March Literature

1. Isolated Multi-Drug-Resistant Wrist Tuberculosis.

Surg Infect (Larchmt). 2022 Mar;23(2):199-200. doi: 10.1089/sur.2021.248. Epub 2021 Oct 5.

Zhong M(1), Xiao K(1).

DOI: 10.1089/sur.2021.248
PMID: 34612704 [Indexed for MEDLINE]

2. Comparative genomic analyses of multi-drug resistant Mycobacterium tuberculosis from Nepal and other geographical locations.

Genomics. 2022 Mar;114(2):110278. doi: 10.1016/j.ygeno.2022.110278. Epub 2022 Feb 7.

Leong KWC(1), Gautam SS(2), Pradhan M(3), Singh YI(3), Kc R(4), Rajbhandari SK(5), Ghimire GR(5), Adhikari K(5), Shrestha U(5), Chaudhary R(3), Ghimire G(3), Khadka S(6), O'Toole RF(7).

Nepal exhibits a tuberculosis (TB) incidence rate that is comparable to neighbouring high TB incidence countries. In addition, it records >500 cases of multi-drug resistant (MDR) TB each year. The objective of this study was to perform whole-genome bioinformatic analysis on MDR-TB isolates from Nepal (n = 19) to identify the specific mutations underlying their phenotypic resistance. In addition, we examined the dominant genotype among the Nepal MDR-TB isolates, the East-Asian Beijing sub-lineage, to determine its relatedness to a panel of 1274 genomes of international strains available from public databases. These analyses provided evidence that the XDR-TB isolates in our collection were not derived from importation of primary XDR-TB to Nepal but were more likely the result of acquisition of second-line drug resistance in Nepal. Resistance to fluoroquinolones was detected among a high proportion of the Nepal isolates. This has implications for the management of TB, including appropriate antimicrobial stewardship and susceptibility testing for fluoroquinolones and other second-line TB drugs, to minimise the development of XDR-TB among Nepal TB cases.

DOI: 10.1016/j.ygeno.2022.110278

PMID: 35143885

3. Drug-resistant tuberculosis: advances in diagnosis and management.

Curr Opin Pulm Med. 2022 Feb 25. doi: 10.1097/MCP.0000000000000866. Online ahead of print.

Günther G(1), Ruswa N, Keller PM.

PURPOSE OF REVIEW: Diagnosis and treatment of drug-resistant tuberculosis (DR-TB) is undergoing substantial changes, owing availability of new diagnostic tools and drugs, coupled with global underdiagnosis and undertreatment. Recent developments are reviewed.
RECENT FINDINGS: Molecular diagnostics, for Mycobacterium tuberculosis complex detection and prediction of drug resistance, implemented in the last decade, accelerated TB diagnosis with improved case detection. Nevertheless, access and coverage of drug-resistance testing remain insufficient. Genome sequencing-based technologies, based on targeted next-generation sequencing show early potential to mitigate some of the challenges in the future. The recommendation to use an all oral, bedaquiline based regimen for treatment of multidrug-resistant/rifampicin-resistant TB is major advancement in DR-TB care. TB regimen using new and repurposed TB drugs demonstrate in recent clinical trials like, NIX-TB, ZeNIX and TB PRACTECAL considerable treatment success, shorten treatment duration and reduce toxicity. Their optimal use is threatened by the rapid occurrence and spread of strains, resistant to new drugs. Children benefit only very slowly from the progress.
SUMMARY: There is notable progress in improved diagnosis and treatment of drug-resistant TB, but complicated by the COVID-19 pandemic the majority of TB patients worldwide don't have (yet) access to the advances.

DOI: 10.1097/MCP.0000000000000866
PMID: 35220372

4. Delamanid-containing regimens and multidrug-resistant tuberculosis: A systematic review and meta-analysis.

Int J Infect Dis. 2022 Mar 2:S1201-9712(22)00125-4. doi: 10.1016/j.ijid.2022.02.043. Online ahead of print.

Nasiri MJ(1), Zangiabadian M(2), Arabpour E(3), Amini S(4), Khalili F(5), Centis

R(6), D'Ambrosio L(7), Denholm JT(8), Schaaf HS(9), van den Boom M(10), Kurhasani X(11), Dalcolmo MP(12), Al-Abri S(13), Chakaya J(14), Alffenaar JW(15), Akkerman O(16), Silva DR(17), Muňoz-Torrico M(18), Seaworth B(19), Pontali E(20), Saderi L(21), Tiberi S(22), Zumla A(23), Migliori GB(24), Sotgiu G(25).

INTRODUCTION: Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening condition needing long poly-chemotherapy regimens. As no systematic reviews/meta-analysis is available to comprehensively evaluate the role of delamanid (DLM), we evaluated its effectiveness and safety.
METHODS: We reviewed the relevant scientific literature published up to January 20, 2022. The pooled success treatment rate with 95% confidence intervals (CI) was assessed using a random-effect model. We assessed studies for quality and bias, and considered P<0.05 to be statistically significant.
RESULTS: After reviewing 626 records, we identified 25 studies that met the inclusion criteria, 22 observational and 3 experimental, with 1276 and 411 patients, respectively. In observational studies the overall pooled treatment success rate of DLM-containing regimens was 80.9% (95% CI 72.6-87.2) with no evidence of publication bias (Begg's test; P >0.05). The overall pooled treatment success rate in DLM and bedaquiline-containing regimens was 75.2% (95% CI 68.1-81.1) with no evidence of publication bias (Begg's test; P >0.05). In experimental studies the pooled treatment success rate of DLM-containing regimens was 72.5 (95% CI 44.2-89.8, P <0.001, I2: 95.1%) with no evidence of publication bias (Begg's test; P >0.05).
CONCLUSIONS: In MDR-TB patients receiving DLM, culture conversion and treatment success rates were high despite extensive resistance with limited adverse events.

DOI: 10.1016/j.ijid.2022.02.043
PMID: 35245659

5. Transmission of multidrug-resistant tuberculosis within family households by DTM-PCR and MIRU-VNTR genotyping.

BMC Infect Dis. 2022 Feb 26;22(1):192. doi: 10.1186/s12879-022-07188-7.

Chen J(#)(1), Chen L(#)(1), Zhou M(2), Wu G(3), Yi F(3), Jiang C(4), Duan Q(5), Zhou M(6).

BACKGROUND: Drug-resistant tuberculosis (TB) continues to be a public health threat. There are few studies on transmission and genotyping of MDR-TB family

households in China. This study aimed to investigate transmission of multidrug-resistant tuberculosis (MDR-TB) within family households by deletion-targeted multiplex polymerase chain reaction (DTM-PCR), mycobacterial interspersed repetitive unit variable number tandem repeats (MIRU-VNTR) genotyping.
METHODS: Among 993 MDR-TB patients registered from Wuhan Institute for Tuberculosis Control, drug resistance and the time interval between the index patients and secondary patients were analyzed in 49 MDR-TB patients from 23 families, in which 22 MDR-TB strains from 11 families who had matched strains were genotyped by DTM-PCR and standard 24-loci MIRU-VNTR genotyping method.
RESULTS: The time interval between the index patients and the secondary patients ranged from half a month to 110 months. Thirteen secondary patients developed active MDR-TB within two years and accounted for 50% (13/26) of all secondary patients. Among eleven pairs of MDR-TB families, six pairs had identical genotypes, the cluster rate was 54.5% (12/22); three pairs had a single MIRU-VNTR locus variation. If a single MIRU-VNTR locus variation was tolerated in the cluster definition, the cluster rate raised to 81.8% (18/22).
CONCLUSIONS: The family households of MDR-TB patients are at risk for infection of MDR-TB. To reduce transmission, MDR-TB patients should be diagnosed earlier and promptly treated in an effective manner, meanwhile, the close family contacts should be screened for TB infection.

DOI: 10.1186/s12879-022-07188-7
PMCID: PMC8881899
PMID: 35219320 [Indexed for MEDLINE]

6. Model-Based Efficacy and Toxicity Comparisons of Moxifloxacin for Multidrug-Resistant Tuberculosis.

Open Forum Infect Dis. 2021 Dec 29;9(3):ofab660. doi: 10.1093/ofid/ofab660. eCollection 2022 Mar.

Yun HY(1), Chang V(2), Radtke KK(2), Wang Q(2), Strydom N(2), Chang MJ(3)(4)(5), Savic RM(2).

BACKGROUND: Moxifloxacin (MOX) is used as a first-choice drug to treat multidrug-resistant tuberculosis (MDR-TB); however, evidence-based dosing optimization should be strengthened by integrative analysis. The primary goal of this study was to evaluate MOX efficacy and toxicity using integrative model-based approaches in MDR-TB patients.
METHODS: In total, 113 MDR-TB patients from 5 different clinical trials were

analyzed for the development of a population pharmacokinetics (PK) model. A final population PK model was merged with a previously developed lung-lesion distribution and QT prolongation model. Monte Carlo simulation was used to calculate the probability target attainment value based on concentration. An area under the concentration-time curve (AUC)-based target was identified as the minimum inhibitory concentration (MIC) of MOX isolated from MDR-TB patients. RESULTS: The presence of human immunodeficiency virus (HIV) increased clearance by 32.7% and decreased the AUC by 27.4%, compared with HIV-negative MDR-TB patients. A daily dose of 800 mg or a 400-mg, twice-daily dose of MOX is expected to be effective in MDR-TB patients with an MIC of ≤0.25 μg/mL, regardless of PK differences resulting from the presence of HIV. The effect of MOX in HIV-positive MDR-TB patients tended to be decreased dramatically from 0.5 μg/mL, in contrast to the findings in HIV-negative patients. A regimen of twice-daily doses of 400 mg should be considered safer than an 800-mg once-daily dosing regimen, because of the narrow fluctuation of concentrations. CONCLUSIONS: Our results suggest that a 400-mg, twice-daily dose of MOX is an optimal dosing regimen for MDR-TB patients because it provides superior efficacy and safety.

DOI: 10.1093/ofid/ofab660
PMCID: PMC8825669
PMID: 35146045

7. Molecular Epidemiology and Genetic Diversity of Multidrug-Resistant Mycobacterium tuberculosis Isolates in Bangladesh.

Microbiol Spectr. 2022 Feb 23;10(1):e0184821. doi: 10.1128/spectrum.01848-21. Epub 2022 Feb 23.

Rahman SMM(1), Rahman A(1)(2), Nasrin R(1), Ather MF(1), Ferdous SS(1), Ahmed S(1), Uddin MKM(1), Khatun R(1), Sarker MS(1), Mahmud AM(3), Rahman MM(4), Banu S(1).

Although the number of multidrug-resistant (MDR) tuberculosis (TB) cases is high overall, a major gap exists in our understanding of the molecular characteristics and transmission dynamics of the MDR Mycobacterium tuberculosis isolates circulating in Bangladesh. The present study aims to characterize the MDR-TB isolates of Bangladesh and to investigate the mode of transmission. A total of 544 MDR-TB isolates were obtained from a nationwide drug-resistant TB surveillance study conducted between October 2011 and March 2017 covering all

geographic divisions of Bangladesh. The isolates were characterized using TbD1 deletion analysis, spoligotyping, and mycobacterial interspersed repetitive-unit-variable-number tandem-repeat (MIRU-VNTR) typing. Deletion analysis showed that 440 (80.9%) isolates were the modern type, while the remainder were the ancestral type. The largest circulating lineage was the Beijing type, comprising 208 isolates (38.2%), followed by T, EAI, and LAM with 93 (17.1%), 58 (10.7%), and 52 (9.5%) isolates, respectively. Combined MIRU-VNTR and spoligotyping analysis demonstrated that the majority of the clustered isolates were of the Beijing and T1 lineages. The overall rate of recent transmission was estimated at 33.8%. In conclusion, the MDR M. tuberculosis isolates circulating in Bangladesh are mostly of the modern virulent type. The Beijing and T lineages are the predominant types and most of the transmission of MDR-TB can be attributed to them. The findings also suggest that, along with the remarkable transmission, the emergence of MDR-TB in Bangladesh is largely due to acquired resistance. Rapid and accurate diagnosis and successful treatment will be crucial for controlling MDR-TB in Bangladesh. IMPORTANCE Multidrug-resistant TB is considered to be the major threat to tuberculosis control activities worldwide, including in Bangladesh. Despite the fact that the number of MDR-TB cases is high, a major gap exists in our understanding of the molecular epidemiology of the MDR-TB isolates in Bangladesh. In our study, we characterized and classified the MDR-TB isolates circulating in Bangladesh and investigated their mode of transmission. Our results demonstrated that the MDR M. tuberculosis isolates circulating in Bangladesh are mostly of the modern virulent type. The Beijing and T lineages are the predominant types and are implicated in the majority of MDR-TB transmission. Our findings reveal that, along with the remarkable transmission, the emergence of MDR-TB in Bangladesh is largely due to acquired resistance, which may be due to nonadherence to treatment or inadequate treatment of TB patients. Rapid diagnosis and adherence to an appropriate treatment regimen are therefore crucial to controlling MDR-TB in Bangladesh.

DOI: 10.1128/spectrum.01848-21
PMCID: PMC8865560
PMID: 35196788 [Indexed for MEDLINE]

8. Frequency and Factors Associated With Adverse Events Among Multi-Drug Resistant Tuberculosis Patients in Pakistan: A Retrospective Study.

Front Med (Lausanne). 2022 Mar 1;8:790718. doi: 10.3389/fmed.2021.790718. eCollection 2021.

Atif M(1), Ahmed W(1), Nouman Iqbal M(2), Ahmad N(3), Ahmad W(1), Malik I(1), Al-Worafi YM(4)(5).

BACKGROUND: Treatment of multi-drug resistant tuberculosis (MDR-TB) for a prolonged period with comparatively less effective and more toxic second-line anti-TB drugs is associated with greater incidence of adverse events.
STUDY AIM: This study aimed to evaluate the frequency and factors associated with occurrence of adverse events among patients with MDR-TB attending the Bahawal Victoria Hospital, Bahawalpur, Pakistan.
STUDY DESIGN: This retrospective study included all patients with MDR-TB who were registered and treated at the study site between June 2014 and December 2016 and had their treatment outcomes available at the time of data collection (i.e., November 2018).
MEASURES AND OUTCOMES: The Electronic Nominal Record System (ERNS) records, medical charts of patients, and laboratory reports were reviewed to obtain the data. Adverse events were reported as per the standard criteria recommended by the WHO. Multivariate binary logistic regression was used to find the independent factors associated with the occurrence of adverse events.
RESULTS: A total of 179 patients with MDR-TB were included in the final analysis. Out of these, 114 (63.7%) patients experienced at least one adverse event during the course of their treatment. Depression was the most common adverse events (33%), followed by nausea and vomiting (27.4%) and arthralgia (27.4%). The factors associated with the occurrence of adverse events included presence of comorbidity (adjusted odds ratio [AOR] 2.951; 95% CI 1.423, 6.118) and being employed (AOR 3.445; 95% CI 1.188, 9.993).
CONCLUSION: Adverse events were prevalent in this cohort, however, resolved with the effective management approaches. Patients with identified factors for occurrence of adverse events need special attention and enhanced clinical management.

DOI: 10.3389/fmed.2021.790718
PMCID: PMC8922404
PMID: 35300176

9. 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

10. Mathematical analysis of a two-strain tuberculosis model in Bangladesh.

Sci Rep. 2022 Mar 7;12(1):3634. doi: 10.1038/s41598-022-07536-2.

Kuddus MA(1)(2)(3), McBryde ES(4)(5), Adekunle AI(4)(6), White LJ(7), Meehan MT(4).

Tuberculosis (TB) is an airborne infectious disease that causes millions of deaths worldwide each year (1.2 million people died in 2019). Alarmingly, several strains of the causative agent, Mycobacterium tuberculosis (MTB)-including drug-susceptible (DS) and drug-resistant (DR) variants-already circulate throughout most developing and developed countries, particularly in Bangladesh, with totally drug-resistant strains starting to emerge. In this study we develop a two-strain DS and DR TB transmission model and perform an analysis of the system properties and solutions. Both analytical and numerical results show that the prevalence of drug-resistant infection increases with an increasing drug use through amplification. Both analytic results and numerical simulations suggest that if the basic reproduction numbers of both DS ([Formula: see text]) and DR ([Formula: see text]) TB are less than one, i.e. [Formula: see text] the disease-free equilibrium is asymptotically stable, meaning that the disease naturally dies out. Furthermore, if [Formula: see text], then DS TB dies out but DR TB persists in the population, and if [Formula: see text] both DS TB and DR TB persist in the population. Further, sensitivity analysis of the model parameters found that the transmission rate of both strains had the greatest influence on DS and DR TB prevalence. We also investigated the effect of treatment rates and amplification on both DS and DR TB prevalence; results indicate that inadequate or inappropriate treatment makes co-existence more likely and increases the relative abundance of DR TB infections.

DOI: 10.1038/s41598-022-07536-2
PMCID: PMC8901732
PMID: 35256670

11. 25 years of surveillance of drug-resistant tuberculosis: achievements, challenges, and way forward.

Lancet Infect Dis. 2022 Mar 3:S1473-3099(21)00808-2. doi: 10.1016/S1473-3099(21)00808-2. Online ahead of print.

Dean AS(1), Tosas Auguet O(2), Glaziou P(2), Zignol M(2), Ismail N(2), Kasaeva T(2), Floyd K(2).

Tuberculosis is second only to COVID-19 as a cause of death from a single infectious agent. In 2020, almost 10 million people were estimated to have developed tuberculosis and it caused 1·5 million deaths. Around a quarter of deaths caused by antimicrobial resistance are due to rifampicin-resistant tuberculosis. Antimicrobial resistance surveillance systems for many bacterial pathogens are still in the early stages of implementation in many countries, and do not yet allow for the estimation of disease burden at the national level. In this Personal View, we present the achievements, challenges, and way forward for the oldest and largest global antimicrobial resistance surveillance system. Hosted by WHO since 1994, the Global Project on Anti-Tuberculosis Drug Resistance Surveillance has served as a platform for the evaluation of the trends in anti-tuberculosis drug resistance for over 25 years at country, regional, and global levels. With an estimated 465 000 incident cases of multidrug-resistant and rifampicin-resistant tuberculosis in 2019, drug-resistant tuberculosis remains a public health crisis. The COVID-19 pandemic has reversed years of progress in providing essential tuberculosis services and reducing disease burden. The number of people diagnosed with drug-resistant tuberculosis has dropped by 22% since before the pandemic, and the number of patients provided with treatment for drug-resistant tuberculosis has dropped by 15%. Now more than ever, closing gaps in the detection of drug-resistant tuberculosis requires investment in research and development of new diagnostic tools and their rollout, expansion of sample transport systems, and the implementation of data connectivity solutions.

DOI: 10.1016/S1473-3099(21)00808-2
PMCID: PMC8893725
PMID: 35248168

12. Identification of thiophene-benzenesulfonamide derivatives for the treatment of multidrug-resistant tuberculosis.

Eur J Med Chem. 2022 Mar 5;231:114145. doi: 10.1016/j.ejmech.2022.114145. Epub 2022 Jan 22.

Qin R(1), Wang P(1), Wang B(2), Fu L(2), Batt SM(3), Besra GS(3), Wu C(1), Wang Y(1), Huang H(4), Lu Y(5), Li G(6).

A series of thiophene-benzenesulfonamide derivatives was designed and synthesized by exploring the structure-activity relationship of lead compounds 2,3-disubstituted thiophenes 25a and 297F as antituberculosis agents, which displayed potent antimycobacterial activity against drug-susceptible and clinically isolated drug-resistant tuberculosis. In particular, compound 17b, which had improved activity (minimum inhibitory concentration of 0.023 μg/mL) compared with the lead compounds, displayed good intracellular antimycobacterial activity in macrophages with a reduction of 1.29 log10 CFU. A druggability evaluation indicated that compound 17b had favorable hepatocyte stability, low cytotoxicity, and low hERG channel inhibition. Moreover, compound 17b exhibited modest in vivo efficacy in an acute mouse model of tuberculosis. In addition, the molecular docking study elucidated the binding mode of compound 17b in the active site of DprE1. Therefore, compound 17b may be a promising antituberculosis lead for further research.

DOI: 10.1016/j.ejmech.2022.114145
PMID: 35101648 [Indexed for MEDLINE]

13. Advances in Key Drug Target Identification and New Drug Development for Tuberculosis.

Biomed Res Int. 2022 Feb 25;2022:5099312. doi: 10.1155/2022/5099312. eCollection 2022.

Mi J(#)(1), Gong W(#)(1), Wu X(1).

Tuberculosis (TB) is a severe infectious disease worldwide. The increasing emergence of drug-resistant Mycobacterium tuberculosis (Mtb) has markedly hampered TB control. Therefore, there is an urgent need to develop new anti-TB drugs to treat drug-resistant TB and shorten the standard therapy. The discovery of targets of drug action will lay a theoretical foundation for new drug development. With the development of molecular biology and the success of Mtb genome sequencing, great progress has been made in the discovery of new targets and their relevant inhibitors. In this review, we summarized 45 important drug targets and 15 new drugs that are currently being tested in clinical stages and several prospective molecules that are still at the level of preclinical studies. A comprehensive understanding of the drug targets of Mtb can provide extensive insights into the development of safer and more efficient drugs and

may contribute new ideas for TB control and treatment.

DOI: 10.1155/2022/5099312
PMCID: PMC8896939
PMID: 35252448

14. Drug-Resistant Characteristics, Genetic Diversity, and Transmission Dynamics of Rifampicin-Resistant Mycobacterium tuberculosis in Hunan, China, Revealed by Whole-Genome Sequencing.

Microbiol Spectr. 2022 Feb 23;10(1):e0154321. doi: 10.1128/spectrum.01543-21. Epub 2022 Feb 16.

He W(1), Tan Y(2), Liu C(3), Wang Y(1), He P(1), Song Z(1), Liu D(3)(4), Zheng H(5), Ma A(1), Zhao B(3), Ou X(3), Xia H(3), Wang S(3), Zhao Y(3).

To gain a deep insight into the additional drug-resistant profiles, genetic diversity, and transmission dynamics of rifampicin-resistant tuberculosis (RR-TB) circulating in Hunan province, drug susceptibility testing and whole-genome-sequencing were performed among RR-TB strains collected from Jan. 2013 to Jun. 2018 in Hunan province. A total of 124 RR-TB strains were recovered successfully and included into the final analysis. Lineage 2.2.1 was the dominant sublineage, accounting for 72.6% (90/124), followed by lineage 4.5 (11.3%, 14/124), lineage 4.4 (8.1%, 10/124), lineage 4.2 (6.5%, 8/124) and lineage 2.2.2 (1.6%, 2/124). Overall, 83.1% (103/124) and 3.2% (4/124) of RR-TB were MDR-TB and XDR-TB, respectively. Nearly 30% of RR-TB isolates were resistant to fluoroquinolones, and 26.6% (33/124) were pre-XDR-TB. Moreover, 30.6% (38/124) of RR-TB strains were identified as phenotypically resistance to pyrazinamide. Totally, 17 clusters containing 48 (38.7%, 48/124) RR-TB strains were identified, ranging in size from 2 to 10 isolates. No significant difference was detected in clustering rate between lineage 2 and lineage 4 ($\chi 2$ = 0.027, P = 0.870). Our study revealed the complexity of RR-TB strains circulating in Hunan province with complex additional drug-resistant profile and relatively higher clustering rates. Comprehensive information based on WGS should be used to guide the design of treatment regimens and tailor public interventions. IMPORTANCE Comprehensive information such as genetic background and drug-resistant profile of MTB strains could help to tailor public interventions. However, these data are limited in Hunan province, one of the provinces with high-TB burden in China. So, this study aimed to provide us with deep insight into the molecular epidemiology of RR-TB isolates circulating in Hunan province by combining phenotypic drug susceptibility testing and

whole-genome sequencing. To our knowledge, this is the first study to use whole-genome sequencing data of RR-TB strains spanning more than 5 years for molecular epidemiology analysis in Hunan province, which allows us to identify genetic background information and clustered strains more accurately. Our study revealed the complexity of RR-TB strains circulating in Hunan province with complex additional drug-resistant profile and relatively higher clustering rates. Comprehensive information based on WGS should be used to guide the design of treatment regimens and tailor public interventions.

DOI: 10.1128/spectrum.01543-21
PMCID: PMC8849054
PMID: 35171016 [Indexed for MEDLINE]

15. Correction to: The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China.

BMC Med. 2022 Mar 1;20(1):99. doi: 10.1186/s12916-022-02306-3.

Weerasuriya CK(1), Harris RC(2)(3), McQuaid CF(2), Bozzani F(4), Ruan Y(5), Li R(5), Li T(5), Rade K(6), Rao R(7), Ginsberg AM(8)(9), Gomez GB(#)(4)(10), White RG(#)(2).

Erratum for
BMC Med. 2021 Feb 26;19(1):60.

DOI: 10.1186/s12916-022-02306-3
PMCID: PMC8887015
PMID: 35227254

16. Phylogeography and transmission of M. tuberculosis in Moldova: A prospective genomic analysis.

PLoS Med. 2022 Feb 22;19(2):e1003933. doi: 10.1371/journal.pmed.1003933. eCollection 2022 Feb.

Yang C(1)(2), Sobkowiak B(3), Naidu V(3), Codreanu A(4), Ciobanu N(4), Gunasekera KS(2), Chitwood MH(2), Alexandru S(4), Bivol S(5), Russi M(2), Havumaki J(2), Cudahy P(2), Fosburgh H(2), Allender CJ(6), Centner H(6), Engelthaler DM(6), Menzies NA(7), Warren JL(8), Crudu V(4), Colijn C(3), Cohen T(2).

BACKGROUND: The incidence of multidrug-resistant tuberculosis (MDR-TB) remains

critically high in countries of the former Soviet Union, where >20% of new cases and >50% of previously treated cases have resistance to rifampin and isoniazid. Transmission of resistant strains, as opposed to resistance selected through inadequate treatment of drug-susceptible tuberculosis (TB), is the main driver of incident MDR-TB in these countries.
METHODS AND FINDINGS: We conducted a prospective, genomic analysis of all culture-positive TB cases diagnosed in 2018 and 2019 in the Republic of Moldova. We used phylogenetic methods to identify putative transmission clusters; spatial and demographic data were analyzed to further describe local transmission of Mycobacterium tuberculosis. Of 2,236 participants, 779 (36%) had MDR-TB, of whom 386 (50%) had never been treated previously for TB. Moreover, 92% of multidrug-resistant M. tuberculosis strains belonged to putative transmission clusters. Phylogenetic reconstruction identified 3 large clades that were comprised nearly uniformly of MDR-TB: 2 of these clades were of Beijing lineage, and 1 of Ural lineage, and each had additional distinct clade-specific second-line drug resistance mutations and geographic distributions. Spatial and temporal proximity between pairs of cases within a cluster was associated with greater genomic similarity. Our study lasted for only 2 years, a relatively short duration compared with the natural history of TB, and, thus, the ability to infer the full extent of transmission is limited.
CONCLUSIONS: The MDR-TB epidemic in Moldova is associated with the local transmission of multiple M. tuberculosis strains, including distinct clades of highly drug-resistant M. tuberculosis with varying geographic distributions and drug resistance profiles. This study demonstrates the role of comprehensive genomic surveillance for understanding the transmission of M. tuberculosis and highlights the urgency of interventions to interrupt transmission of highly drug-resistant M. tuberculosis.

DOI: 10.1371/journal.pmed.1003933
PMCID: PMC8903246
PMID: 35192619

17. 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]

18. Treatment outcomes among childhood extensively drug-resistant tuberculosis patients in Pakistan.

ERJ Open Res. 2022 Feb 21;8(1):00551-2021. doi: 10.1183/23120541.00551-2021. eCollection 2022 Jan.

Abubakar M(1), Ahmad N(1), Atif M(2), Hayat Khan A(3), Ghafoor A(4).

Treatment outcomes of childhood XDR-TB patients in Pakistan are better than in adult patients but still disappointing https://bit.ly/3rkQ9sw.

DOI: 10.1183/23120541.00551-2021
PMCID: PMC8859504
PMID: 35198629

19. 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.

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PMCID: PMC8857659
PMID: 35243010

20. Disseminated drug-resistant tuberculosis and multiple autoimmune syndrome in a child with selective IgA deficiency-An uncustomary combination.

Int J Rheum Dis. 2022 Mar;25(3):367-372. doi: 10.1111/1756-185X.14289. Epub 2022 Jan 20.

Nori H(1), Vohra V(1), Banday AZ(1), Jindal AK(1), Tyagi R(1), Sodhi MK(2), Bal A(3), Suri D(1).

Polyautoimmunity or multiple autoimmune syndrome (MAIS) is increasingly being

recognized in pediatric clinical practice, often in conjunction with systemic lupus erythematosus (SLE). Besides multi-organ autoimmunity, children with SLE are often at a higher risk of developing infections including tuberculosis. The tendency to develop infections and multiple autoimmune diseases in childhood SLE often occurs in the absence of monogenic primary immunodeficiency disease. Conversely, children with inborn errors of immunity, of which selective IgA deficiency (sIgAD) is the most common, may develop recurrent infections and autoimmune disorders including SLE. Herein, we report a child with MAIS (including SLE) and sIgAD who developed drug-resistant tuberculosis, which was managed successfully with second-line anti-tubercular drug therapy. To the best of our knowledge, this combination of rare findings has not been reported previously in the pediatric literature. Although a majority of patients with sIgAD are either asymptomatic or have mild infections/autoimmunity, the index child had a myriad of infectious illnesses and multi-organ autoimmunity. Our case highlights the prudence of thoroughly evaluating children with SLE for other autoimmune diseases and vice versa. Given the higher probability of inherited disorders, including early complement deficiencies and monogenic interferonopathies, in childhood SLE compared with adult SLE, it may be prudent to perform a basic immunological workup (for example, immunoglobulin levels, 50% hemolytic complement) in such patients. A more extensive immunological and genetic evaluation (including next-generation sequencing) may also be required in the presence of unusual clinical or laboratory features, a positive family history, or a complicated clinical course.

DOI: 10.1111/1756-185X.14289
PMID: 35048520 [Indexed for MEDLINE]

21. 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
PMID: 35303463

22. Development of potential proteasome inhibitors against Mycobacterium tuberculosis.

J Biomol Struct Dyn. 2022 Mar;40(5):2189-2203. doi: 10.1080/07391102.2020.1835722. Epub 2020 Oct 19.

Tyagi R(1), Srivastava M(2), Jain P(3), Pandey RP(1), Asthana S(2), Kumar D(4), Raj VS(1).

Tuberculosis (TB) has been recently declared as a health emergency because of sporadic increase in Multidrug-resistant Tuberculosis (MDR-TB) problem throughout the world. TB causing bacteria, Mycobacterium tuberculosis has become resistant to the first line of treatment along with second line of treatment and drugs, which are accessible to us. Thus, there is an urgent need of identification of key targets and development of potential therapeutic approach(s), which can overcome the Mycobacterium tuberculosis complications. In the present study, Mycobacterium tuberculosis proteasome has been taken as a potential target as it is one of the key regulatory proteins in Mycobacterium tuberculosis propagation. Further, a library of 400 compounds (small molecule) from Medicines for Malaria Venture (MMV) were screened against the target (proteasome) using molecular docking and simulation approach, and selected lead compounds were validated in in vitro model. In this study, we have identified two potent small molecules from the MMV Pathogen Box library, MMV019838 and MMV687146 with -9.8 kcal/mol and -8.7 kcal/mol binding energy respectively, which actively interact with the catalytic domain/active domain of Mycobacterium tuberculosis proteasome and inhibit the Mycobacterium tuberculosis growth in in vitro culture. Furthermore, the molecular docking and simulation study of MMV019838 and MMV687146 with proteasome show strong and stable interaction with Mycobacterium tuberculosis compared to human proteasome and show no cytotoxicity effect. A better understanding of proteasome inhibition in Mycobacterium tuberculosis in in vitro and in vivo model would eventually allow us to understand the molecular mechanism(s) and discover a novel and potent therapeutic agent against Tuberculosis. Active efflux of drugs mediated by efflux pumps that confer drug resistance is one of the mechanisms developed by bacteria to counter the adverse effects of antibiotics and chemicals. Efflux pump activity was tested for a specific compound MMV019838 which was showing good in silico results than MIC values.Communicated by Ramaswamy H. Sarma.

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PMID: 33074049 [Indexed for MEDLINE]

23. Sudapyridine (WX-081), a Novel Compound against Mycobacterium tuberculosis.

Microbiol Spectr. 2022 Feb 23;10(1):e0247721. doi: 10.1128/spectrum.02477-21. Epub 2022 Feb 16.

Yao R(#)(1)(2), Wang B(#)(1)(2), Fu L(1)(2), Li L(3), You K(3), Li YG(3), Lu Y(1)(2).

Bedaquiline (BDQ) was historically listed by the World Health Organization (WHO) in 2018 as the preferred option for rifampin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB). However, when there is no other effective regimen, the side effects and weaknesses of BDQ limit its use of MDR-TB. There is a black box warning in the package insert of BDQ to warn patients and health care professionals that this drug may increase the risk of unexplained mortality and QT prolongation, which may lead to abnormal and potentially fatal cardiac rhythm. In addition, the phenomenon of elevated liver enzymes in clinical trials of BDQ is a potential sign of hepatotoxicity. Therefore, it is still a medical need to develop new compounds with better safety profiles, patient compliance, affordability, and the ability to retain the efficacy of BDQ. After extensive lead generation and optimization, a new analog, sudapyridine (WX-081), was selected as a potential new antituberculosis candidate to move into clinical trials. Here, we evaluated WX-081's overall preclinical profile, including efficacy, pharmacokinetics, and toxicology. The in vitro activity of WX-081 against drug-sensitive and drug-resistant tuberculosis was comparable to that of BDQ, and there was comparable efficacy between WX-081 and BDQ in both acute and chronic mouse tuberculosis models using low-dose aerosol infection. Moreover, WX-081 improved pharmacokinetic parameters and, more importantly, had no adverse effects on blood pressure, heart rate, or qualitative ECG parameters from nonclinical toxicology studies. WX-081 is under investigation in a phase 2 study in patients. IMPORTANCE This study is aimed at chemotherapy for multidrug-resistant tuberculosis (MDR-TB), mainly to develop new anti-TB drugs to kill Mycobacterium tuberculosis, a microorganism with strong drug resistance. In this study, the structure of a potent antituberculosis compound, bedaquiline (BDQ), was optimized to generate a new compound, sudapyridine (WX-081). This experiment showed that its efficacy was similar to that of BDQ, its cardiotoxicity was lower, and it had good kinetic characteristics. This compound will certainly achieve significant results in the control and treatment of tuberculosis in the future.

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PMCID: PMC8849072
PMID: 35170994 [Indexed for MEDLINE]

24. Quinoline heterocyclic containing plant and marine candidates against drug-resistant Mycobacterium tuberculosis: A systematic drug-ability

investigation.

Eur J Med Chem. 2022 Mar 15;232:114173. doi: 10.1016/j.ejmech.2022.114173. Epub 2022 Feb 4.

Swain SS(1), Pati S(2), Hussain T(3).

Today, tuberculosis (TB) caused by the acid-fast bacilli, Mycobacterium tuberculosis (Mtb) is the most infectious killer disease globally with high morbidity and mortality rates. The rapid development of multi-drug-resistant (MDR) strains via intrinsic (efflux pumps) and acquired (biological mutations) mechanisms reduce the efficacy of applied anti-TB regimens. Nevertheless, only bedaquiline (BDQ) and pretomanid (PMD) were added to anti-TB therapy in the last decade. The existing anti-TB drugs also exhibited cytotoxicity and hepatotoxicity from long-term treatment. Thus, exploring or developing potential and less toxic anti-TB candidates, preferably natural-based candidates, is the call of the day. At present, 'quinoline' could be considered one of the versatile scaffolds presented in most mainstream medicines from comprehensive drug reports. Notably, BDQ with two clinically evaluating anti-TB candidates, TBJA-587 and DC-159a was motivated for utilizing quinoline heterocycles. Accordingly, we have selected 65 natural quinoline heterocycles bearing potential anti-TB agents (40 plant-derived and 25 marine-derived) within MIC value ≤ 50 μg/mL from an extensive literature search. Briefly, source, drug chemistry, structural activity relationship, prior pharmacokinetics profiles with drug-ability, toxicity, and hierarchical clustering analysis using various computational tools to identify the most 'drug-able lead' candidate is the uniqueness of the review. From extensive drug analysis, tetrandrine, 2'-nortiliacorinine, tiliacorine, globospiramine, evocarpine, allocuspareine from plant sources, and ecteinascidin 770, 6-hydroxymanzamine E, (-)-8-hydroxymanzamine A, ecteinascidin 786, manzamine F from marine sources are the most potential-cum-drug-able anti-TB candidates. We hope the systematic and critical drug analyses on quinoline-bearing natural anti-TB candidates are helpful to design potential-cum-less toxic anti-TB drugs in the future.

DOI: 10.1016/j.ejmech.2022.114173
PMID: 35168150 [Indexed for MEDLINE]

25. Characterization of embB mutations involved in ethambutol resistance in multi-drug resistant Mycobacterium tuberculosis isolates in Zambia.

Tuberculosis (Edinb). 2022 Mar;133:102184. doi: 10.1016/j.tube.2022.102184. Epub

2022 Feb 24.

Bwalya P(1), Solo ES(2), Chizimu JY(3), Shrestha D(4), Mbulo G(2), Thapa J(5), Nakajima C(6), Suzuki Y(7).

BACKGROUND: Ethambutol (EMB) is an important anti-tuberculosis drug used in the management of multi-drug resistant tuberculosis (MDR-TB). Mutations in embB are the major mechanism of resistance. This study investigated embB mutations among MDR-TB isolates and analyzed their correlations with phenotypic drug susceptibility testing (DST) in Zambia.
METHOD: A total of 132 MDR-TB isolates were collected from January 2014 to April 2017 and characterized using MGIT 960 systems, embB sequencing, and spoligotyping.
RESULTS: Out of 61 phenotypically EMB resistant isolates, 53 had mutations in embB. Among the 71 EMB susceptible isolates, 47 had embB mutations. Sensitivity of embB mutations was 86.9% while specificity was 33.8%. CAS1_Kili (SIT21) had high odds of having embB mutations, particularly, G918A (Met306eIl) (Odds ratio 16.7, $p < 0.0001$).
CONCLUSION: Molecular EMB resistance testing by DNA sequencing can improve detection of EMB resistance among MDR-TB patients in Zambia. Additionally, CAS1_Kili was associated with embB amino acid substitution Met306Ile suggesting transmission. A detailed investigation to track and determine transmission hotspot area for MDR-TB could help optimize control strategies.

DOI: 10.1016/j.tube.2022.102184
PMID: 35240539

26. An updated patent review on drugs for the treatment of tuberculosis (2018-present).

Expert Opin Ther Pat. 2022 Mar;32(3):243-260. doi: 10.1080/13543776.2022.2012151. Epub 2021 Dec 30.

Ahmed S(1), Nandi S(1), Saxena AK(1).

INTRODUCTION: Tuberculosis (TB) caused by Mycobacterium tuberculosis (M.tb) has been a global challenge as 1.4 million deaths were reported in 2019, which included deaths attributed to HIV-TB co-infection. It is curable by the prescribed Directly Observed Treatment Short (DOTS) course, but the situation becomes critical and alarming due to multi-drug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. Hence there has been an urgent need to

develop novel M.tb chemotherapeutics to overcome this situation.
AREAS COVERED: This review provides an overview and update on recent developments on the novel therapeutics for the treatment of TB from the important published and granted patents (2018-present).
EXPERT OPINION: The discovery of potent chemotherapeutics with reduced toxicity to combat M.tb particularly MDR and XDR-TB is a major challenge in antitubercular drug development. The missing of any doses during the DOTS treatment and poor immunity particularly in HIV patients has been a major cause for the development of drug resistance. Hence the major focus has to be on novel targets with their inhibitors and novel molecules both of natural and synthetic origins along with repurposed drugs for the complete eradication of tuberculosis.

DOI: 10.1080/13543776.2022.2012151
PMID: 34846976 [Indexed for MEDLINE]

27. Transborder molecular analysis of drug-resistant tuberculosis in Mongolia and Eastern Siberia, Russia.

Transbound Emerg Dis. 2022 Mar 16. doi: 10.1111/tbed.14515. Online ahead of print.

Zhdanova S(1), Mokrousov I(2), Orlova E(1), Sinkov V(1), Ogarkov O(1).

Eastern Siberia (Russia) and Mongolia are borderline regions in Asia with a high incidence of tuberculosis (TB). In this study, we investigated the transborder transmission of Mycobacterium tuberculosis with a focus on endemic and epidemic clones and drug resistance. M. tuberculosis isolates (287 from Mongolia and 754 from Russia) were collected using cross-sectional population-based surveys between 2010 and 2016. The isolates were genotyped using 24 variable number of tandem repeat (VNTR) loci and by testing of the key markers to discriminate within the Beijing genotype. All isolates were divided into 427 MIRU-types that were assigned to Lineage 2 (Beijing) and Lineage 4 (Ural, Haarlem, Latin American-Mediterranean [LAM], S, unclassified). The Beijing genotype was dominant in both countries (69% in Russia, 75% in Mongolia). However, the Beijing isolates differed significantly between the countries, in terms of the identified subtypes. LAM was the most common non-Beijing genotype (11.1% in Mongolia and 14.9% in Russia) and LAM isolates mostly belonged to the LAM-RUS branch in both countries. The MDR rate was higher in Russia than in Mongolia among newly diagnosed patients: 29.4% versus 5.6% ($p < 0.001$). In Mongolia, the MDR rate was similar in Beijing (29.7%) and non-Beijing (27.5%) genotypes. In Russia, a higher MDR rate was observed in (i) Beijing compared to non-Beijing (48.7% versus 38.3%, $p = 0.03$) and (ii) Beijing B0/W148 compared to Beijing

Central Asian/Russian (63.4% versus 37.3%, p<0.001). In conclusion, the M. tuberculosis population structure in Mongolia was shaped by mainly historical interaction with China (dominance of the Beijing genotype) and Northern Eurasia (presence of the LAM-RUS branch). In contrast, the transborder transmission of M. tuberculosis since the 1990s between Mongolia and its neighbors has been negligible, and the adverse trends of MDR-TB in Russia did not impact the current situation in Mongolia.

DOI: 10.1111/tbed.14515
PMID: 35294112

28. Safety and effectiveness outcomes from a 14-country cohort of patients with multi-drug resistant tuberculosis treated concomitantly with bedaquiline, delamanid and other second-line drugs.

Clin Infect Dis. 2022 Mar 4:ciac176. doi: 10.1093/cid/ciac176. Online ahead of print.

Huerga H(1), Khan U(2), Bastard M(1), Mitnick CD(3)(4)(5), Lachenal N(6), Khan PY(2)(7), Seung KJ(3)(4)(5), Melikyan N(1), Ahmed S(8), Rich ML(3)(4)(5), Varaine F(9), Osso E(3)(6), Rashitov M(10), Salahuddin N(11), Salia G(12), Sánchez E(13), Serobyan A(14), Siddiqui MR(15), Tefera DG(16), Vetushko D(17), Yeghiazaryan L(18), Holtzman D(19), Islam S(20), Kumsa A(21), Leblanc GJ(22), Leonovich O(23), Mamsa S(20), Manzur-Ul-Alam M(24), Myint Z(25), Padayachee S(26), Franke MF(3), Hewison C(9); endTB study observational study team.

BACKGROUND: Concomitant use of bedaquiline (Bdq) and delamanid (Dlm) for multi-drug/rifampicin resistant tuberculosis (MDR/RR-TB) has raised concerns about a potentially poor risk-benefit ratio. Yet, this combination is an important alternative for patients infected with strains of TB with complex drug resistance profiles or who cannot tolerate other therapies. We assessed safety and treatment outcomes of MDR/RR-TB patients receiving concomitant Bdq and Dlm, along with other second-line anti-TB drugs.
METHODS: We conducted a multi-centric, prospective observational cohort study across 14 countries among patients receiving concomitant Bdq-Dlm treatment. Patients were recruited between April 2015 and September 2018 and were followed until the end of treatment. All serious adverse events and adverse events of special interest (AESI), leading to a treatment change, or judged significant by a clinician, were systematically monitored and documented.
RESULTS: Overall, 472 patients received Bdq and Dlm concomitantly. A large

majority also received linezolid (89.6%) and clofazimine (84.5%). Nearly all (90.3%) had extensive disease; most (74.2%) had resistance to fluoroquinolones. The most common AESI were peripheral neuropathy (134, 28.4%) and electrolyte depletion (94, 19.9%). Acute kidney injury and myelosuppression were seen in 40 (8.5%) and 24 (5.1%) of patients, respectively. QT prolongation occurred in 7 (1.5%). Overall, 78.0% (358/458) had successful treatment outcomes, 8.9% died and 7.2% experienced treatment failure.
CONCLUSIONS: Concomitant use of Bdq and Dlm, along with linezolid and clofazimine, is safe and effective for MDR/RR-TB patients with extensive disease. Using these drugs concomitantly is a good therapeutic option for patients with resistance to many anti-TB drugs.

DOI: 10.1093/cid/ciac176
PMID: 35243494

29. 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

30. Application of Amplicon-Based Targeted NGS Technology for Diagnosis of Drug-Resistant Tuberculosis Using FFPE Specimens.

Microbiol Spectr. 2022 Feb 23;10(1):e0135821. doi: 10.1128/spectrum.01358-21. Epub 2022 Feb 9.

Song J(#)(1), Du W(#)(1), Liu Z(#)(1), Che J(1), Li K(1), Che N(1).

Next-generation sequencing (NGS) enables rapid identification of common and rare drug-resistant genetic variations from tuberculosis (TB) patients' sputum samples and MTB isolates. However, whether this technology is effective for formalin-fixed and paraffin-embedded (FFPE) tissues remains unclear. An amplicon-based targeted NGS sequencing panel was developed to predict susceptibility to 9 antituberculosis drugs, including 3 first-line drugs, by directly detecting FFPE tissues. A total of 178 tissue samples from TB patients who underwent phenotypic drug susceptibility test were retrospectively tested from January 2017 to October 2019 in the Department of Pathology, Beijing Chest Hospital, China. Phenotypic drug susceptibility test results were used as the reference standard. We identified 22 high-quality mutations from 178 FFPE tissue samples, including 15 high+moderate+minimal confidence-level mutations associated with drug resistance (rpoB D435V, S450F/L; KatG S315T; inhA-fabG promoter c-15t; embB G406S, M306V; rpsL K43R, K88R, rrs a1401g, a514c; gyrA D94G/Y/A, A90V), 6 mutations not associated with resistance (rpoB D435Y, H445S, L430P, L452P; embB G406A/D), and one mutation site embB M306I defined as indeterminate. Compared to the phenotypic method, sensitivities (95% CI) for rifampicin, isoniazid, and ethambutol were 96% (79.65-99.90%), 93.55% (78.58-99.21%), and 71.43% (35.24-92.44%), respectively; while for second-line drugs, it varied from 23.53% (9.05-47.77%) for capreomycin to 86.84% (72.20-94.72%) for streptomycin. Specificities for all drugs were satisfactory (>94.51%). Therefore, important pathological FFPE tissue samples, despite partially degraded DNA, can be used as essential specimens for molecular diagnosis of drug resistant TB by amplicon-based targeted NGS technology. IMPORTANCE Amplicon-based targeted NGS technology focuses on a set of gene mutations of known or suspected associations with drug susceptibility in Mycobacterium tuberculosis (MTB). This method offers many benefits, such as low sequencing cost, easy customization, high throughput, shorter testing time and not culture dependent. Formalin-fixed and paraffin-embedded (FFPE) tissues are important pathological specimen in diagnosing tuberculous disease because they are noninfectious and provide excellent preservation of tissue morphology with low storage cost. However, the performance of amplicon-based targeted NGS method on FFPE samples has not been reported yet. Therefore, we evaluated the performance of this method using FFPE samples collected from January 2017 to October 2019 in the Department of Pathology, Beijing Chest Hospital, China. We

demonstrate that the amplicon-based targeted NGS method performs excellent on FFPE samples, and it can be applied to pathological diagnosis of drug resistant tuberculosis.

DOI: 10.1128/spectrum.01358-21
PMCID: PMC8826733
PMID: 35138166 [Indexed for MEDLINE]

31. Clinical Impact of the Line Probe Assay and Xpert® MTB/RIF Assay in the Presumptive Diagnosis of Drug-Resistant Tuberculosis in Brazil: A Pragmatic Clinical Trial.

Rev Soc Bras Med Trop. 2022 Feb 25;55:e0191. doi: 10.1590/0037-8682-0191-2021. eCollection 2022.

Kritski A(1), Oliveira MM(1), Almeida IN(2), Ramalho D(1), Andrade MKN(1)(3), Carvalho M(3), Miranda PFC(1), Dalcolmo MP(3), Braga JU(4), Brígido T(5), Mesquita E(6), Dias C(7), Gambirasio A(8), Souza Filho JB(9), Detjen A(10), Phillips PPJ(11)(12), Langley I(13), Fujiwara P(12), Squire SB(13).

BACKGROUND: Rapid molecular methods such as the line probe assay (LPA) and Xpert® MTB/RIF assay (Xpert) have been recommended by the World Health Organization for drug-resistant tuberculosis (DR-TB) diagnosis. We conducted an interventional trial in DR-TB reference centers in Brazil to evaluate the impact of the use of LPA and Xpert.
METHODS: Patients with DR-TB were eligible if their drug susceptibility testing results were available to the treating physician at the time of consultation. The standard reference MGITTM 960 was compared with Xpert (arm 1) and LPA (arm 2). Effectiveness was considered as the start of the appropriate TB regimen that matched drug susceptibility testing (DST) and the proportions of culture conversion and favorable treatment outcomes after 6 months.
RESULTS: A higher rate of empirical treatment was observed with MGIT alone than with the Xpert assay (97.0% vs. 45.0%) and LPA (98.2% vs. 67.5%). Patients started appropriate TB treatment more quickly than those in the MGIT group (median 15.0 vs. 40.5 days; $p<0.01$) in arm 1. Compared to the MGIT group, culture conversion after 6 months was higher for Xpert in arm 1 (90.9% vs. 79.3%, $p=0.39$) and LPA in arm 2 (80.0% vs. 83.0%, $p=0.81$).
CONCLUSIONS: In the Xpert arm, there was a significant reduction in days to the start of appropriate anti-TB treatment and a trend towards greater culture conversion in the sixth month.

DOI: 10.1590/0037-8682-0191-2021
PMID: 35239898 [Indexed for MEDLINE]

32. 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.

DOI: 10.1016/j.jctube.2022.100299
PMCID: PMC8802117
PMID: 35146133

33. Bedaquiline adherence measured by electronic dose monitoring predicts clinical outcomes in the treatment of patients with multidrug-resistant tuberculosis and HIV/AIDS.

J Acquir Immune Defic Syndr. 2022 Feb 21. doi: 10.1097/QAI.0000000000002940. Online ahead of print.

O'Donnell MR(1), Padayatchi N, Wolf A, Zelnick J, Daftary A, Orrell C, Nimmo C, Baldwin M, Boodhram R, Maharaj B, Amico KR, Naidoo K, Friedland G.

BACKGROUND: Novel regimens have revolutionized multidrug-resistant tuberculosis (MDR-TB) treatment; however, medication adherence remains challenging and poorly characterized. We hypothesized that bedaquiline adherence, measured using electronic dose monitoring, would predict MDR-TB treatment outcomes.
SETTING: Prospective cohort study in KwaZulu-Natal, South Africa.
METHODS: Adults with MDR-TB and HIV initiating bedaquiline and on antiretroviral therapy (ART) were eligible. Separate electronic dose monitoring devices measured bedaquiline and ART adherence through six months, calculated as observed versus expected doses. Whole genome sequencing was performed to identify bedaquiline resistance-associated variants.
RESULTS: From November 2016 through February 2018, 199 participants with MDR-TB and HIV were enrolled and followed through treatment completion (median 17.2 months IQR 12.2-19.6). Median bedaquiline adherence was higher than ART adherence (97 vs. 89%, $p<0.001$), but correlated ($r2=0.68$, $p<0.001$). High bedaquiline adherence (≥90%) compared to lower adherence was associated with

improved rates of end of treatment successful outcome (83.4% vs. 46.3%, p<0.001), decreased mortality (11.0% vs. 29.6% p=0.004), and improved retention in care through end of treatment (94.5% vs. 79.6% p=0.002). Modelling identified a highly significant, but linear association between bedaquiline adherence and outcome. On multivariable analysis, bedaquiline adherence was independently associated with mortality and outcome. Bedaquiline resistance-associated variants were seen in 12% (7/57) of sequenced isolates (7% baseline, 5% emergent) with only 28.6% experiencing successful treatment outcome.
CONCLUSIONS: Bedaquiline adherence through 6-months independently predicted end of MDR-TB treatment outcome, but a specific bedaquiline adherence threshold was not identified. Interventions to optimize bedaquiline adherence are urgently needed to improve MDR-TB HIV treatment outcomes.

DOI: 10.1097/QAI.0000000000002940
PMID: 35195572

34. Prognostic accuracy of time to sputum culture conversion in predicting cure in extensively drug-resistant tuberculosis patients: a multicentre retrospective observational study.

BMC Infect Dis. 2022 Mar 2;22(1):204. doi: 10.1186/s12879-022-07202-y.

Abubakar M(1), Ahmad N(2), Atif M(3), Ahmad I(4), Wahid A(1), Khan A(1), Saleem F(1), Ghafoor A(5).

BACKGROUND: There was a lack of information about prognostic accuracy of time to sputum culture conversion (SCC) in forecasting cure among extensively drug-resistant tuberculosis (XDR-TB) patients. Therefore, this study evaluated the prognostic accuracy of SCC at various time points in forecasting cure among XDR-TB patients.
METHODS: This retrospective observational study included 355 eligible pulmonary XDR-TB patients treated at 27 centers in Pakistan between 01-05-2010 and 30-06-2017. The baseline and follow-up information of patients from treatment initiation until the end of treatment were retrieved from electronic nominal recording and reporting system. Time to SCC was analyzed by Kaplan-Meier method, and differences between groups were compared through log-rank test. Predictors of time to SCC and cure were respectively evaluated by multivariate Cox proportional hazards and binary logistic regression analyses. A p-value<0.05 was considered statistically significant.
RESULTS: A total of 226 (63.6%) and 146 (41.1%) patients respectively achieved SCC and cure. Median time to SCC was significantly shorter in patients who

achieved cure, 3 months (95% confidence interval [CI]: 2.47-3.53), than those who did not (median: 10 months, 95% CI: 5.24-14.76) (p-value<0.001, Log-rank test). Patient's age>40 years (hazards ratio [HR]=0.632, p-value=0.004), baseline sputum grading of scanty,+1 (HR=0.511, p-value=0.002), +2, +3 (HR=0.523, p-value=0.001) and use of high dose isoniazid (HR=0.463, p-value=0.004) were significantly associated with early SCC. Only SCC at 6 month of treatment had statistically significant association with cure (odds ratio=15.603, p-value<0.001). In predicting cure, the sensitivities of SCC at 2, 4 and 6 months were respectively 41.8% (95%CI: 33.7-50.2), 69.9% (95%CI: 61.7-77.2) and 84.9% (95%CI: 78.1-90.3), specificities were respectively, 82.8% (95%CI: 76.9-87.6), 74.6% (95%CI: 68.2-80.4) and 69.4% (95%CI: 62.6-75.5) and prognostic accuracies were respectively 65.9% (95%CI: 60.7-70.8), 72.7% (95%CI: 67.7-77.2) and 75.8% (95%CI: 71.0-80.1).
CONCLUSION: In forecasting cure, SCC at month 6 of treatment performed better than SCC at 2 and 4 months. However, it would be too long for clinicians to wait for 6 months to decide about the regimen efficacy. Therefore, with somewhat comparable prognostic accuracy to that SCC at 6 month, using SCC at 4 month of treatment as a prognostic marker in predicting cure among XDR-TB patients can decrease the clinicians waiting time to decide about the regimen efficacy.

DOI: 10.1186/s12879-022-07202-y
PMCID: PMC8889712
PMID: 35236307 [Indexed for MEDLINE]

35. Screening approaches and therapeutic targets: The two driving wheels of tuberculosis drug discovery.

Biochem Pharmacol. 2022 Mar;197:114906. doi: 10.1016/j.bcp.2021.114906. Epub 2022 Jan 4.

Perveen S(1), Sharma R(2).

Tuberculosis (TB) is an infectious disease, infecting a quarter of world's population. Drug resistant TB further exacerbates the grim scenario of the drying TB drug discovery pipeline. The limited arsenal to fight TB presses the need for thorough efforts for identifying promising hits to combat the disease. The review highlights the efforts in the field of tuberculosis drug discovery, with an emphasis on massive drug screening campaigns for identifying novel hits against Mtb in both industry and academia. As an intracellular pathogen, mycobacteria reside in a complicated intracellular environment with multiple factors at play. Here, we outline various strategies employed in an effort to

mimic the intracellular milieu for bringing the screening models closer to the actual settings. The review also focuses on the novel targets and pathways that could aid in target-based drug discovery in TB. The recent high throughput screening efforts resulting in the identification of potent hits against Mtb has been summarized in this article. There is a pressing need for effective screening strategies and approaches employing innovative tools and recent technologies; including nanotechnology, gene-editing tools such as CRISPR-cas system, host-directed bacterial killing and high content screening to augment the TB drug discovery pipeline with safer and shorter drug regimens.

DOI: 10.1016/j.bcp.2021.114906
PMID: 34990594 [Indexed for MEDLINE]

36. Molecular Characteristic of Both Levofloxacin and Moxifloxacin Resistance in Mycobacterium tuberculosis from Individuals Diagnosed with Preextensive Drug-Resistant Tuberculosis.

Microb Drug Resist. 2022 Mar;28(3):280-287. doi: 10.1089/mdr.2021.0212. Epub 2021 Dec 31.

Zhang X(1), Chen X(2), Wang B(2), Fu L(2), Huo F(3), Gao T(1), Pang Y(4), Lu Y(2), Li Q(5).

Aim: Fluoroquinolones (FQs) are the cornerstone in treating drug-resistant tuberculosis (TB); the prevalence of TB among the population is diverse in different regions, understanding the relationship between resistance pattern and molecular characteristic of FQs in preextensive drug-resistant (pre-XDR) clinical isolates is limited in China. Methods: A total of 141 pre-XDR clinical isolates from different individuals stored at the National Clinical Centre were collected from the Beijing Chest Hospital, minimal inhibitory concentrations of levofloxacin (Lfx) and moxifloxacin (Mfx) as well as sequences of quinolone-resistant determining regions in gyrA and gyrB genes were examined. Results: One hundred twelve pre-XDR clinical isolates were resistant to both Lfx and Mfx, molecular analyses showed that 87.50%, 0.89%, and 6.25% of the pre-XDR clinical isolates harbored FQ resistance mutations in gyrA, gyrB, and in both. We found five amino acid mutation positions in gyrA and four in gyrB, The mutation position in gyrA included codons 94, 91, 90, 88, and 74, and in gyrB included codons 504, 500, 512, and 501. Codon 94 of gyrA was the most prevalent mutation (83.04%), containing the Asp amino acid substitution with Gly (50.89%), Asn (15.17%), Ala (8.93%), Tyr (6.25%), and His (1.79%). Conclusions: The mutations of gyrA were most common and the frequency of Asp94Gly was the highest

in pre-XDR clinical isolates in Beijing, China. The mutations at codon 94 significantly contributed to the resistance to both Lfx and Mfx in pre-XDR clinical isolates and may cause a high resistance level.

DOI: 10.1089/mdr.2021.0212
PMID: 34981969 [Indexed for MEDLINE]

37. Evaluation of a Molecular Test for Detection of Mycobacterium tuberculosis Isolates Resistant to Rifampicin and Isoniazid.

Clin Lab. 2022 Mar 1;68(3). doi: 10.7754/Clin.Lab.2021.210614.

Benaissa E, Benlahlou Y, Bssaibis F, Maleb A, Elouennass M.

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) is increasing worldwide and is a major cause of death in many countries. It has become a major challenge for national tuberculosis control programs. Therefore, rapid identification of MDR strains of Mycobacterium tuberculosis and monitoring of their transmission could contribute significantly to the fight against tuberculosis. The GenoType MTBDRplus assay has been recommended by the World Health Organization to identify rifampicin (RIF)- and isoniazid (INH)-resistant M. Tuberculosis isolates. The objectives of this study were to evaluate the performance of the GenoType MTBDRplus test in the detection of rifampicin and isoniazid resistance of M. tuberculosis isolates in a Moroccan hospital and then to determine the frequency of mutations associated with resistance to these two major anti-tuberculosis drugs.
METHODS: This is a retrospective study conducted at the bacteriology department of the Mohammed V military hospital over a period of one year from 01/01/2018 to 12/31/2019. A total of 92 isolates of M. tuberculosis from pulmonary and extra-pulmonary specimens were evaluated for drug susceptibility by MGIT™ 960 AST system and compared to the GenoType MTBDRplus assay. The MGIT™ 960 AST system was used as the gold standard for the evaluation of the GenoType MTBDRplus assay.
RESULTS: Sensitivity and specificity of the GenoType MTBDRplus assay for the detection of RIF-resistant M. tuberculosis isolates were 83.33% and 100%, respectively. Its sensitivity and specificity for the detection of INH-resistant M. tuberculosis were 88.23% and 100% respectively. The concordances of the GenoType MTBDRplus assay and the MGIT™ 960 AST system for the detection of sensitivity to RIF and INH were 99% (1/92) and 98% (2/92), respectively. Among the five RIF-resistant isolates, the MUT3 mutation in the rpoB gene (codon S531L mutation) was present in 80% of isolates, whereas mutations in the rpoB MUT1 gene were present in only one (20%) RIF-resistant isolate. INH resistance was detected in 15 isolates, of which nine isolates (60%) had specific mutations of

the katG gene (codon S315T1) and conferred a high level of resistance to INH. CONCLUSIONS: The results of this study have shown that the GenoType MTBDRplus test has a high sensitivity and specificity for the detection of resistance to RIF and INH.

DOI: 10.7754/Clin.Lab.2021.210614
PMID: 35254025 [Indexed for MEDLINE]

38. Practical management of suspected hypersensitivity reactions to anti-tuberculosis drugs.

Clin Exp Allergy. 2022 Mar;52(3):375-386. doi: 10.1111/cea.14084. Epub 2022 Jan 20.

Bermingham WH(1), Bhogal R(2), Arudi Nagarajan S(3), Mutlu L(1), El-Shabrawy RM(4), Madhan R(5), Krishnaswamy UM(6), Murali MR(7), Kudagammana ST(8)(9), Shrestha R(10), Sumantri S(11), Christopher DJ(12), Mahesh PA(13), Dedicoat M(14), Krishna MT(1)(15).

Tuberculosis (TB) is the commonest cause of death by a single infectious agent globally and ranks amongst the top ten causes of global mortality. The incidence of TB is highest in Low-Middle Income countries (LMICs). Prompt institution of, and compliance with, therapy are cornerstones for a favourable outcome in TB and to mitigate the risk of multiple drug resistant (MDR)-TB, which is challenging to treat. There is some evidence that adverse drug reactions (ADRs) and hypersensitivity reactions (HSRs) to anti-TB drugs occur in over 60% and 3%-4% of patients respectively. Both ADRs and HSRs represent significant barriers to treatment adherence and are recognised risk factors for MDR-TB. HSRs to anti-TB drugs are usually cutaneous and benign, occur within few weeks after commencement of therapy and are likely to be T-cell mediated. Severe and systemic T-cell mediated HSRs and IgE mediated anaphylaxis to anti-TB drugs are relatively rare, but important to recognise and treat promptly. T-cell-mediated HSRs are more frequent amongst patients with co-existing HIV infection. Some patients develop multiple sensitisation to anti-TB drugs. Whilst skin tests, patch tests and in vitro diagnostics have been used in the investigation of HSRs to anti-TB drugs, their predictive value is not established, they are onerous, require specialist input of an allergist and are resource-dependent. This is compounded by the global, unmet demand for allergy specialists, particularly in low-income countries (LICs)/LMICs and now the challenging circumstances of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. This narrative review provides a critical analysis of the limited published evidence on this topic and proposes a cautious and pragmatic approach to optimise and standardise the management of HSRs to anti-TB drugs. This includes clinical risk

stratification and a dual strategy involving sequential re-challenge and rapid drug desensitisation. Furthermore, a concerted international effort is needed to generate real-time data on ADRs, HSRs, safety and clinical outcomes of these interventions.

DOI: 10.1111/cea.14084
PMID: 34939251 [Indexed for MEDLINE]

39. 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).

DOI: 10.1016/S2214-109X(22)00045-6
PMCID: PMC8923690
PMID: 35303445

40. SAM-TB: a whole genome sequencing data analysis website for detection of Mycobacterium tuberculosis drug resistance and transmission.

Brief Bioinform. 2022 Mar 10;23(2):bbac030. doi: 10.1093/bib/bbac030.

Yang T(1), Gan M(2), Liu Q(2), Liang W(3), Tang Q(3), Luo G(4), Zuo T(5), Guo Y(6), Hong C(7), Li Q(3), Tan W(7), Gao Q(4).

Whole genome sequencing (WGS) can provide insight into drug-resistance, transmission chains and the identification of outbreaks, but data analysis remains an obstacle to its routine clinical use. Although several drug-resistance prediction tools have appeared, until now no website integrates drug-resistance prediction with strain genetic relationships and species identification of nontuberculous mycobacteria (NTM). We have established a free, function-rich, user-friendly online platform for MTB WGS data analysis (SAM-TB, http://samtb.szmbzx.com) that integrates drug-resistance prediction for 17 antituberculosis drugs, detection of variants, analysis of genetic relationships and NTM species identification. The accuracy of SAM-TB in predicting drug-resistance was assessed using 3177 sequenced clinical isolates with results of phenotypic drug-susceptibility tests (pDST). Compared to pDST, the sensitivity of SAM-TB for detecting multidrug-resistant tuberculosis was 93.9%

[95% confidence interval (CI) 92.6-95.1%] with specificity of 96.2% (95% CI 95.2-97.1%). SAM-TB also analyzes the genetic relationships between multiple strains by reconstructing phylogenetic trees and calculating pairwise single nucleotide polymorphism (SNP) distances to identify genomic clusters. The incorporated mlstverse software identifies NTM species with an accuracy of 98.2% and Kraken2 software can detect mixed MTB and NTM samples. SAM-TB also has the capacity to share both sequence data and analysis between users. SAM-TB is a multifunctional integrated website that uses WGS raw data to accurately predict antituberculosis drug-resistance profiles, analyze genetic relationships between multiple strains and identify NTM species and mixed samples containing both NTM and MTB. SAM-TB is a useful tool for guiding both treatment and epidemiological investigation.

DOI: 10.1093/bib/bbac030
PMCID: PMC8921607
PMID: 35211720

41. Optimized Loading Dose Strategies for Bedaquiline When Restarting Interrupted Drug-Resistant Tuberculosis Treatment.

Antimicrob Agents Chemother. 2022 Mar 15;66(3):e0174921. doi: 10.1128/AAC.01749-21. Epub 2022 Jan 10.

Koele SE(1), van Beek SW(1), Maartens G(2)(3), Brust JCM(4), Svensson EM(1)(5).

Interruption of treatment is common in drug-resistant tuberculosis patients. Bedaquiline has a long terminal half-life; therefore, restarting after an interruption without a loading dose could increase the risk of suboptimal treatment outcome and resistance development. We aimed to identify the most suitable loading dose strategies for bedaquiline restart after an interruption. A model-based simulation study was performed. Pharmacokinetic profiles of bedaquiline and its metabolite M2 (associated with QT prolongation) were simulated for 5,000 virtual patients for different durations and starting points of treatment interruption. Weekly bedaquiline area under the concentration-time curve (AUC) and M2 maximum concentration (Cmax) deviation before interruption and after reloading were assessed to evaluate the efficacy and safety, respectively, of the reloading strategies. Bedaquiline weekly AUC and M2 Cmax deviation were mainly driven by the duration of interruption and only marginally by the starting point of interruption. For interruptions with a duration shorter than 2 weeks, no new loading dose is needed. For interruptions with durations between 2 weeks and 1 month, 1 month and 1 year, and longer than 1 year,

reloading periods of 3 days, 1 week, and 2 weeks, respectively, are recommended. This reloading strategy results in an average bedaquiline AUC deviation of 1.88% to 5.98% compared with -16.4% to -59.8% without reloading for interruptions of 2 weeks and 1 year, respectively, without increasing M2 Cmax. This study presents easy-to-implement reloading strategies for restarting a patient on bedaquiline treatment after an interruption.

DOI: 10.1128/AAC.01749-21
PMCID: PMC8923200
PMID: 35007141

42. Paediatric admissions to a TB hospital: reasons for admission, clinical profile and outcomes.

Int J Tuberc Lung Dis. 2022 Mar 1;26(3):217-223. doi: 10.5588/ijtld.21.0538.

Musonda HK(1), Rose PC(1), Switala J(2), Schaaf HS(3).

BACKGROUND: Brooklyn Chest Hospital (BCH) is a specialised TB hospital in Cape Town, South Africa. We describe reasons for admission, patient profiles and hospital-discharge outcomes in children admitted to BCH. This was compared to a previous study (2000-2001).METHODS: This retrospective, descriptive study included all children (0-14 years) admitted to BCH from January 2016 to December 2017. Data collected from patient folders and a laboratory database included demographic data, reasons for admission, clinical data and hospital outcomes.RESULTS: Of 263 children admitted, 133 (50.6%) were male. The median age was 32 months (IQR 15-75); 48 (18.3%) were HIV-positive and 150 (57.0%) had bacteriologically confirmed TB. Reasons for admission included social/caregiver-related (n = 119, 45.2%), drug-resistant TB (n = 114, 43.3%), TB meningitis (n = 86, 32.7%) and other severe types of TB (n = 63, 24.0%); 110 (41.8%) children had >1 reason for admission. TB meningitis admissions decreased (P = 0.014) and those for drug-resistant TB increased (P < 0.001) compared to 2000-2001. Pulmonary TB was diagnosed in 234 (89.0%), extrapulmonary TB in 149 (56.7%) and 126 (47.9%) had both. At discharge, 73 (27.8%) had completed treatment, 182 (69.2%) were transferred out to complete treatment at community clinics, and 6 (2.3%) died.CONCLUSIONS: Although most children were admitted for clinical reasons, social/caregiver-related reasons were also important.

DOI: 10.5588/ijtld.21.0538
PMID: 35197161

43. Can the GeneXpert MTB/XDR deliver on the promise of expanded, near-patient

tuberculosis drug-susceptibility testing?

Lancet Infect Dis. 2022 Feb 25:S1473-3099(21)00613-7. doi: 10.1016/S1473-3099(21)00613-7. Online ahead of print.

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.

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PMID: 35227392

44. A treatment recommender clinical decision support system for personalized medicine: method development and proof-of-concept for drug resistant tuberculosis.

BMC Med Inform Decis Mak. 2022 Mar 2;22(1):56. doi: 10.1186/s12911-022-01790-0.

Verboven L(1)(2), Calders T(3), Callens S(4), Black J(5), Maartens G(6), Dooley KE(7), Potgieter S(8), Warren RM(9), Laukens K(3), Van Rie A(10).

BACKGROUND: Personalized medicine tailors care based on the patient's or

pathogen's genotypic and phenotypic characteristics. An automated Clinical Decision Support System (CDSS) could help translate the genotypic and phenotypic characteristics into optimal treatment and thus facilitate implementation of individualized treatment by less experienced physicians.
METHODS: We developed a hybrid knowledge- and data-driven treatment recommender CDSS. Stakeholders and experts first define the knowledge base by identifying and quantifying drug and regimen features for the prototype model input. In an iterative manner, feedback from experts is harvested to generate model training datasets, machine learning methods are applied to identify complex relations and patterns in the data, and model performance is assessed by estimating the precision at one, mean reciprocal rank and mean average precision. Once the model performance no longer iteratively increases, a validation dataset is used to assess model overfitting.
RESULTS: We applied the novel methodology to develop a treatment recommender CDSS for individualized treatment of drug resistant tuberculosis as a proof of concept. Using input from stakeholders and three rounds of expert feedback on a dataset of 355 patients with 129 unique drug resistance profiles, the model had a 95% precision at 1 indicating that the highest ranked treatment regimen was considered appropriate by the experts in 95% of cases. Use of a validation data set however suggested substantial model overfitting, with a reduction in precision at 1 to 78%.
CONCLUSION: Our novel and flexible hybrid knowledge- and data-driven treatment recommender CDSS is a first step towards the automation of individualized treatment for personalized medicine. Further research should assess its value in fields other than drug resistant tuberculosis, develop solid statistical approaches to assess model performance, and evaluate their accuracy in real-life clinical settings.

DOI: 10.1186/s12911-022-01790-0
PMCID: PMC8892778
PMID: 35236355

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

Bioorg Med Chem Lett. 2022 Mar 1;63:128650. doi: 10.1016/j.bmcl.2022.128650. Online ahead of print.

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

46. 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

47. Synthesis and biological evaluation of orally active prodrugs and analogs of para-aminosalicylic acid (PAS).

Eur J Med Chem. 2022 Mar 15;232:114201. doi: 10.1016/j.ejmech.2022.114201. Epub 2022 Feb 19.

Hegde PV(1), Howe MD(2), Zimmerman MD(3), Boshoff HIM(4), Sharma S(1), Remache B(3), Jia Z(2), Pan Y(3), Baughn AD(2), Dartois V(3), Aldrich CC(5).

Tuberculosis (TB) is one of the world's most deadly infectious diseases resulting in nearly 1.3 million deaths annually and infecting nearly one-quarter of the population. para-Aminosalicylic acid (PAS), an important second-line agent for treating drug-resistant Mycobacterium tuberculosis, has moderate bioavailability and rapid clearance that necessitate high daily doses of up to 12 g per day, which in turn causes severe gastrointestinal disturbances presumably by disruption of gut microbiota and host epithelial cells. We first synthesized a series of alkyl, acyloxy and alkyloxycarbonyloxyalkyl ester prodrugs to increase the oral bioavailability and thereby prevent intestinal accumulation as well as undesirable bioactivation by the gut microbiome to non-natural folate species that exhibit cytotoxicity. The pivoxyl prodrug of PAS was superior to all of the prodrugs examined and showed nearly quantitative absorption. While the conceptually simple prodrug approach improved the oral bioavailability of PAS, it did not address the intrinsic rapid clearance of PAS mediated by N-acetyltransferase-1 (NAT-1). Thus, we next modified the PAS scaffold to reduce NAT-1 catalyzed inactivation by introduction of groups to sterically block N-acetylation and fluorination of the aryl ring of PAS to attenuate N-acetylation by electronically deactivating the para-amino group. Among the mono-fluorinated analogs prepared, 5-fluoro-PAS, exhibited the best activity and an 11-fold decreased rate of inactivation by NAT-1 that translated to a 5-fold improved exposure as measured by area-under-the-curve (AUC) following oral dosing to CD-1 mice. The pivoxyl prodrug and fluorination at the 5-position of PAS address the primary limitations of PAS and have the potential

to revitalize this second-line TB drug.

DOI: 10.1016/j.ejmech.2022.114201
PMID: 35219151 [Indexed for MEDLINE]

48. Retrospective Cohort Study of Effects of the COVID-19 Pandemic on Tuberculosis Notifications, Vietnam, 2020.

Emerg Infect Dis. 2022 Mar;28(3):684-692. doi: 10.3201/eid2803.211919.

Hasan T, Nguyen VN, Nguyen HB, Nguyen TA, Le HTT, Pham CD, Hoang N, Nguyen PTM, Beardsley J, Marks GB, Fox GJ.

We evaluated the effects of the coronavirus disease pandemic on diagnosis of and treatment for tuberculosis (TB) in Vietnam. We obtained quarterly notifications for TB and multidrug-resistant/rifampin-resistant (MDR/RR) TB from 2015-2020 and evaluated changes in monthly TB case notifications. We used an interrupted time series to assess the change in notifications and treatment outcomes. Overall, TB case notifications were 8% lower in 2020 than in 2019; MDR/RR TB notifications were 1% lower. TB case notifications decreased by 364 (95% CI -1,236 to 508) notifications per quarter and MDR/RR TB by 1 (95% CI -129 to 132) notification per quarter. The proportion of successful TB treatment outcomes decreased by 0.1% per quarter (95% CI -1.1% to 0.8%) in 2020 compared with previous years. Our study suggests that Vietnam was able to maintain its TB response in 2020, despite the pandemic.

DOI: 10.3201/eid2803.211919
PMCID: PMC8888245
PMID: 35202526 [Indexed for MEDLINE]

49. Discovery of Inhibitors for Mycobacterium Tuberculosis Peptide Deformylase Based on Virtual Screening in Silico.

Mol Inform. 2022 Mar;41(3):e2100002. doi: 10.1002/minf.202100002. Epub 2021 Oct 27.

Li X(1), Jiang Q(2), Yang X(1).

Tuberculosis has been the serious disease threatening human health and public safety due to the emergence of MDR and XDR-TB. Mycobacterium tuberculosis

peptide deformylase (MtPDF) is a valuable target for antituberculotics. In order to discover new potential inhibitor candidates of MtPDF as leads for antituberculotics, Discovery Studio (DS) 2019 was used to perform molecular docking for virtual screening in silico with the bioactive compound library-I (L1700) against MtPDF. Six compounds with high docking scores and favourable ligand-protein interactions by LibDock and CDOCKER were selected for the evaluation of the inhibition potencies against MtPDF and Mycobacterium smegmatis. GST-6×His tagged MtPDF was recombinant expressed and purified firstly by Glutathione Sepharose 4B, and secondly by Ni Sepharose 6 FF after the cleavage of human rhinovirus 3C protease. These compounds showed IC50 values from 0.5 μmol/L to 112 μmol/L against MtPDF, among which CUDC-101 bearing hydroxamic acid exhibited IC50 of 0.5 μmol/L on MtPDF and MIC against Mycobacterium smegmatis of 32 μg/mL, and Ixazomib Citrate with IC50 of 63 μmol/L and MIC of 16 μg/mL. CUDC-101 and Ixazomib Citrate are promising as the potential leads for antituberculotics.

DOI: 10.1002/minf.202100002
PMID: 34708566

50. Probing the Molecular Basis of Cofactor Affinity and Conformational Dynamics of Mycobacterium tuberculosis Elongation Factor Tu: An Integrated Approach Employing Steered Molecular Dynamics and Umbrella Sampling Simulations.

J Phys Chem B. 2022 Feb 24;126(7):1447-1461. doi: 10.1021/acs.jpcb.1c09438. Epub 2022 Feb 15.

Kumar N(1), Garg P(1).

The emergence of multidrug-resistant and extensively drug-resistant tuberculosis strains is the reason that the infectious tuberculosis pathogen is still the most common cause of death. The quest for new antitubercular drugs that can fit into multidrug regimens, function swiftly, and overcome the ever-increasing prevalence of drug resistance continues. The crucial role of MtbEF-Tu in translation and trans-translation processes makes it an excellent target for antitubercular drug design. In this study, the primary sequence of MtbEF-Tu was used to model the three-dimensional structures of MtbEF-Tu in the presence of GDP ("off" state) and GTP ("on" state). The binding free energy computed using both the molecular mechanics/Poisson-Boltzmann surface area and umbrella sampling approaches shows that GDP binds to MtbEF-Tu with an ∼2-fold affinity compared to GTP. The steered molecular dynamics (SMD) and umbrella sampling simulation also shows that the dissociation of GDP from MtbEF-Tu in the presence

of Mg2+ is a thermodynamically intensive process, while in the absence of Mg2+, the destabilized GDP dissociates very easily from the MtbEF-Tu. Naturally, the dissociation of Mg2+ from the MtbEF-Tu is facilitated by the nucleotide exchange factor EF-Ts, and this prior release of magnesium makes the dissociation process of destabilized GDP easy, similar to that observed in the umbrella sampling and SMD study. The MD simulations of MtbEF-Tu's "on" state conformation in the presence of GTP reveal that the secondary structure of switch-I and Mg2+ coordination network remains similar to its template despite the absence of identity in the conserved region of switch-I. On the other hand, the secondary structure in the conserved region of the switch-I of MtbEF-Tu unwinds from a helix to a loop in the presence of GDP. The major conformational changes observed in switch-I and the movement of Thr64 away from Mg2+ mainly reflect essential conformational changes to make the shift of MtbEF-Tu's "on" state to the "off" state in the presence of GDP. These obtained structural and functional insights into MtbEF-Tu are pivotal for a better understanding of structural-functional linkages of MtbEF-Tu, and these findings may serve as a basis for the design and development of MtbEF-Tu-specific inhibitors.

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PMID: 35167282

51. An amiloride derivative is active against the F(1)F(o)-ATP synthase and cytochrome bd oxidase of Mycobacterium tuberculosis.

Commun Biol. 2022 Feb 24;5(1):166. doi: 10.1038/s42003-022-03110-8.

Hards K(#)(1)(2), Cheung CY(#)(1), Waller N(1), Adolph C(1), Keighley L(1), Tee ZS(1), Harold LK(1)(2), Menorca A(1), Bujaroski RS(3)(4), Buckley BJ(3)(4), Tyndall JDA(5), McNeil MB(1)(2), Rhee KY(6), Opel-Reading HK(7), Krause K(2), Preiss L(8)(9), Langer JD(10), Meier T(11)(12), Hasenoehrl EJ(13), Berney M(13), Kelso MJ(14)(15), Cook GM(16)(17).

Increasing antimicrobial resistance compels the search for next-generation inhibitors with differing or multiple molecular targets. In this regard, energy conservation in Mycobacterium tuberculosis has been clinically validated as a promising new drug target for combatting drug-resistant strains of M. tuberculosis. Here, we show that HM2-16F, a 6-substituted derivative of the FDA-approved drug amiloride, is an anti-tubercular inhibitor with bactericidal properties comparable to the FDA-approved drug bedaquiline (BDQ; Sirturo®) and inhibits the growth of bedaquiline-resistant mutants. We show that HM2-16F weakly inhibits the F1Fo-ATP synthase, depletes ATP, and affects the entry of acetyl-CoA into the Krebs cycle. HM2-16F synergizes with the cytochrome bcc-aa3 oxidase inhibitor Q203 (Telacebec) and co-administration with Q203 sterilizes in

vitro cultures in 14 days. Synergy with Q203 occurs via direct inhibition of the cytochrome bd oxidase by HM2-16F. This study shows that amiloride derivatives represent a promising discovery platform for targeting energy generation in drug-resistant tuberculosis.

DOI: 10.1038/s42003-022-03110-8
PMCID: PMC8873251
PMID: 35210534

52. Reevaluating Rifampicin Breakpoint Concentrations for Mycobacterium tuberculosis Isolates with Disputed rpoB Mutations and Discordant Susceptibility Phenotypes.

Microbiol Spectr. 2022 Feb 23;10(1):e0208721. doi: 10.1128/spectrum.02087-21. Epub 2022 Feb 2.

Wang W(#)(1), Liu R(#)(2), Yao C(#)(1), Huo F(3), Shang Y(1), Zhang X(1), Wang Y(4), Xue Z(1), Ma L(2), Pang Y(1).

In this study, rifampicin resistance breakpoints based on MICs of disrupted rpoB mutants of Mycobacterium tuberculosis (MTB) were explored using the Mycobacteria Growth Indicator Tube (MGIT) system and microplate alamarBlue assay (MABA). Sixty-one MTB isolates with disputed low-level rifampicin resistance-associated rpoB mutations and 40 RIF-susceptible wild-type isolates were included. Among the 61 resistant isolates, 25 (41.0%) had MICs ≥2.0 mg/L via MABA, while 16 (26.2%) were identified as RIF resistant via MGIT. Epidemiological cut-off (ECOFF) values obtained using MABA and MGIT were 0.25 and 0.125 mg/L, respectively. Based on 0.125 mg/L as a tentative critical concentration (CC), MABA RIF resistance-detection sensitivity was 93.4%, prompting the reduction of the MGIT CC to 0.125 mg/L, given that only a single isolate (1.6%) with the borderline mutation would be misclassified as susceptible to RIF based on this CC. Based on DNA sequencing of RRDR as the gold standard, the diagnostic accuracy of MGIT (99.0%) was significantly higher than that of MABA (91.1%). MICs of Leu511Pro mutant isolates were negatively correlated with time to liquid culture positivity (TTP) in our analysis ($R = 0.957$, $P<0.01$). In conclusion, our results demonstrated missed detection of a high proportion of rifampicin-resistant isolates based on the WHO-endorsed CC. Such missed detections would be avoided by reducing the optimal MGIT RIF CC to 0.125 mg/L. In addition, MGIT based on reduced CC outperformed MABA in detecting borderline RIF resistance, with MABA MIC results obtained for isolates with the same mutation correlating with MTB growth rate. IMPORTANCE Tuberculosis (TB) is still one of the world's leading infectious disease killers. The early and accurate

diagnosis of RIF resistance is necessary to deliver timely and appropriate treatment for TB patients and improve their clinical outcome. Actually, a proportion of MTB isolates with disputed rpoB mutations present a diagnostic dilemma between Xpert and phenotypical drug susceptibility testing (pDST). Recently, WHO reported a pragmatic approach by lowering critical concentration (CC) to boost sensitivity of resistance detection of pDST. Therefore, a detailed analysis of the association between RIF susceptibility and disrupted mutations within rpoB gene would lay a foundation to assess the diagnostic accuracy of pDST with lowering RIF CC. In this study, we aim to determine the MICs of MTB isolates with disrupted mutations by MGIT and microplate alamarBlue assay (MABA). We also aimed to determine the optimal breakpoints for MTB isolates with these mutations.

DOI: 10.1128/spectrum.02087-21
PMCID: PMC8809345
PMID: 35107324 [Indexed for MEDLINE]

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

Int J Pharm. 2022 Feb 21;617:121606. doi: 10.1016/j.ijpharm.2022.121606. Online ahead of print.

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

54. Patterns of genomic interrelatedness of publicly available samples in the TB portals database.

Tuberculosis (Edinb). 2022 Mar;133:102171. doi: 10.1016/j.tube.2022.102171. Epub 2022 Jan 24.

Wollenberg KR(1), Jeffrey BM(2), Harris MA(3), Gabrielian A(4), Hurt DE(5), Rosenthal A(6).

The TB Portals program is an international collaboration for the collection and dissemination of tuberculosis data from patient cases focused on drug resistance. The central database is a patient-oriented resource containing both patient and pathogen clinical and genomic information. Herein we provide a summary of the pathogen genomic data available through the TB Portals and show one potential application by examining patterns of genomic pairwise distances. Distributions of pairwise distances highlight overall patterns of genome variability within and between Mycobacterium tuberculosis phylogenomic lineages. Closely related isolates (based on whole-genome pairwise distances and time between sample collection dates) from different countries were identified as potential evidence of international transmission of drug-resistant tuberculosis. These high-level views of genomic relatedness provide information that can stimulate hypotheses for further and more detailed research.

DOI: 10.1016/j.tube.2022.102171
PMID: 35101846

55. Alcohol drinking delays the rate of sputum smear conversion among DR-TB patients in northwest Ethiopia; A retrospective follow-up study.

PLoS One. 2022 Mar 9;17(3):e0264852. doi: 10.1371/journal.pone.0264852. eCollection 2022.

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

BACKGROUND: Sputum smear microscopy is simple and feasible technique to assess the presence of acid-fast bacilli (AFB) in the respiratory tract of patients with Drug Resistance Tuberculosis (DR-TB). Conversion of sputum smear from

positive to negative is considered as an interim indicator of efficacy of anti-tubercular treatment and the program effectiveness. Although evidences regarding the factors affecting the sputum smear conversion are available on drug susceptible TB patients, there is dearth of literature about smear conversion and its predictors among DR-TB patients in the study setting. Hence, shortening the time to sputum smear conversion is desirable to reduce the likelihood of mycobacterial transmission. This study has therefore aimed at estimating the median time of sputum smear conversion and to determine its predictors.
METHODS: This was a retrospective follow-up study conducted among DR-TB patients registered for second-line anti-TB treatment in the four hospitals of Amhara regional state, Northwest Ethiopia. Of all patients enrolled to DR-TB treatment in the study setting from 2010 to 2017, 436 patients have been include for this study who fulfilled the eligibility criteria. The cox proportional hazard model was fitted and the adjusted hazard ratio (AHR) with 95% confidence interval (CI) and p <0.05 was used to declare statistical significance of the variables associated with the smear conversion.
RESULTS: From the 436 patients with sputum smear positive at baseline, 351 (80.5%) converted sputum smear at a median time of 48 (IQR: 30-78) days. The median time of smear conversion was 59 (95% CI: 42, 74) and 44 (95% CI: 37, 54) days among patients who had and had no history of alcohol drinking, respectively. Similarly, the median time to smear conversion was 61 (95% CI: 36, 73) days among patients with comorbid conditions and 44 (95% CI: 38, 54) days among patients with no comorbid conditions. In the multi-variable analysis, only history of alcohol consumption [AHR = 0.66 (0.50, 0.87)] was found to delay significantly the rate of sputum smear conversion.
CONCLUSION: In our study, the median time of sputum smear conversion was with in the expected time frame of conversion. History of alcohol consumption was found to delay significantly the rate of sputum smear conversion. The DR-TB patients are strongly advised to avoid alcohol consumption.

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PMCID: PMC8906643
PMID: 35263367

56. 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

57. Expansion of social protection is necessary towards zero catastrophic costs due to TB: The first national TB patient cost survey in the Philippines.

PLoS One. 2022 Feb 28;17(2):e0264689. doi: 10.1371/journal.pone.0264689. eCollection 2022.

Florentino JL(1), Arao RML(1), Garfin AMC(2), Gaviola DMG(2), Tan CR(1), Yadav RP(3), Hiatt T(3), Morishita F(4), Siroka A(5), Yamanaka T(5)(6)(7), Nishikiori N(5).

BACKGROUND: Tuberculosis (TB) is a disease associated with poverty. Moreover, a significant proportion of TB patients face a substantial financial burden before and during TB care. One of the top targets in the End TB strategy was to achieve zero catastrophic costs due to TB by 2020. To assess patient costs related to TB care and the proportion of TB-affected households that faced catastrophic costs, the Philippines National TB Programme (NTP) conducted a national TB patient cost survey in 2016-2017.
METHODS: A cross-sectional survey of 1,912 TB patients taking treatment in health facilities engaged with the NTP. The sample consists of 786 drug-sensitive TB (DS-TB) patients in urban facilities, 806 DS-TB patients in rural facilities, and 320 drug-resistant TB (DR-TB) patients. Catastrophic cost due to TB is defined as total costs, consisting of direct medical and non-medical costs and indirect costs net of social assistance, exceeding 20% of annual household income.
RESULTS: The overall mean total cost including pre- and post-diagnostic costs was US$601. The mean total cost was five times higher among DR-TB patients than DS-TB patients. Direct non-medical costs and income loss accounted for 42.7% and 40.4% of the total cost of TB, respectively. More than 40% of households had to rely on dissaving, taking loans, or selling their assets to cope with the costs. Overall, 42.4% (95% confidence interval (95% CI): 40.2-44.6) of TB-affected households faced catastrophic costs due to TB, and it was significantly higher among DR-TB patients (89.7%, 95%CI: 86.3-93.0). A TB enabler package, which 70% of DR-TB patients received, reduced catastrophic costs by 13.1 percentage points (89.7% to 76.6%) among DR-TB patients, but only by 0.4 percentage points (42.4% to 42.0%), overall.
CONCLUSIONS: TB patients in the Philippines face a substantial financial burden due to TB despite free TB services provided by the National TB Programme. The TB enabler package mitigated catastrophic costs to some extent, but only for DR-TB patients. Enhancing the current social and welfare support through multisectoral collaboration is urgently required to achieve zero catastrophic costs due to TB.

DOI: 10.1371/journal.pone.0264689
PMCID: PMC8884492
PMID: 35226705 [Indexed for MEDLINE]

58. Optimizing cardio, hepato and phospholipidosis toxicity of the Bedaquiline by chemoinformatics and molecular modelling approach.

SAR QSAR Environ Res. 2022 Mar;33(3):215-235. doi: 10.1080/1062936X.2022.2041724. Epub 2022 Feb 28.

Girase R(1), Ahmad I(1), Pawara R(1), Patel H(1).

The FDA granted expedited approval for Johnson and Johnson's Bedaquiline to treat pulmonary multidrug resistant tuberculosis on 28 December 2012 which is more common in China, Russian Federation and India. Bedaquiline is the first anti-tubercular drug approved by the FDA in the last 40 years, and it has become a cynosure in the circles of synthetic chemists researching new anti-tubercular drugs. Bedaquiline's highly lipophilic nature raises major concerns like suppression of the hERG gene, hepatotoxicity, and phospholipidosis despite its potential antitubercular profile. To address these toxicity concerns, in the present work, we have employed the structural optimization of Bedaquiline using the ADMETopt web server, which optimizes lead with scaffold hopping and ADMET screening. The ADMETopt web server yielded the 476 structures through optimization of three sites in Bedaquiline. Further, we have validated the optimized structures for their activity by performing molecular docking and molecular dynamics (MD) simulations against the mycobacterial ATP synthase enzyme and density functional theory (DFT) study further provides insight into the reactivity of the compounds. After screening and analysis, compound #449 was observed to be the most promising mycobacterial ATP synthase inhibitor with minimal cardiotoxicity, hepatotoxicity and phospholipidosis.

DOI: 10.1080/1062936X.2022.2041724
PMID: 35225110

59. 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]

60. Utility of the Whole Genome Sequencing based methodologies in routine European tuberculosis reference laboratory network setting.

Tuberculosis (Edinb). 2022 Feb 21;134:102185. doi: 10.1016/j.tube.2022.102185.

Online ahead of print.

Holicka Y(1), Tagliani E(2), Cirillo DM(2), Nikolayevskyy V(3).

This study aims to gather observational evidence of Whole Genome Sequencing's (WGS) impact in the pathogen identification, antimicrobial resistance profiling and transmission tracking from its users' observation within the diagnostic setting of the European reference laboratories for tuberculosis. Sixteen laboratories that have been utilising WGS in their tuberculosis diagnostic laboratory were invited and twelve (75%) responded to our online questionnaire. Key findings include its primary utilisation for drug resistance prediction and epidemiological services; Mtb surveillance and outbreak investigation. 92% reported significant improvements to the performance of TB drug resistance testing and the reduction of false clustering. Despite the public health benefits of the WGS technology was largely positive in non-tuberculous mycobacteria disease management, multidrug-resistant TB patient management, reputational aspects and turnaround times, further studies are required to review the financial impact as various regulations and service aspects have added to the complexity to disentangle this aspect.

DOI: 10.1016/j.tube.2022.102185
PMID: 35247779

61. 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]

62. Early Bactericidal Activity of Meropenem Plus Clavulanate (+/-Rifampin) For TB: The COMRADE Randomized, Phase 2 Trial.

Am J Respir Crit Care Med. 2022 Mar 8. doi: 10.1164/rccm.202108-1976OC. Online ahead of print.

De Jager V(1), Gupte N(2), Nunes S(1), Barnes GL(3), van Wijk RC(4), Mostert J(1), Dorman SE(5), Abulfathi AA(6)(7), Upton CM(8), Faraj A(4), Nuermberger EL(3), Lamichhane G(3), Svensson EM(9), Simonsson U(10), Diacon AH(11), Dooley KE(12); and the COMRADE Study Team.

RATIONALE: Carbapenems are recommended for treatment of drug-resistant tuberculosis. Optimal dosing remains uncertain.
OBJECTIVE: Evaluate the fourteen-day bactericidal activity of meropenem, at different doses, with or without rifampin,.
METHODS: Individuals with pulmonary tuberculosis were randomized to one of four intravenous meropenem-based arms: 2 grams 8 hourly (Arm C), 2 grams 8 hourly plus rifampin 20 mg/kg once daily (Arm D), 1 gram 8 hourly (Arm E) or 3 grams once daily (Arm F). All participants received amoxicillin/clavulanate with each meropenem dose. Serial overnight sputum samples were collected from baseline and throughout treatment. Median daily fall in colony forming unit (CFU) counts per mL of sputum (solid culture)(EBACFU0-14) and increase in time to liquid culture positivity (TTP) were estimated with mixed-effects modelling. Serial blood samples were collected for pharmacokinetic analysis on Day 13.
MEASUREMENTS AND MAIN RESULTS: Sixty participants enrolled. Median (2.5th-97.5th

percentiles) EBACFU0-14 was 0.22 (0.12-0.33), 0.12 (0.057-0.21), 0.059 (0.033-0.097) and 0.053 (0.035-0.081); TTP increased by 0.34 (0.21-0.75), 0.11 (0.052-0.37), 0.094 (0.034-0.23), and 0.12 (0.04-0.41) (log10h), for Arms C, D, E, and F, respectively. Meropenem pharmacokinetics were not impacted by rifampin co-administration. Twelve participants withdrew early, many of whom cited gastrointestinal adverse events.
CONCLUSIONS: Bactericidal activity was greater with the World Health Organization recommended total daily dose of 6 grams daily than a lower dose of 3 grams daily. This difference was only detectable with solid culture. Tolerability of intravenous meropenem, with amoxicillin/clavulanate, though, was poor at all doses, calling into question the utility of this drug in second-line regimens. Clinical trial registration available at www.
CLINICALTRIALS: gov, ID: NCT03174184.

DOI: 10.1164/rccm.202108-1976OC
PMID: 35258443

63. Experimental Confirmation that an Uncommon rrs Gene Mutation (g878a) of Mycobacterium tuberculosis Confers Resistance to Streptomycin.

Antimicrob Agents Chemother. 2022 Mar 15;66(3):e0191521. doi: 10.1128/AAC.01915-21. Epub 2022 Jan 24.

Domenech P(1)(2), Mouhoub E(1)(2)(3), Reed MB(1)(2)(3)(4).

The effective treatment of patients diagnosed with drug-resistant tuberculosis is highly dependent on the ability to rapidly and accurately determine the antibiotic susceptibility profile of the Mycobacterium tuberculosis isolate(s) involved. Thus, as more clinical microbiology laboratories advance toward the use of DNA sequence-based diagnostics, it is imperative that their predictive functions extend beyond the well-known resistance mutations in order to also encompass as many of the lower-frequency mutations as possible. However, in most cases, fundamental experimental proof that links these uncommon mutations with phenotypic resistance is lacking. One such example is the g878a polymorphism within the rrs 16S rRNA gene. We, and others, have identified this mutation within a small number of drug-resistant isolates, although a consensus regarding exactly which aminoglycoside antibiotic(s) it confers resistance to has not previously been reached. Here, we have employed oligonucleotide-mediated recombineering to introduce the g878a polymorphism into the rrs gene of Mycobacterium bovis BCG, a close relative of M. tuberculosis, and demonstrate that it confers low-level resistance to streptomycin alone. It does not confer cross-resistance to amikacin, capreomycin, or kanamycin. We also demonstrate that the rrsg878a mutation exerts a substantial fitness defect in vitro that may

at least in part explain why clinical isolates bearing this mutation appear to be quite rare. Overall, this study provides clarity to the phenotype attributable to the rrsg878a mutation and is relevant to the future implementation of genomics-based diagnostics as well as the clinical management of patients in whom this particular polymorphism is encountered.

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March News

1. Surge of HIV, tuberculosis and COVID feared amid war in Ukraine