneXpert MTB/RIF, with a concordance of 100% for resistance to RFP.
CONCLUSIONS: In present study, a novel SOE PCR diagnostic method was successfully developed for the accurate detection of M. tuberculosis drug resistance. Our results using this method have a high consistency with that of traditional phenotypic DST or GeneXpert MTB/RIF, and SOE PCR testing in clinical isolates can also be conducted rapidly and simultaneously for detection of drug resistance to RFP, EMB, and INH.

DOI: 10.1186/s40249-022-00953-5
PMCID: PMC8942611
PMID: 35321759 [Indexed for MEDLINE]

46. **Epigenetic changes in Mycobacterium tuberculosis and its host provide potential**

targets or biomarkers for drug discovery and clinical diagnosis.

Pharmacol Res. 2022 Mar 29;179:106195. doi: 10.1016/j.phrs.2022.106195. Online ahead of print.

Sui J(1), Qiao W(2), Xiang X(1), Luo Y(3).

Tuberculosis infection caused by the contagious pathogen Mycobacterium tuberculosis (MTB) is one of the ancient diseases in the world. The problem of drug resistance is a difficulty in tuberculosis treatment. MTB engendered epigenetic changes play vital parts in escaping the host immune response and bring about the persistence as well as bacterial expansion. This article describes the epigenetic changes that occur in the pathogen MTB and its host during infection, including DNA methylation, histone modification and microRNA, and summarizes their research progress in drug discovery and tuberculosis diagnosis, providing new ideas and strategies to combat against drug-resistant tuberculosis.

DOI: 10.1016/j.phrs.2022.106195
PMID: 35364247

47. **Structure-activity relationship of 2-aminodibenzothiophene pharmacophore and the discovery of aminobenzothiophenes as potent inhibitors of Mycobacterium smegmatis.**

Bioorg Med Chem Lett. 2022 May 1;63:128650. doi: 10.1016/j.bmcl.2022.128650. Epub 2022 Mar 1.

Alelaiwi SH(1), Heindl JE(2), Sivaganesh V(2), Peethambaran B(2), McKee JR(3).

Tuberculosis (TB) is one of the deadliest infectious diseases worldwide and its current treatments have been complicated with the emergence of multi-drug resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains. Therefore, the discovery of new antitubercular agents is in need to overcome this problem. In our efforts to discover novel candidates for the treatment of tuberculosis, we describe in this work in vitro activityagainstM. smegmatis for a series of aminated benzo-fused heterocycles, particularly, dibenzothiophene to explore the structure-activity relationship of 2-aminodibenzothiophene 3aa. From these studies, three compounds 5-aminobenzothiophene 3ia, 6-aminobenzothiophene 3ma (MIC: 0.78 μg/mL) and 5-aminobenzofuran 3ja (MIC: 1.56 μg/mL) were identified as potent inhibitors of M. smegmatis with low cytotoxicity. These results suggested

the significance of these compounds 3ia, 3ja and 3ma for the future development of candidate agents to treat tuberculosis.

DOI: 10.1016/j.bmcl.2022.128650
PMID: 35245664

48. **Detecting rifampin and isoniazid resistance in Mycobacterium tuberculosis direct from patient sputum using an automated integrated system.**

J Clin Tuberc Other Mycobact Dis. 2022 Feb 22;27:100304. doi: 10.1016/j.jctube.2022.100304. eCollection 2022 May.

Colman RE(1), Hagan C(1), Chiles P(1), Seifert M(1), Catanzaro DG(2), Kukhtin AV(3), Norville R(3), Hauns L(3), Bueno A(3), Holmberg RC(3), Cooney CG(3), Rodwell TC(1).

While there has been progress in detection of drug resistant tuberculosis globally, WHO estimates only about half of the patients with bacteriologically confirmed tuberculosis were tested for rifampicin resistance over the past two years. To close this drug resistance diagnostic gap, an expansion of testing for rifampicin and isoniazid resistance is critically needed. The Akonni Biosystem Integrated System combines DNA extraction and a Lab-on-a-Film assembly (LFA) to perform rapid probe and PCR-based detection of resistance associated mutations to first-line anti-tuberculosis drugs. Using raw sputum samples from 25 tuberculosis patients at risk for drug resistance, we conducted a proof-of-concept study of the Integrated System with an MDR-TB assay. Performance of the Integrated System was compared to liquid Mycobacteria Growth Indicator Tube (MGIT) culture reference phenotypes using 2012 WHO endorsed critical concentrations for rifampicin and isoniazid. The overall percent agreement for rifampicin and isoniazid was 91.7% and 100% respectively, with agreement for rifampicin increasing to 95.7% after low-level resistance mutations in rpoB were excluded. The Integrated System, combining DNA extraction and LFA amplification, is a promising new tool for detection of both rifampicin and isoniazid using liquefied raw sputum.

DOI: 10.1016/j.jctube.2022.100304
PMCID: PMC8891689
PMID: 35252594

49. **Economic burden of tuberculosis in Tanzania: a national survey of costs faced by tuberculosis-affected households.**

BMC Public Health. 2022 Mar 29;22(1):600. doi: 10.1186/s12889-022-12987-3.

Kilale AM(1), Pantoja A(2), Jani B(3), Range N(4), Ngowi BJ(4)(5), Makasi C(4), Majaha M(4), Manga CD(4), Haule S(4), Wilfred A(4), Hilary P(4), Mahamba V(6), Nkiligi E(7), Muhandiki W(7), Matechi E(7), Mutayoba B(7), Nishkiori N(2), Ershova J(8).

BACKGROUND: Although tuberculosis (TB) care is free in Tanzania, TB-associated costs may compromise access to services and treatment adherence resulting in poor outcomes and increased risk of transmission in the community. TB can impact economically patients and their households. We assessed the economic burden of TB on patients and their households in Tanzania and identified cost drivers to inform policies and programs for potential interventions to mitigate costs.
METHODS: We conducted a nationally representative cross-sectional survey using a standard methodology recommended by World Health Organization. TB patients of all ages and with all types of TB from 30 clusters across Tanzania were interviewed during July - September 2019. We used the human capital approach to assess the indirect costs and a threshold of 20% of the household annual expenditure to determine the proportion of TB-affected households experiencing catastrophic cost. We descriptively analyzed the cost data and fitted multivariable logistic regression models to identify potential predictors of catastrophic costs.
RESULTS: Of the 777 TB-affected households, 44.9% faced catastrophic costs due to TB. This proportion was higher (80.0%) among households of patients with multi-drug resistant TB (MDR-TB). Overall, cost was driven by income loss while accessing TB services (33.7%), nutritional supplements (32.6%), and medical costs (15.1%). Most income loss was associated with hospitalization and time for picking up TB drugs. Most TB patients (85.9%) reported worsening financial situations due to TB, and over fifty percent (53.0%) borrowed money or sold assets to finance TB treatment. In multivariable analysis, the factors associated with catastrophic costs included hospitalization (adjusted odds ratio [aOR] = 34.9; 95% confidence interval (CI):12.5-146.17), living in semi-urban (aOR = 1.6; 95% CI:1.0-2.5) or rural areas (aOR = 2.6; 95% CI:1.8-3.7), having MDR-TB (aOR = 3.4; 95% CI:1.2-10.9), and facility-based directly-observed treatment (DOT) (aOR = 7.2; 95% CI:2.4-26.6).
CONCLUSION: We found that the cost of TB care is catastrophic for almost half of the TB-affected households in Tanzania; our findings support the results from other surveys recently conducted in sub-Saharan Africa. Collaborative efforts across health, employment and social welfare sectors are imperative to minimize household costs due to TB disease and improve access to care, patient adherence

and outcomes.

DOI: 10.1186/s12889-022-12987-3
PMCID: PMC8961947
PMID: 35351063 [Indexed for MEDLINE]

50. **Identification of Potent DNA Gyrase Inhibitors Active against Mycobacterium tuberculosis.**

J Chem Inf Model. 2022 Apr 11;62(7):1680-1690. doi: 10.1021/acs.jcim.1c01390. Epub 2022 Mar 29.

Pakamwong B(1), Thongdee P(1), Kamsri B(1), Phusi N(1), Kamsri P(2), Punkvang A(2), Ketrat S(3), Saparpakorn P(4), Hannongbua S(4), Ariyachaokun K(5), Suttisintong K(6), Sureram S(7), Kittakoop P(7)(8)(9), Hongmanee P(10), Santanirand P(10), Spencer J(11), Mulholland AJ(12), Pungpo P(1).

Mycobacterium tuberculosis DNA gyrase manipulates the DNA topology using controlled breakage and religation of DNA driven by ATP hydrolysis. DNA gyrase has been validated as the enzyme target of fluoroquinolones (FQs), second-line antibiotics used for the treatment of multidrug-resistant tuberculosis. Mutations around the DNA gyrase DNA-binding site result in the emergence of FQ resistance in M. tuberculosis; inhibition of DNA gyrase ATPase activity is one strategy to overcome this. Here, virtual screening, subsequently validated by biological assays, was applied to select candidate inhibitors of the M. tuberculosis DNA gyrase ATPase activity from the Specs compound library (www.specs.net). Thirty compounds were identified and selected as hits for in vitro biological assays, of which two compounds, G24 and G26, inhibited the growth of M. tuberculosis H37Rv with a minimal inhibitory concentration of 12.5 μg/mL. The two compounds inhibited DNA gyrase ATPase activity with IC50 values of 2.69 and 2.46 μM, respectively, suggesting this to be the likely basis of their antitubercular activity. Models of complexes of compounds G24 and G26 bound to the M. tuberculosis DNA gyrase ATP-binding site, generated by molecular dynamics simulations followed by pharmacophore mapping analysis, showed hydrophobic interactions of inhibitor hydrophobic headgroups and electrostatic and hydrogen bond interactions of the polar tails, which are likely to be important for their inhibition. Decreasing compound lipophilicity by increasing the polarity of these tails then presents a likely route to improving the solubility and activity. Thus, compounds G24 and G26 provide attractive starting templates for the optimization of antitubercular agents that act by targeting DNA gyrase.

DOI: 10.1021/acs.jcim.1c01390
PMID: 35347987 [Indexed for MEDLINE]

51. **Examining family planning and adverse pregnancy outcomes for women with active tuberculosis disease: a systematic review.**

BMJ Open. 2022 Mar 28;12(3):e054833. doi: 10.1136/bmjopen-2021-054833.

Nguyen Y(1), McNabb KC(2), Farley JE(2), Warren N(2).

OBJECTIVES: (1) Summarise and evaluate the current evidence of tuberculosis (TB)-associated pregnancy outcomes, (2) evaluate the state of the science of family planning during TB treatment and (3) provide recommendations to move forward to improve care and outcomes during TB disease.
DESIGN: Systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.
DATA SOURCES: PubMed, Embase, CINAHL, Cochrane, Web of Science and Scopus were searched from September 2009 to November 2021.
ELIGIBILITY CRITERIA: Studies were included if they assessed pregnant women with active TB, drug-resistant TB (DR-TB) or TB/HIV coinfection and examined pregnancy, maternal, fetal/birth and TB or TB/HIV coinfection outcomes. Studies were also included if they examined family planning services among women initiating TB treatment.
DATA EXTRACTION AND SYNTHESIS: Two independent reviewers extracted data using PRISMA guidelines and conducted quality assessment using the Joanna-Briggs Institute Critical Appraisal Tools. The level of evidence was reported using the Johns Hopkins Evidence-Based Practice guidelines.
RESULTS: 69 studies were included in this review. Case reports, case series, case controls, cohort studies, secondary data analyses and a service delivery improvement project conducted in 26 countries made up the totality of the evidence. Most studies reported pregnancy complications for mothers (anaemia, postpartum haemorrhage, deaths) and fetuses or newborns (low birth weight, premature birth, and spontaneous or induced abortions). Few studies discussed the value of offering family planning to prevent adverse pregnancy outcomes. One study examined the effect of a provider training on contraceptive use with reported increased contraceptive use.
CONCLUSIONS: Integrating family planning services within a TB treatment programme is essential to reduce adverse TB-associated maternal-child outcomes. Despite well-established adverse pregnancy outcomes, little attention has been paid to family planning to prevent poor pregnancy outcomes for women with TB/DR-TB. Recommendations for clinicians, TB programmes and researchers are provided and reflect evidence presented in this review.

DOI: 10.1136/bmjopen-2021-054833
PMCID: PMC8961125
PMID: 35351713 [Indexed for MEDLINE]

52. **The host-pathogen-environment triad: Lessons learned through the study of the multidrug-resistant Mycobacterium tuberculosis M strain.**

Tuberculosis (Edinb). 2022 Mar 21;134:102200. doi: 10.1016/j.tube.2022.102200. Online ahead of print.

Yokobori N(1), López B(2), Ritacco V(3).

Multidrug-resistant tuberculosis is one of the major obstacles that face the tuberculosis eradication efforts. Drug-resistant Mycobacterium tuberculosis clones were initially disregarded as a public health threat, because they were assumed to have paid a high fitness cost in exchange of resistance acquisition. However, some genotypes manage to overcome the impact of drug-resistance conferring mutations, retain transmissibility and cause large outbreaks. In Argentina, the HIV-AIDS epidemics fuelled the expansion of the so-called M strain in the early 1990s, which is responsible for the largest recorded multidrug-resistant tuberculosis cluster of Latin America. The aim of this work is to review the knowledge gathered after nearly three decades of multidisciplinary research on epidemiological, microbiological and immunological aspects of this highly successful strain. Collectively, our results indicate that the successful transmission of the M strain could be ascribed to its unaltered virulence, low Th1/Th17 response, a low fitness cost imposed by the resistance conferring mutations and a high resistance to host-related stress. In the early 2000s, the incident cases due to the M strain steadily declined and stabilized in the latest years. Improvements in the management, diagnosis and treatment of multidrug-resistant tuberculosis along with societal factors such as the low domestic and international mobility of the patients affected by this strain probably contributed to the outbreak containment. This stresses the importance of sustaining the public health interventions to avoid the resurgence of this conspicuous multidrug-resistant strain.

DOI: 10.1016/j.tube.2022.102200
PMID: 35339874

53. **Essential tuberculosis medicines and health outcomes in countries with a national essential medicines list.**

J Clin Tuberc Other Mycobact Dis. 2022 Feb 23;27:100305. doi: 10.1016/j.jctube.2022.100305. eCollection 2022 May.

Maraj D(1), Steiner L(1), Persaud N(2).

BACKGROUND: Tuberculosis (TB) remains a major cause of morbidity and mortality globally despite effective treatments. Along with high-quality health services, essential medicines are a key tool in curbing TB related mortality. Examining relationships between listing TB medicines on national essential medicines lists (NEMLs) and population health outcomes related to amenable mortality is one way to assess TB care.
METHODS: In this cross-sectional study of 137 countries, we used linear regression to examine the relationship between the number of TB medicines listed on NEMLs and TB related mortality while controlling for country income, region and TB burden.
RESULTS: Most countries listed essential TB medicines to treat latent, drug-sensitive and disseminated TB but few listed enough for multi-drug resistant TB (MDR-TB) therapy. The total number of TB medicines listed ranged from 1 to 29 (median: 19, interquartile range: 15 to 22). Over 75% of the variation in health outcomes were explained by the number of TB medicines listed, gross domestic product (GDP) per capita, region and high-burden MDR-TB status. The number of TB medicines listed was not associated with TB mortality.
CONCLUSION: Most countries list essential TB treatments and the variation in TB outcomes is explained by other factors such as GDP.

DOI: 10.1016/j.jctube.2022.100305
PMCID: PMC8924688
PMID: 35308809

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

J Appl Toxicol. 2022 Mar 22. doi: 10.1002/jat.4324. Online ahead of print.

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

Ethionamide (ETH), a second-line drug for multidrug-resistant tuberculosis, is known to cause hepatic steatosis in rats and humans. To investigate predictive biomarkers for ETH-induced steatosis, we performed lipidomics analysis using plasma and liver samples collected from rats treated orally with ETH at 30 and 100 mg/kg for 14 days. The ETH-treated rats developed hepatic steatosis with Oil Red O staining-positive vacuolation in the centrilobular hepatocytes accompanied by increased hepatic contents of triglycerides (TG) and decreased plasma TG and total cholesterol levels. A multivariate analysis for lipid profiles revealed differences in each of the 35 lipid species in the plasma and liver between the control and the ETH-treated rats. Of those lipids, phosphatidylcholine (PC) (18:0/20:4) decreased dose-dependently in both the plasma and liver. Moreover, serum TG-rich very low-density lipoprotein (VLDL) levels, especially the large particle fraction of VLDL composed of PC containing arachidonic acid (20:4) involved in hepatic secretion of TG, were decreased dose-dependently. In conclusion, the decreased PC (18:0/20:4) in the liver, possibly leading to suppression of hepatic TG secretion, was considered to be involved in the pathogenesis of the ETH-induced hepatic steatosis. Therefore, plasma PC (18:0/20:4) levels are proposed as mechanism-related biomarkers for ETH-induced hepatic steatosis.

DOI: 10.1002/jat.4324
PMID: 35315511

55. **Cost-effectiveness of a medication event monitoring system for tuberculosis management in Morocco.**

PLoS One. 2022 Apr 19;17(4):e0267292. doi: 10.1371/journal.pone.0267292. eCollection 2022.

Yang J(1), Kim HY(2), Park S(3), Sentissi I(4), Green N(5), Oh BK(3), Kim Y(1), Oh KH(6)(7), Paek E(3), Park YJ(3), Oh IH(8), Lee SH(3)(9).

BACKGROUND: Digital health technologies have been used to enhance adherence to TB medication, but the cost-effectiveness remains unclear.
METHODS: We used the real data from the study conducted from April 2014 to December 2020 in Morocco using a smart pillbox with a web-based medication monitoring system, called Medication Event Monitoring Systems (MEMS). Cost-effectiveness was evaluated using a decision analysis model including Markov model for Multi-drug resistant (MDR) TB from the health system

perspective. The primary outcome was the incremental cost-effectiveness ratio (ICER) per disability adjusted life-year (DALY) averted. Two-way sensitive analysis was done for the treatment success rate between MEMS and standard of care.
RESULTS: The average total per-patient health system costs for treating a new TB patient under MEMS versus standard of care were $398.70 and $155.70, respectively. The MEMS strategy would reduce the number of drug-susceptible TB cases by 0.17 and MDR-TB cases by 0.01 per patient over five years. The ICER of MEMS was $434/DALY averted relative to standard of care, and was most susceptible to the TB treatment success rate of both strategies followed by the managing cost of MEMS.
CONCLUSION: MEMS is considered cost-effective for managing infectious active TB in Morocco.

DOI: 10.1371/journal.pone.0267292
PMID: 35439273

56. **The WHO Global Tuberculosis 2021 Report - not so good news and turning the tide back to End TB.**

Int J Infect Dis. 2022 Mar 20:S1201-9712(22)00149-7. doi: 10.1016/j.ijid.2022.03.011. Online ahead of print.

Jeremiah C(1), Petersen E(2), Nantanda R(3), Mungai BN(4), Migliori GB(5), Amanullah F(6), Lungu P(7), Ntoumi F(8), Kumarasamy N(9), Maeurer M(10), Zumla A(11).

OBJECTIVE: To review the data presented in the 2021 WHO global TB report and discuss the current constraints in the global response.
INTRODUCTION AND METHODS: The WHO global TB reports, consolidate TB data from countries and provide up to date assessment of the global TB epidemic. We reviewed the data presented in the 2021 report.
RESULTS: We noted that the 2021 WHO global TB report presents a rather grim picture on the trajectory of the global epidemic of TB including a stagnation in the annual decline in TB incidence, a decline in TB notifications and an increase in estimated TB deaths. All the targets set at the 2018 United Nations High Level Meeting on TB were off track.
INTERPRETATION AND CONCLUSION: The sub-optimal global performance on achieving TB control targets in 2020 is attributed to the on-going COVID-19 pandemic, however, TB programs were already off track well before the onset of the pandemic, suggesting that the pandemic amplified an already fragile global TB response. We emphasize that ending the global TB epidemic will require bold leadership, optimization of existing interventions, widespread coverage,

addressing social determinants of TB and importantly mobilization of adequate funding required for TB care and prevention.

DOI: 10.1016/j.ijid.2022.03.011
PMCID: PMC8934249
PMID: 35321845

57. **Linezolid Pharmacokinetics/Pharmacodynamics-Based Optimal Dosing for Multidrug-Resistant Tuberculosis.**

Int J Antimicrob Agents. 2022 Apr 8:106589. doi: 10.1016/j.ijantimicag.2022.106589. Online ahead of print.

Zhou W(1), Nie W(1), Wang Q(1), Shi W(1), Yang Y(1), Li Q(1), Zhu H(2), Liu Z(2), Ding Y(2), Lu Y(3), Chu N(4).

Linezolid can significantly impact drug-resistant tuberculosis (DR-TB) patient outcomes. However, the long-term use of this drug for TB treatment has been limited by adverse reactions and uncertainty regarding optimal dosage regimens for balancing drug efficacy and safety across different populations. Here, the ratio between the area under the free drug plasma concentration-time curve to the minimum inhibitory concentration (fAUC/MIC) of >119 and trough concentration (Cmin) ≤2 mg/L served as efficacy and safety targets, respectively, toward the formulation of optimal dosage regimens based on a ≥90% cumulative fraction of response (CFR). 355 blood samples were collected from 126 DR-TB patients. Population pharmacokinetic (PK) analysis (using a one-compartment model) and dose simulations were conducted using NONMEM and R software. Body weight and blood urea nitrogen (BUN) level were the most significant covariates of apparent volume (V/F), while creatinine clearance (Ccr) and hemoglobin (HGB) level significantly influenced apparent clearance (CL/F). The probability of target attainment (PTA) for different dosage regimens was evaluated via Monte Carlo simulation. For subjects with MIC of 0.125, 0.25, and 0.5 mg/L, specific total daily doses of ≥300 mg, ≥450 mg and ≥900 mg to reach the target, respectively. Subjects with body weights ≤70 kg and MIC ≥1 mg/L received a total 1200-mg daily dose to reach the PTA target. Notably, single dosing was safer than multiple dosing at the same daily dose. The optimal dosage regimens for subjects with body weights <50 kg and ≥50 kg were 450 mg/d and 600 mg/d (once daily), respectively.

DOI: 10.1016/j.ijantimicag.2022.106589
PMID: 35405268

58. **In vitro antimycobacterial activity of medicinal plants Lantana camara, Cryptolepis sanguinolenta, and Zanthoxylum leprieurii.**

J Clin Tuberc Other Mycobact Dis. 2022 Mar 3;27:100307. doi: 10.1016/j.jctube.2022.100307. eCollection 2022 May.

Tuyiringire N(1)(2), Taremwa Mugisha I(3), Tusubira D(4), Munyampundu JP(5), Mambo Muvunyi C(6), Vander Heyden Y(7).

BACKGROUND: Imperative need exists to search for new anti-TB drugs that are safer, and more effective against drug-resistant strains. Medicinal plants have been the source of active ingredients for drug development. However, the slow growth and biosafety level requirements of M. tuberculosis culture are considerable challenges. M. smegmatis can be used as a surrogate for M. tuberculosis. In the current study, preliminary phytochemical screening and antimycobacterial activity evaluation of crude methanolic extracts of medicinal plants against M. smegmatis, and two M. tuberculosis strains, were conducted.
MATERIALS AND METHODS: Crude methanolic extracts, obtained from the leaves of L. camara, roots of C. sanguinolenta, and stem barks of Z. leprieurii, were tested for antimycobacterial activity against M. smegmatis (mc2155), pan-sensitive (H37Rv), and rifampicin-resistant (TMC-331) M. tuberculosis, using visual Resazurin Microtiter Assay (REMA) on 96 well plates. Preliminary qualitative phytochemical screening tests were performed using standard chemical methods.
RESULTS: The three methanolic extracts inhibited mycobacterial growth in vitro. They were more active against rifampicin-resistant strain with MICs of 176, 97, and 45 µg/mL for L. camara, C. sanguinolenta, and Z. leprieurii extracts, respectively. The lowest activity was observed against M. smegmatis with MICs of 574, 325, and 520 µg/mL, respectively. Against H37Rv, activity was intermediate to those of TMC-331 and mc2155. However, L. camara extract showed the same activity against H37Rv and M. smegmatis. Preliminary phytochemical analysis revealed alkaloids, flavonoids, phenolic compounds, saponins, tannins, and terpenoids.
CONCLUSIONS: Leaves of L. camara, roots of C. sanguinolenta, and stem barks of Z. leprieurii exhibit antimycobacterial activity against M. smegmatis, pan-sensitive, and rifampicin-resistant M. tuberculosis. This offers the possibilities for novel therapeutic opportunities against TB including multidrug-resistant TB. Further investigations on safety and mechanisms of action are required. These studies could be done using M. smegmatis as a surrogate for the highly pathogenic M. tuberculosis.

DOI: 10.1016/j.jctube.2022.100307
PMCID: PMC8904236
PMID: 35284659

59. **Improving TB Surveillance and Patients' Quality of Care Through Improved Data Collection in Angola: Development of an Electronic Medical Record System in Two Health Facilities of Luanda.**

Front Public Health. 2022 Mar 24;10:745928. doi: 10.3389/fpubh.2022.745928. eCollection 2022.

Robbiati C(1), Tosti ME(2), Mezzabotta G(1), Dal Maso F(3), Lulua Sachicola OM(4), Siene Tienabe P(4), Nsuka J(4), Simonelli M(2), Dente MG(2), Putoto G(1).

TB Programs should promote the use of digital health platforms, like Electronic Medical Records (EMR) to collect patients' information, thus reducing data incompleteness and low accuracy and eventually improving patients' care. Nevertheless, the potential of digital health systems remains largely unexploited in low-resource settings. Angola is one of the 14 countries with a triple burden of TB, TB/HIV and MDR-TB (multidrug-resistant TB) and it is among the three countries, together with Congo and Liberia that have never completed a drug-resistance survey so far. The Sanatorium Hospital of Luanda and the Tuberculosis Dispensary of Luanda are the two reference health facilities in Luanda dealing with most of the TB cases, and they both rely entirely on paper-based data collection. The aim of this paper is to describe a three-stage process for the development of a TB EMR system in these two health facilities of Luanda and to share the lessons learned. The description is focused on the activities that took place from March 2019 to January 2020. Main lessons learned were identified in the importance of engaging all the stakeholders in the development process, in the mainstream of the "think digital" transition, in the promotion of a monitoring and evaluation (M&E) culture and in the planning of the system's sustainability. This approach may be replicated in similar contexts where the development of a TB EMR system is sought, and the lessons learned could assist and facilitate the programming of the interventions.

DOI: 10.3389/fpubh.2022.745928
PMCID: PMC9009439
PMID: 35433613 [Indexed for MEDLINE]

60. **Comparative Evaluation of GeneXpert MTB/RIF Ultra and GeneXpert MTB/RIF for Detecting Tuberculosis and Identifying Rifampicin Resistance in Pars Plana Vitrectomy Samples of Patients with Ocular Tuberculosis.**

Ocul Immunol Inflamm. 2022 Apr 20:1-7. doi: 10.1080/09273948.2022.2064880. Online ahead of print.

Sharma K(1), Sharma M(1)(2), Ayyadurai N(3), Dogra M(3), Sharma A(4), Gupta V(3), Singh R(3), Gupta A(3).

BACKGROUND: Xpert MTB/RIF Ultra (Ultra) was evaluated for the first time on Ocular tuberculosis (OTB) samples and compared with Xpert.
METHODS: Seventy five vitreous fluid samples (3 confirmed OTB, 47 clinically suspected OTB, and 25 controls) were subjected to Ultra, Xpert and Multiplex-PCR and compared against culture, composite reference standard (CRS), and gene sequencing.
RESULTS: The sensitivity of Ultra was 50% in diagnosing OTB (100% against culture and 46.8% against CRS). The overall sensitivity of Xpert and MPCR was 16% and 72%, respectively. Xpert missed three culture-positive cases and MPCR detected additional 11. Ultra and Xpert missed two and four cases of RifR, respectively. A total of 13(59%) cases were reported 'trace' by Ultra in which RifR could not be evaluated.
CONCLUSION: Ultra outperformed Xpert in diagnosing OTB. The advantage of Ultra's simultaneous RifR detection is lost since the trace bacterial loads in the specimens cause indeterminate results of RifR testing.Abbreviations: OTB: Ocular tuberculosis; Ultra: Xpert MTB/RIF Ultra; Xpert: Xpert MTB/RIF, MPCR: multiplex polymerase chain reaction; NAATs: Nucleic acid amplification tests; MLAMP: multitargeted loop-mediated isothermal amplification; PPV: positive predictive value; NPV: negative predictive value; EPTB: extrapulmonary tuberculosis; VF: vitreous fluid; DNA: deoxyribonucleic acid; ATT: antitubercular therapy; RifR: Rifampicin resistance; RifS: Rifampicin susceptible; RifI: Rifampicin indeterminate.

DOI: 10.1080/09273948.2022.2064880
PMID: 35442853

61. **Spoligotyping of Mycobacterium tuberculosis isolates from Pulmonary Tuberculosis patients from North Karnataka, India.**

Trop Doct. 2022 Apr 18:494755221080584. doi: 10.1177/00494755221080584. Online ahead of print.

Bellad R(1), Nagamoti M(1), Sharma P(2), Chauhan DS(3).

Tuberculosis (TB) is a leading cause of morbidity and mortality in low income countries. Multi-drug resistant (MDR-TB) is seen as the reason for many TB outbreaks globally and is also a threat to control programmes. India accounts for 27% TB cases worldwide. Our study was undertaken to understand the outbreaks related to MTB. All the sputum samples were subjected to microscopy and smear positive samples were cultured on Lowenstein-Jensen (L-J) media. Identification was carried by biochemical analysis. A total of 57 isolates were subjected to Drug Susceptibility testing (DST) and spoligotyping, where eleven MDR-TB isolates were confirmed, of which ten were SIT1/Beijing and one SIT53/T1. Spoligotyping results showed that the predominant lineage in this region was SIT1/Beijing followed by SIT124/U and the strains which did not match spoligodatabase were named as orphans. In this study, MDR-TB was associated with SIT1/Beijing and mono resistance belonged to CAS1_DEL.

DOI: 10.1177/00494755221080584
PMID: 35435077

62. **A longitudinal community-based ototoxicity monitoring programme and treatment effects for drug-resistant tuberculosis treatment, Western Cape.**

Stevenson S Afr J Commun Disord. 2022 Mar 31;69(1):e1-e13. doi: 10.4102/sajcd.v69i1.886.

LJ(1), Biagio-de Jager L, Graham MA, Swanepoel W.

BACKGROUND: South Africa has a high burden of drug-resistant tuberculosis (DRTB) and until recently, ototoxic aminoglycosides were predominant in treatment regimens. Community-based ototoxicity monitoring programmes (OMPs) have been implemented for early detection of hearing loss and increased patient access.
OBJECTIVES: A longitudinal study was conducted to describe the service delivery characteristics of a community-based OMP for DRTB patients facilitated by CHWs as well as observed ototoxic hearing loss in this population.
METHOD: A descriptive retrospective record review of longitudinal ototoxicity monitoring of 194 DRTB patients undergoing treatment at community-based clinics in the city of Cape Town between 2013 and 2017.
RESULTS: Follow-up rates between consecutive monitoring assessments reached as high as 80.6% for patients assessed by CHWs. Few patients (14.2% - 32.6%) were assessed with the regularity (≥ 6 assessments) and frequency required for effective ototoxicity monitoring, with assessments conducted, on average, every 53.4-64.3 days. Following DRTB treatment, 51.5% of patients presented with a

significant ototoxic shift meeting one or more of the American Speech-Language-Hearing Association (ASHA) criteria. Deterioration in hearing thresholds was bilateral and most pronounced at high frequencies (4 kHz - 8 kHz). The presence of pre-existing hearing loss, human immunodeficiency virus co-infection and a history of noise exposure were significant predictors of ototoxicity in patients.
CONCLUSION: DRTB treatment with kanamycin resulted in significant deterioration of hearing longitudinally, predominantly at high frequencies. With ongoing training and supportive supervision, CHWs can facilitate community-based ototoxicity monitoring of DRTB patients. Current protocols and guidelines may require reassessment for appropriate community-based ototoxicity monitoring.

DOI: 10.4102/sajcd.v69i1.886
PMCID: PMC8991219
PMID: 35384675 [Indexed for MEDLINE]

63. **Factors Associated with Non-Adherence for Prescribed Treatment in 201 Patients with Multidrug-Resistant and Rifampicin-Resistant Tuberculosis in Anhui Province, China.**

Med Sci Monit. 2022 Apr 19;28:e935334. doi: 10.12659/MSM.935334.

Zhu QQ(1), Wang J(2)(3), Sam NB(4), Luo J(5), Liu J(1), Pan HF(2)(3).

BACKGROUND This study aimed to investigate the factors associated with non-adherence of prescribed treatment in patients with multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) in Anhui Province, China. MATERIAL AND METHODS A cross-sectional survey was conducted in each designated hospital between March 2020 and May 2021. A structured questionnaire was designed to collect categorical characteristics and the historical data of the study participants. Non-adherence was determined from patient medical records and face-to-face interviews using the questionnaire at each designated hospital for MDR/RR-TB. RESULTS A total of 201 patients with confirmed sputum cultures positive for MDR/RR-TB were enrolled, 27.4% of whom were non-adherent to MDR/RR-TB treatment. In Anhui, MDR patients had a high incidence of adverse events, of which gastrointestinal reactions accounted for the majority. Absence of other chronic diseases (odds ratio (OR) 0.401; 95% confidence interval (CI) 0.203-0.791) and having no drug discontinuation (OR 0.040; 95% CI 0.018-0.091) were protective predictors of adherence. Patients with MDR/RR-TB with secondary education level and above and monthly family income of $309.4 USD or higher were more likely to follow the guidelines. Those who received anti-tuberculosis treatment and those who lived in suburban areas were less likely to adhere to the treatment. Binary-logistic regression indicated that the risk factor of

non-adherence was drug discontinuation. CONCLUSIONS Low education level, place of residence, poor financial conditions, presence of other chronic diseases, discontinuation of medication, and frequency of anti-tuberculosis treatments were influential factors of adherence to MDR/RR-TB treatment.

DOI: 10.12659/MSM.935334
PMID: 35437301 [Indexed for MEDLINE]

64. **Formulation of rifampicin softpellets for high dose delivery to the lungs with a novel high dose dry powder inhaler.**

Int J Pharm. 2022 Apr 5;617:121606. doi: 10.1016/j.ijpharm.2022.121606. Epub 2022 Feb 21.

Etschmann C(1), Scherließ R(2).

Lung tuberculosis (TB) is the most deadly infectious disease worldwide although it is treatable. High doses of antibiotics are used for therapy over a period of at least 6 months. Since in many treated patients only subtherapeutic concentrations are reached in the infected tissue of the lung, about half a million cases of multi drug resistant tuberculosis (MDR TB) occur every year. In order to increase the concentration of the active pharmaceutical ingredient (API) at the site of the primary infection, inhalation of antibiotics seems to be promising. In this study, we show the capability of softpellets, engineered dry powder agglomerates, to deliver high doses to the lungs. For this, the antibiotic rifampicin was milled and processed into softpellets which were then dispersed utilising a novel high dose dry powder inhaler, the 8Shot from Hovione Technology. Aerodynamic assessment resulted in a fine particle dose of 21.35 mg with a device retention of < 15% after loading all eight chambers of the inhaler with 10 mg softpellet formulation. At the same time, we present a new process design to produce softpellets, namely vibro-pelletisation.

DOI: 10.1016/j.ijpharm.2022.121606
PMID: 35202727 [Indexed for MEDLINE]

65. **Recently developed drugs for the treatment of drug-resistant tuberculosis: a research and development case study.**

BMJ Glob Health. 2022 Apr;7(4):e007490. doi: 10.1136/bmjgh-2021-007490.

Perrin C(1), Athersuch K(2), Elder G(2), Martin M(2), Alsalhani A(3).

Two drugs with novel mechanisms of action, the diarylquinoline bedaquiline and the nitroimidazole delamanid-as well as pretomanid from the same class of drugs as delamanid-have recently become available to treat drug-resistant tuberculosis (DR-TB) after many decades of little innovation in the field of DR-TB treatment. Despite evidence of improved efficacy and reduced toxicity of multidrug regimens including the two agents, access to bedaquiline and delamanid has been limited in many settings with a high burden of DR-TB and consistently poor treatment outcomes. Aside from regulatory, logistic and cost barriers at country level, uptake of the novel agents was complicated by gaps in knowledge for optimal use in clinical practice after initial market approval. The main incentives of the current pharmaceutical research and development paradigm are structured around obtaining regulatory approval, which in turn requires efficacy and safety data generated by clinical trials. Recently completed and ongoing clinical trials did not answer critical questions of how to provide shorter, less toxic treatment DR-TB treatment regimens containing bedaquiline and delamanid and improve patient outcomes. Voluntary generation of evidence that is not part of this process-yet essential from a clinical or policy perspective-has been left to non-sponsor partners and researchers, often without collaborative efforts to improve post-regulatory approval access to life-saving drugs. Additionally, these efforts are currently not recognised in the value chain of the research and development process, and there are no incentives to make this critical research happen in a coordinated way.

DOI: 10.1136/bmjgh-2021-007490
PMID: 35440441

66. **Quinoline derivatives as potential anti-tubercular agents: Synthesis, molecular docking and mechanism of action.**

Microb Pathog. 2022 Apr;165:105507. doi: 10.1016/j.micpath.2022.105507. Epub 2022 Mar 27.

Liu CX(1), Zhao X(1), Wang L(1), Yang ZC(2).

Development of new drugs with novel mechanisms of action is required to combat the problem of drug-resistant Mycobacterium tuberculosis. The present investigation is aimed at combining two pharmacophores (quinoline or isoquinolines and thiosemicarbazide) to synthesize a series of compounds. Seven

compounds were synthesized based on combination principle in this study. The compound 1-7 showed activities against M. tuberculosis H37Rv strain with MIC values rang from 2 to 8 μg/ml. Compound 5 exhibited remarkable antimycobacterial activity (MIC = 2 μg/ml), and was therefore selected for study of the mechanism of action. Molecular docking suggested initially that compound 5 could occupy the active site of KatG of M. tuberculosis. Furthermore compound 5 exhibited potent inhibitory effect on activity of KatG. RT-PCR finally displayed that compound 5 could up-regulate the transcription of katG of M. tuberculosis. Together, these studies reveal that compound 5 might be the inhibitor of KatG of Mycobacterium tuberculosis. One of the more significant findings to emerge from this study is that KatG of M.tuberculosis can be used as a putative novel target for new anti-tubercular drug design.

DOI: 10.1016/j.micpath.2022.105507
PMID: 35354076 [Indexed for MEDLINE]

67. **Developing strategies to address barriers for tuberculosis case finding and retention in care among refugees in slums in Kampala, Uganda: a qualitative study using the COM-B model.**

BMC Infect Dis. 2022 Mar 28;22(1):301. doi: 10.1186/s12879-022-07283-9.

Buregyeya E(1), Atusingwize E(2), Sekandi JN(3), Mugambe R(2), Nuwematsiko R(2), Atuyambe L(4).

BACKGROUND: Globally, displaced populations face an increased burden of tuberculosis (TB). Uganda is currently hosting unprecedented big numbers of refugees from the East African region. Recent evidence shows increased spread of multi-drug resistant TB (MDR-TB) across East Africa as a result of migrants from Somalia- a high MDR-TB prevalent country, calling for urgent identification and management of cases for the countries in the region. One of the strategies recommended is optimization of diagnosis, treatment and prevention of TB in refugees. This study aimed at exploring the barriers to and facilitators for TB case finding and retention in care among urban slum refugees and suggestions on how to improve. This was to guide the development of interventions to improve TB case finding and retention in care among the said population.
METHODS: A cross-sectional study utilizing qualitative methods was conducted among refugees in an urban slum in Kampala City, Uganda. Key informant interviews with health care workers and community leaders and in-depths interviews with refugee TB patients and care takers of TB patients were conducted (30 interviews in total). Interview questions were based on constructs

from the COMB-B model (Capability, Opportunity and Motivation Model of Behaviour change). Manual content analysis was performed and identified targeted intervention strategies guided by the related Behavior Change Wheel implementation framework.
RESULTS: Key barriers included; physical capability (availability of and easily accessible private facilities in the community with no capacity to diagnose and treat TB), psychological capability (lack of knowledge about TB among refugees), social opportunity (wide spread TB stigma and language barrier), physical opportunity (poor living conditions, mobility of refugees), reflective motivation (lack of facilitation for health workers), automatic motivation (discrimination and rejection of TB patients). Facilitators were; physical capability (availability of free TB services in the public health facilities), social opportunity (availability of translators). We identified education, incentivization, training, enablement, and restructuring of the service environment as relevant intervention functions with potential to address barriers to and enhance facilitators of TB case finding and retention among refugees in urban slums.
CONCLUSION: The key barriers to TB control among refugees living urban slums in Kampala- Uganda, included; poor access to health services, limited knowledge about TB, TB stigma, language barrier and lack of facilitation of community health workers. Identified intervention strategies included; education, training, enablement, environmental restructuring and persuasion. The findings could serve as a guide for the design and implementation of interventions for improving the same.

DOI: 10.1186/s12879-022-07283-9
PMCID: PMC8962141
PMID: 35346094 [Indexed for MEDLINE]

68. **Assessment of prevalence of depression and its associated factors among tuberculosis patients in Ernakulam district, Kerala.**

Indian J Tuberc. 2022 Apr;69(2):172-177. doi: 10.1016/j.ijtb.2021.06.013. Epub 2021 Jun 18.

Retnakumar C(1), George LS(2).

BACKGROUND: India is one of the few countries where Tuberculosis is still widely prevalent. People with TB, often suffers from depression. It is estimated that more than 300 million people suffer from depression at the global level, accounting to 4.4 percent of the world's population.

OBJECTIVES: Primary objective-To assess the prevalence of depression among tuberculosis patients in Ernakulam district using PHQ9. Secondary objective-To assess the factors associated with depression among tuberculosis patients in Ernakulam district.
METHODOLOGY: A cross sectional study was carried out among the tuberculosis patients who were currently under treatment from December 2019 to March 2020 in Ernakulam district of Kerala. From the 8 TUs of Ernakulam, 8 clusters were selected using PPS. 485 adult TB patients from these clusters were interviewed using PHQ9 questionnaire to assess prevalence of depression.
RESULTS: The prevalence of depression among the TB patients in Ernakulam district was found to be 16.1%. The proportion of TB patients with depression were significantly higher among the age group of 18-40 years (36.3%), unmarried (54%) and from urban area of residence (19%). It was also significantly higher among previously treated patients (45.7%) & MDR TB patients (43.8%).
CONCLUSION: It was observed that one-sixth of TB patients suffered from depression. Hence it is crucial that TB patients need to be regularly assessed for depression and managed appropriately. Since depression has affects adherence to TB treatment & thereby result in delay of TB elimination in the state.

DOI: 10.1016/j.ijtb.2021.06.013
PMID: 35379398 [Indexed for MEDLINE]

69. **Use of Whole-Genome Sequencing to Predict Mycobacterium tuberculosis Complex Drug Resistance from Early Positive Liquid Cultures.**

Microbiol Spectr. 2022 Mar 21:e0251621. doi: 10.1128/spectrum.02516-21. Online ahead of print.

Wu X(#)(1), Tan G(#)(2), Sha W(3), Liu H(4), Yang J(1), Guo Y(1), Shen X(5), Wu Z(5), Shen H(3), Yu F(1).

Our objective was to evaluate the performance of whole-genome sequencing (WGS) from early positive liquid cultures for predicting Mycobacterium tuberculosis complex (MTBC) drug resistance. Clinical isolates were obtained from tuberculosis patients at Shanghai Pulmonary Hospital (SPH). Antimicrobial susceptibility testing (AST) was performed, and WGS from early Bactec mycobacterial growth indicator tube (MGIT) 960-positive liquid cultures was performed to predict the drug resistance using the TB-Profiler informatics platform. A total of 182 clinical isolates were enrolled in this study. Using phenotypic AST as the gold standard, the overall sensitivity and specificity for

WGS were, respectively, 97.1% (89.8 to 99.6%) and 90.4% (83.4 to 95.1%) for rifampin, 91.0% (82.4 to 96.3%) and 95.2% (89.1 to 98.4%) for isoniazid, 100.0% (89.4 to 100.0%) and 87.3% (80.8 to 92.1%) for ethambutol, 96.6% (88.3 to 99.6%) and 61.8% (52.6 to 70.4%) for streptomycin, 86.8% (71.9 to 95.6%) and 95.8% (91.2 to 98.5%) for moxifloxacin, 86.5% (71.2 to 91.5%) and 95.2% (90.3 to 98.0%) for ofloxacin, 100.0% (54.1 to 100.0%) and 67.6% (60.2 to 74.5%) for amikacin, 100.0% (63.1 to 100.0%) and 67.2% (59.7 to 74.2%) for kanamycin, 62.5% (24.5 to 91.5%) and 88.5% (82.8 to 92.8%) for ethionamide, 33.3% (4.3 to 77.7%) and 98.3% (95.1 to 99.7%) for para-aminosalicylic acid, and 0.0% (0.0 to 12.3%) and 100.0% (97.6 to 100.0%) for cycloserine. The concordances of WGS-based AST and phenotypic AST were as follows: rifampin (92.9%), isoniazid (93.4%), ethambutol (89.6%), streptomycin (73.1%), moxifloxacin (94.0%), ofloxacin (93.4%), amikacin (68.7%), kanamycin (68.7%), ethionamide (87.4%), para-aminosalicylic acid (96.2%) and cycloserine (84.6%). We conclude that WGS could be a promising approach to predict MTBC resistance from early positive liquid cultures. IMPORTANCE In this study, we used whole-genome sequencing (WGS) from early positive liquid (MGIT) cultures instead of solid cultures to predict drug resistance of 182 Mycobacterium tuberculosis complex (MTBC) clinical isolates to predict drug resistance using the TB-Profiler informatics platform. Our study indicates that WGS may be a promising method for predicting MTBC resistance using early positive liquid cultures.

DOI: 10.1128/spectrum.02516-21
PMID: 35311541

70. **Evaluating the clinical impact of routine whole genome sequencing in tuberculosis treatment decisions and the issue of isoniazid mono-resistance.**

BMC Infect Dis. 2022 Apr 7;22(1):349. doi: 10.1186/s12879-022-07329-y.

Park M(1)(2), Lalvani A(3), Satta G(4), Kon OM(5)(6).

BACKGROUND: The UK has implemented routine use of whole genome sequencing (WGS) in TB diagnostics. The WHO recommends addition of a fluoroquinolone for isoniazid mono-resistance, so early detection may be of use. The aim of this study was to describe the clinical utility and impact of WGS on treatment decisions for TB in a low incidence high resource clinical setting. The clinical turnaround time (TAT) for WGS was analysed in comparison to TB PCR using Xpert MTB/RIF (Cepheid, Sunnyvale, CA) results where available and subsequent phenotypic drug susceptibility testing (DST) when required.
METHODS: This was a retrospective analysis of TB cases from January 2018 to March 2019 in London. Susceptibility and TAT by WGS, phenotypic DST, TB PCR using Xpert MTB/RIF were correlated to drug changes in order to describe the

utility of WGS on treatment decisions on isoniazid mono-resistance in a low incidence high resource setting.
RESULTS: 189 TB cases were identified; median age 44 years (IQR 28-60), m:f ratio 112:77, 7 with HIV and 6 with previous TB. 80/189 cases had a positive culture and WGS result. 50/80 were fully sensitive to 1st line treatment on WGS, and the rest required additional DST. 20/80 cases required drug changes; 12 were defined by WGS: 8 cases had isoniazid mono-resistance, 2 had MDR-TB, 1 had isoniazid and pyrazinamide resistance and 1 had ethambutol resistance. The median TAT for positive culture was 16 days (IQR 12.5-20.5); for WGS was 35 days (IQR 29.5-38.75) and for subsequent DST was 86 days (IQR 69.5-96.75), resulting in non-WHO regimens for a median of 50.5 days (IQR 28.0-65.0). 9/12 has TB PCRs (Xpert MTB/RIF), with a median TAT of 1 day.
CONCLUSION: WGS clearly has a substantial role in our routine UK clinical settings with faster turnaround times in comparison to phenotypic DST. However, the majority of treatment changes defined by WGS were related to isoniazid resistance and given the 1 month TAT for WGS, it would be preferable to identify isoniazid resistance more quickly. Therefore if resources allow, diagnostic pathways should be optimised by parallel use of WGS and new molecular tests to rapidly identify isoniazid resistance in addition to rifampicin resistance and to minimise delays in starting WHO isoniazid resistance treatment.

DOI: 10.1186/s12879-022-07329-y
PMCID: PMC8991524
PMID: 35392842 [Indexed for MEDLINE]

71. **Estimating the contribution of transmission in primary healthcare clinics to community-wide TB disease incidence, and the impact of infection prevention and control interventions, in KwaZulu-Natal, South Africa.**

BMJ Glob Health. 2022 Apr;7(4):e007136. doi: 10.1136/bmjgh-2021-007136.

McCreesh N(1), Karat AS(2)(3), Govender I(2)(4), Baisley K(2), Diaconu K(3), Yates TA(5), Houben RM(2), Kielmann K(3), Grant AD(2)(4)(6), White R(2).

BACKGROUND: There is a high risk of Mycobacterium tuberculosis (Mtb) transmission in healthcare facilities in high burden settings. WHO guidelines on tuberculosis (TB) infection prevention and control (IPC) recommend a range of measures to reduce transmission in healthcare settings. These were evaluated primarily based on evidence for their effects on transmission to healthcare workers in hospitals. To estimate the overall impact of IPC interventions, it is necessary to also consider their impact on community-wide TB incidence and

mortality.
METHODS: We developed an individual-based model of Mtb transmission in households, primary healthcare (PHC) clinics, and all other congregate settings. The model was parameterised using data from a high HIV prevalence community in South Africa, including data on social contact by setting, by sex, age, and HIV/antiretroviral therapy status; and data on TB prevalence in clinic attendees and the general population. We estimated the proportion of disease in adults that resulted from transmission in PHC clinics, and the impact of a range of IPC interventions in clinics on community-wide TB.
RESULTS: We estimate that 7.6% (plausible range 3.9%-13.9%) of non-multidrug resistant and multidrug resistant TB in adults resulted directly from transmission in PHC clinics in the community in 2019. The proportion is higher in HIV-positive people, at 9.3% (4.8%-16.8%), compared with 5.3% (2.7%-10.1%) in HIV-negative people. We estimate that IPC interventions could reduce incident TB cases in the community in 2021-2030 by 3.4%-8.0%, and deaths by 3.0%-7.2%.
CONCLUSIONS: A non-trivial proportion of TB results from transmission in clinics in the study community, particularly in HIV-positive people. Implementing IPC interventions could lead to moderate reductions in disease burden. We recommend that IPC measures in clinics should be implemented for their benefits to staff and patients, but also for their likely effects on TB incidence and mortality in the surrounding community.

DOI: 10.1136/bmjgh-2021-007136
PMID: 35396264 [Indexed for MEDLINE]

72. **Novel Use of Fostemsavir for 2 Multidrug-Resistant Persons With Human Immunodeficiency Virus.**

Ann Pharmacother. 2022 Apr;56(4):501-502. doi: 10.1177/10600280211035510. Epub 2021 Jul 30.

Pecora Fulco P(1), Nixon D(1), Gomes DC(1).

DOI: 10.1177/10600280211035510
PMID: 34328023 [Indexed for MEDLINE]

73. **The dynamic impacts of environmental-health and MDR-TB diseases and their influence on environmental sustainability at Chinese hospitals.**

Environ Sci Pollut Res Int. 2022 Mar 30. doi: 10.1007/s11356-022-19593-1. Online ahead of print.

Dai Z(1), Sadiq M(2), Kannaiah D(3), Khan N(4), Shabbir MS(5), Bilal K(6), Tabash MI(7).

The purpose of this study is to identify at what extent multidrug-resistant tuberculosis (MDR-TB) diseases effect on environmental health issues in selected provinces of Chinese hospitals. In survival analysis approach, this study employs the Cox proportional hazard model (CPM) to incorporate the duration of event, probability of occurrence of an event, and the issue of right censoring. An advantage of using CPM is that one does not need to specify the distribution of baseline hazard H0 (t) as it considers a common value for all units in population. The results indicate that male and travel expenditures have negative association with the duration of cure. Furthermore, the medical expenditures and the spatial characteristic of time expenditure have positive association with the duration of cure of MDR-TB patients. The inconsistent behavior of males in taking medicines as compared to females and males is also more prone to tuberculosis (TB).

DOI: 10.1007/s11356-022-19593-1
PMID: 35353303

74. **Application of Next Generation Sequencing for Diagnosis and Clinical Management of Drug-Resistant Tuberculosis: Updates on Recent Developments in the Field.**

Front Microbiol. 2022 Mar 24;13:775030. doi: 10.3389/fmicb.2022.775030. eCollection 2022.

Dookie N(1), Khan A(1), Padayatchi N(1)(2), Naidoo K(1)(2).

The World Health Organization's End TB Strategy prioritizes universal access to an early diagnosis and comprehensive drug susceptibility testing (DST) for all individuals with tuberculosis (TB) as a key component of integrated, patient-centered TB care. Next generation whole genome sequencing (WGS) and its associated technology has demonstrated exceptional potential for reliable and comprehensive resistance prediction for Mycobacterium tuberculosis isolates, allowing for accurate clinical decisions. This review presents a descriptive analysis of research describing the potential of WGS to accelerate delivery of individualized care, recent advances in sputum-based WGS technology and the role

of targeted sequencing for resistance detection. We provide an update on recent research describing the mechanisms of resistance to new and repurposed drugs and the dynamics of mixed infections and its potential implication on TB diagnosis and treatment. Whilst the studies reviewed here have greatly improved our understanding of recent advances in this arena, it highlights significant challenges that remain. The wide-spread introduction of new drugs in the absence of standardized DST has led to rapid emergence of drug resistance. This review highlights apparent gaps in our knowledge of the mechanisms contributing to resistance for these new drugs and challenges that limit the clinical utility of next generation sequencing techniques. It is recommended that a combination of genotypic and phenotypic techniques is warranted to monitor treatment response, curb emerging resistance and further dissemination of drug resistance.

DOI: 10.3389/fmicb.2022.775030
PMCID: PMC8988194
PMID: 35401475

75. **A Review on Benzimidazole Scaffolds as Inhibitors of Mycobacterium Tuberculosis Mycolyl-arabinogalactan-peptidoglycan complex Biosynthesis.**

Comb Chem High Throughput Screen. 2022 Apr 15. doi: 10.2174/1386207325666220415144511. Online ahead of print.

Bhaskar V(1), Kumar S(1), Nair AS(2), Rajappan KP(2), Sudevan ST(2), Parambi DGT(3), Al-Sehemi AG(4)(5), Zachariah SM(2), Pappachen LK(6).

BACKGROUND: Tuberculosis is one of the oldest known infectious diseases to mankind, caused by Mycobacterium tuberculosis. Although current treatment using first-line anti-tubercular drugs is proven to be effective, an infection caused by resistant strains as in multidrug-resistant and extensive drug- resistant tuberculosis is still an impending challenge to treat.
OBJECTIVE: Our objective is to focus on reporting benzimidazole derivatives that are targeting mycobacterial membrane biosynthesis, particularly the mycobacterial mycolyl-arabinogalactan-peptidoglycan complexes. From the literature survey, it has been noted that targeting Mycobacterium tuberculosis cell membrane biosynthesis is an effective approach to fight against drug resistance in tuberculosis.
METHODS: Articles on benzimidazole derivatives as inhibitors of proteins responsible for the biosynthesis of the mycobacterial mycolyl-arabinogalactan-peptidoglycan complex have been selected.
RESULTS: By reviewing the anti-tubercular activity of the reported benzimidazole

derivatives, we have concluded that there exists a correlation between benzimidazole derivatives and their biological activity. It has been noted that benzimidazole derivative with substitution at N1, C2, C5, and C6 positions have shown greater affinity towards target proteins.
CONCLUSION: Even though scientific advancement towards the prevention of tuberculosis has been quite significant in the past few decades, still infection caused by resistant strains is a major concern. We have collected data on benzimidazole derivatives that inhibit the biosynthesis of mycolic acid, arabinogalactan and, peptidoglycan and from our observations, we conclude that majority of the molecules have given anti-tubercular activity in nanomolar range but there are few mycobacterial membrane biosynthesis proteins where benzimidazole as an inhibitor has yet to be explored.

DOI: 10.2174/1386207325666220415144511
PMID: 35430964

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

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

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

Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis (Mtb). Clarithromycin (CTY), an analog of erythromycin (ERY), is more potent against multidrug-resistance (MDR) TB. ERY and CTY were previously reported to bind to the nascent polypeptide exit tunnel (NPET) near peptidyl transferase center (PTC), but the only available CTY structure in complex with D. radiodurans (Dra) ribosome could be misinterpreted due to resolution limitation. To date, the mechanism of specificity and efficacy of CTY for Mtb remains elusive since the Mtb ribosome-CTY complex structure is still unknown. Here, we employed new sample preparation methods and solved the Mtb ribosome-CTY complex structure at 3.3Å with cryo-EM technique, where the crucial gate site A2062 (E. coli numbering) is located at the CTY binding site within NPET. Two alternative conformations of A2062, a novel syn-conformation as well as a swayed conformation bound with water molecule at interface, may play a role in coordinating the binding of specific drug molecules. The previously overlooked C-H hydrogen bond (H-bond) and π interaction may collectively contribute to the

enhanced binding affinity. Together, our structure data provide a structural basis for the dynamic binding as well as the specificity of CTY and explain of how a single methyl group in CTY improves its potency, which provides new evidence to reveal previously unclear mechanism of translational modulation for future drug design and anti-TB therapy. Furthermore, our sample preparation method may facilitate drug discovery based on the complexes with low water solubility drugs by cryo-EM technique.

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

77. **Delamanid Added to an Optimized Background Regimen in Children with Multidrug-Resistant Tuberculosis: Results of a Phase I/II Clinical Trial.**

Antimicrob Agents Chemother. 2022 Apr 11:e0214421. doi: 10.1128/aac.02144-21. Online ahead of print.

Garcia-Prats AJ(1), Frias M(2), van der Laan L(1), De Leon A(3), Gler MT(2), Schaaf HS(1), Hesseling AC(1), Malikaarjun S(4), Hafkin J(4).

Delamanid has been demonstrated to be safe and effective for treatment of adult multidrug-resistant tuberculosis (MDR-TB) and has been approved by the European Commission for treatment of pediatric MDR-TB patients at least 10 kg in weight, making the drug no longer limited to adults. A 10-day phase I age deescalation study was conducted, followed by a 6-month phase II extension study, to assess the pharmacokinetics, safety, tolerability, and preliminary efficacy of delamanid when combined with optimized background regimen (OBR) in children (birth to 17 years) with MDR-TB. Delamanid administered at 100 mg twice-daily (BID), 50 mg BID, and 25 mg BID resulted in exposures in 12- to 17- (n = 7), 6- to 11- (n = 6), and 3- to 5-year-olds (n = 12), respectively, comparable with those in adults at the approved adult dosage (100 mg BID). Exposures in 0- to 2-year-olds (n = 12) following a weight-based dosing regimen (5 mg once daily [QD] to 10 mg BID) were lower than predicted from pharmacokinetic modeling of the older three age groups and below target exposures in adults. Overall, the safety profile of delamanid in children 0 to 17 years of age was similar to the adult profile. At 24 months after the first delamanid dose, 33/37 children (89.2%) had favorable treatment outcomes, as defined by the World Health Organization (15/37 [40.5%] cured and 18/37 [48.6%] completed treatment). A new pediatric delamanid formulation used in 0- to 2-year-olds and 3- to 5-year-olds was palatable per child/parent and nurse/investigator reports. Data from initial phase I/II studies inform our understanding of delamanid use in children and support its further assessment in the setting of pediatric MDR-TB. (This study

has been registered at ClinicalTrials.gov under identifiers NCT01856634 [phase I trial] and NCT01859923 [phase II trial].).

DOI: 10.1128/aac.02144-21
PMID: 35404075

78. **Weak spots inhibition in the Mycobacterium tuberculosis antigen 85C target for antitubercular drug design through selective irreversible covalent inhibitor-SER124.**

J Biomol Struct Dyn. 2022 Apr;40(7):2934-2954. doi: 10.1080/07391102.2020.1844061. Epub 2020 Nov 6.

Adewumi AT(1), Elrashedy A(1), Soremekun OS(1), Ajadi MB(2), Soliman MES(1).

Mycobacterium tuberculosis (Mtb) encoded secreted antigen 85 enzymes (Ag85A/Ag85B/Ag85C) play that critical roles in the virulence, survival and drug-resistant TB of the pathogen. Ag85 proteins are potential antitubercular drug targets because they are essential in the catalytic synthesis of trehalose moieties and mycolic acid attachment to the Mtb cell wall. Recently, experimental protocols led to the discovery of a selective covalent Ag85 inhibitor, β-isomer monocyclic enolphosphorus Cycliphostin (CyC8β) compound, which targets the Ag85 serine 124 to exhibit a promising therapeutic activity. For the first time, our study unravelled the structural features among Mtb Ag85C homologs and motions and dynamics of Ag85C when the CyC8β bound covalently and in open model conformations to the protein using bioinformatics tools and integrated Molecular dynamics simulations. Comparative Ag85C sequence analysis revealed conserved regions; 70% active site, 90% Adeniyi loop L1 and 50% loop L2, which acts as a switch between open and closed conformations. The average C-α atoms RMSD (2.05 Å) and RMSF (0.9 Å) revealed instability and high induced flexibility in the CyC8β covalent-bound compared to the apo and open model systems, which displayed more stability and lower fluctuations. DSSP showed structural transitions of α-helices to bend and loops to 310-helices in the bound systems. SASA of CyC8β covalent bound showed active site hydrophobic residues exposure to huge solvent. Therefore, these findings present the potential opportunity hotspots in Ag85C protein that would aid the structure-based design of novel chemical entities capable of resulting in potent antitubercular drugs.Communicated by Ramaswamy H. Sarma.

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PMID: 33155529

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

Trans R Soc Trop Med Hyg. 2022 Apr 4:trac021. doi: 10.1093/trstmh/trac021.
Online ahead of print.

Thakur V(1)(2), Ganeshkumar P(1), Lakshmanan S(1), Rubeshkumar P(1).

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

DOI: 10.1093/trstmh/trac021
PMID: 35380728