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1. Drug-resistant tuberculosis is a global cause of concern.

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[Article in Danish]

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The number of patients with drug-resistant tuberculosis (DR-TB) is increasing worldwide. This review summarises the global epidemiology of DR-TB and current treatment challenges. Luckily, novel regimens comprising bedaquiline, pretomanid, linezolid, and moxifloxacin have seemingly mitigated the global threat posed by DR-TB. However, emerging resistance against bedaquiline and pretomanid, among other factors, persists as ongoing concerns in the global fight against DR-TB. While the new regimens are groundbreaking, the sustained development of novel drugs targeting the most resistant forms of tuberculosis is of utmost importance for future efforts against DR-TB.

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2. Molecular determinants of multidrug-resistant tuberculosis in Sierra Leone.

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Multidrug-resistant tuberculosis (MDR-TB) management has become a serious global health challenge. Understanding its epidemic determinants on the regional level is crucial for developing effective control measures. We used whole genome sequencing data of 238 of Mycobacterium tuberculosis complex (MTBC) strains to determine drug resistance profiles, phylogeny, and transmission dynamics of MDR/rifampicin-resistant (RR) MTBC strains from Sierra Leone. Forty-two strains were classified as RR, 196 as MDR, 5 were resistant to bedaquiline (BDQ) and clofazimine (CFZ), but none was found to be resistant to fluoroquinolones. Sixty-one (26%) strains were resistant to all first-line drugs, three of which had additional resistance to BDQ/CFZ. The strains were classified into six major MTBC lineages (L), with strains of L4 being the most prevalent, 62% (n = 147), followed by L6 (Mycobacterium africanum) strains, (21%, n = 50). The overall clustering rate (using ≤d12 single-nucleotide polymorphism threshold) was 44%, stratified into 31 clusters ranging from 2 to 16 strains. The largest cluster (n = 16) was formed by sublineage 2.2.1 Beijing Ancestral 3 strains, which developed MDR several times. Meanwhile, 10 of the L6 strains had a primary MDR transmission. We observed a high diversity of drug resistance mutations, including borderline resistance mutations to isoniazid and rifampicin, and mutations were not detected by commercial assays. In conclusion, one in five

strains investigated was resistant to all first-line drugs, three of which had evidence of BDQ/CFZ resistance. Implementation of interventions such as rapid diagnostics that prevent further resistance development and stop MDR-TB transmission chains in the country is urgently needed.
IMPORTANCE: A substantial proportion of MDR-TB strains in Sierra Leone were resistant against all first line drugs; however this makes the all-oral-six-month BPaLM regimen or other 6-9 months all oral regimens still viable, mainly because there was no FQ resistance.Resistance to BDQ was detected, as well as RR, due to mutations outside of the hotspot region. While the prevalence of those resistances was low, it is still cause for concern and needs to be closely monitored.

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3. Prison as a driver of recent transmissions of multidrug-resistant tuberculosis in Callao, Peru: a cross-sectional study.

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BACKGROUND: We sought to identify resistance patterns and key drivers of recent multidrug-resistant tuberculosis (MDR-TB) transmission in a TB-prevalent area in Peru.
METHODS: Cross-sectional study including MDR Mycobacterium tuberculosis complex (Mtbc) strains identified in Callao-Peru between April 2017 and February 2019. Mtbc DNA was extracted for whole genome sequencing which was used for phylogenetic inference, clustering, and resistance mutation analyses. Clusters indicative of recent transmission were defined based on a strain-to-strain distance of ≤5 (D5) single nucleotide polymorphisms (SNPs). Epidemiologic factors linked to MDR-TB clustering were analyzed using Poisson regression.
FINDINGS: 171 unique MDR-Mtbc strains were included; 22 (13%) had additional fluoroquinolone resistance and were classified as pre-XDR. Six strains (3.5%) harboured bedaquiline (BDQ) resistance mutations and were classified as MDR + BDQ. 158 (92%) Mtbc strains belonged to lineage 4 and 13 (8%) to lineage 2. Using a cluster threshold of ≤5 SNPs, 98 (57%) strains were grouped in one of the 17 D5 clusters indicative of recent transmission, ranging in size from 2 to the largest cluster formed by 53 4.3.3 strains (group_1). Lineage 4.3.3 strains showed the overall highest cluster rate (43%). In multivariate analyses, current or previous imprisonment was independently associated with being part of any MDR-TB transmission clusters (adjusted prevalence ratio [aPR], 1.45; 95% CI, 1.09-1.92).
INTERPRETATION: Pre-XDR-TB emerged in more than 10% of the MDR-TB strains investigated. Transmission of 4.3.3 Mtbc strains especially of the dominant group_1 clone is a major driver of the MDR-TB epidemic in Callao. Current or previous imprisonment was linked to recent MDR-TB transmissions, indicating an important role of prisons in driving the MDR-TB epidemic.
FUNDING: This work was supported in part by the ERANet-LAC Network of the European Union, Latin America and the Caribbean Countries on Joint Innovation and Research Activities, and FONDECYT. Additional support was received from Leibniz Science Campus Evolutionary Medicine of the Lung, the Deutsche Forschungsgemeinschaft (German Research Foundation, under Germany's Excellence Strategy-EXC 2167 Precision Medicine in Inflammation), and the Research Training Group 2501 TransEvo.

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4. Management of drug-resistant tuberculosis in Indonesia: a four-year cascade of care analysis.

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BACKGROUND: In Indonesia, drug resistance testing for TB largely relies on Xpert MTB/RIF, and it is unknown what proportion of drug-resistant (DR) TB is adequately diagnosed and treated.

METHODS: We conducted a cascade of care analysis on a cohort of presumptive rifampicin-resistant (RR) TB patients registered in 2015-2018 in a tertiary hospital in Indonesia. Estimated incidences of (presumptive) DR-TB cases were assumption-based using global reports. Data on diagnosis and consecutive cascades steps, including their timing were collected from national electronic registers, and medical records. We described a secondary cascade for patients receiving treatment not supported by phenotypic drug susceptibility testing (pDST). Factors associated with delay and loss between diagnosis and treatment were identified using logistic regression.
FINDINGS: Less than a third of estimated incident TB cases at risk of DR-TB were identified as presumptive DR-TB case and tested, and 9.8% (982/10,065) of estimated true DR-TB cases was diagnosed. Of those diagnosed, only 45.1% (443/982) had treatment regimens supported by pDST results, but this did not significantly influence treatment outcomes. Only 25.5% (250/982) of diagnosed patients completed all steps of the cascade including successful treatment. Delays between diagnosis and treatment were substantial, and more common among those referred from a primary healthcare facility, and among those who were employed, living outside of Bandung, and reporting engagement with the private sector.
INTERPRETATION: The DR-TB care cascade in this urban setting in Indonesia is characterized by substantial attrition and delays. Strategies to increase access to DR-TB diagnosis accompanied by optimisation of clinical care could substantially improve outcomes and reduce onward transmission.
FUNDING: Radboud university medical center and University of Otago.

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Conflict of interest statement: We declare no competing interests.

5. Multi-platform whole genome sequencing for tuberculosis clinical and surveillance applications.

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Whole genome sequencing (WGS) of Mycobacterium tuberculosis offers valuable insights for tuberculosis (TB) control. High throughput platforms like Illumina and Oxford Nanopore Technology (ONT) are increasingly used globally, although ONT is known for higher error rates and is less established for genomic studies. Here we present a study comparing the sequencing outputs of both Illumina and ONT platforms, analysing DNA from 59 clinical isolates in highly endemic TB regions of Thailand. The resulting sequence data were used to profile the M. tuberculosis pairs for their lineage, drug resistance and presence in transmission chains, and were compared to publicly available WGS data from Thailand (n = 1456). Our results revealed isolates that are predominantly from lineages 1 and 2, with consistent drug resistance profiles, including six multidrug-resistant strains; however, analysis of ONT data showed longer phylogenetic branches, emphasising the technologies higher error rate. An analysis incorporating the larger dataset identified fifteen of our samples within six potential transmission clusters, including a significant clade of 41 multi-drug resistant isolates. ONT's extended sequences also revealed strain-specific structural variants in pe/ppe genes (e.g. ppe50), which are candidate loci for vaccine development. Despite some limitations, our results show that ONT sequencing is a promising approach for TB genomic research, supporting precision medicine and decision-making in areas with less developed infrastructure, which is crucial for tackling the disease's significant regional burden.

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

6. Spatial Analysis of Drug-Susceptible and Multidrug-Resistant Cases of Tuberculosis, Ho Chi Minh City, Vietnam, 2020-2023.

Emerg Infect Dis. 2024 Mar;30(3):499-509. doi: 10.3201/eid3003.231309.

Spies R, Hong HN, Trieu PP, Lan LK, Lan K, Hue NN, Huong NTL, Thao TTLN, Quang NL, Anh TDD, Vinh TV, Ha DTM, Dat PT, Hai NP, Van LH, Thwaites GE, Thuong NTT, Watson JA, Walker TM.

We characterized the spatial distribution of drug-susceptible (DS) and multidrug-resistant (MDR) tuberculosis (TB) cases in Ho Chi Minh City, Vietnam, a major metropolis in southeastern Asia, and explored demographic and socioeconomic factors associated with local TB burden. Hot spots of DS and MDR TB incidence were observed in the central parts of Ho Chi Minh City, and substantial heterogeneity was observed across wards. Positive spatial autocorrelation was observed for both DS TB and MDR TB. Ward-level TB incidence was associated with HIV prevalence and the male proportion of the population. No ward-level demographic and socioeconomic indicators were associated with MDR TB case count relative to total TB case count. Our findings might inform spatially targeted TB control strategies and provide insights for generating hypotheses about the nature of the relationship between DS and MDR TB in Ho Chi Minh City and the wider southeastern region of Asia.

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PMCID: PMC10902525
PMID: 38407176 [Indexed for MEDLINE]

7. Bedaquiline Resistance after Effective Treatment of Multidrug-Resistant Tuberculosis, Namibia.

Emerg Infect Dis. 2024 Mar;30(3):568-571. doi: 10.3201/eid3003.240134.

Günther G, Mhuulu L, Diergaardt A, Dreyer V, Moses M, Anyolo K, Ruswa N, Claassens M, Niemann S, Nepolo E.

Bedaquiline is currently a key drug for treating multidrug-resistant or rifampin-resistant tuberculosis. We report and discuss the unusual development of resistance to bedaquiline in a teenager in Namibia, despite an optimal background regimen and adherence. The report highlights the risk for bedaquiline

resistance development and the need for rapid drug-resistance testing.

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PMID: 38407158 [Indexed for MEDLINE]

8. Association between biomarkers of inflammation and dyslipidemia in drug resistant tuberculosis in Uganda.

Lipids Health Dis. 2024 Mar 1;23(1):65. doi: 10.1186/s12944-024-02063-7.

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BACKGROUND: Active tuberculosis (TB) significantly increases the risk of cardiovascular disease, but the underlying mechanisms remain unclear. This study aimed to investigate the association between inflammation biomarkers and dyslipidemia in patients with drug-resistant TB (DR-TB).
METHODS: This was a secondary analysis of data from a cross-sectional multi-center study in Uganda conducted 2021. Participants underwent anthropometric measurements and laboratory tests included a lipid profile, full haemogram and serology for HIV infection. Dyslipidemia was defined as total cholesterol > 5.0 mmol/l and/or low-density lipoprotein cholesterol > 4.14 mmol/l, and/or triglycerides (TG) ≥ 1.7 mmol/l, and/or high density lipoprotein cholesterol (HDL-c) < 1.03 mmol/l for men and < 1.29 mmol/l for women. Biomarkers of inflammation were leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, as well as neutrophil/lymphocyte (NLR), platelet/lymphocyte, and lymphocyte/monocyte (LMR) ratios, mean corpuscular volume (MCV), and the systemic immune inflammation index (SII) (neutrophil × platelet/lymphocyte). Modified Poisson Regression analysis was used for determining the association of the biomarkers and dyslipidemia.

RESULTS: Of 171 participants, 118 (69.0%) were co-infected with HIV. The prevalence of dyslipidemia was 70.2% (120/171) with low HDL-c (40.4%, 69/171) and hypertriglyceridemia (22.5%, 38/169) being the most common components. Patients with dyslipidemia had significantly higher lymphocyte (P = 0.008), monocyte (P < 0.001), and platelet counts (P = 0.014) in addition to a lower MCV (P < 0.001) than those without dyslipidemia. Further, patients with dyslipidemia had lower leucocyte (P < 0.001) and neutrophil (P = 0.001) counts, NLR (P = 0.008), LMR (P = 0.006), and SII (P = 0.049). The MCV was inversely associated with low HDL-C (adjusted prevalence ratio (aPR) = 0.97, 95% CI 0.94-0.99, P = 0.023) but was positively associated with hypertriglyceridemia (aPR = 1.04, 95% CI 1.00-1.08, P = 0.052).
CONCLUSIONS: Individuals with dyslipidemia exhibited elevated lymphocyte, monocyte, and platelet counts compared to those without. However, only MCV demonstrated an independent association with specific components of dyslipidemia. There is need for further scientific inquiry into the potential impact of dyslipidemia on red cell morphology and a pro-thrombotic state among patients with TB.

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9. Trends of Drug-Resistant Tuberculosis in an Urban and a Rural Area in China: A 10-Year Population-Based Molecular Epidemiological Study.

Infect Drug Resist. 2024 Mar 8;17:919-926. doi: 10.2147/IDR.S436563. eCollection 2024.

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OBJECTIVE: Drug resistance is the critical determinant for appropriate tuberculosis (TB) treatment regimens and an important indicator of the local TB burden. We aimed to investigate and compare trends in TB drug resistance in the urban Songjiang District of Shanghai from 2011 to 2020, and the rural Wusheng County of Sichuan Province from 2009 to 2020, to assess the effectiveness of local TB control and treatment programs.
METHODS: Whole-genome sequencing data of Mycobacterium tuberculosis were used to predict drug-resistance profiles and identify genomic clusters. Clustered, retreated cases of drug-resistant TB with identical resistance mutations, as well as all new resistant cases, were defined as transmitted resistance. The Cochran-Armitage trend test was used to identify trends in the proportions. Differences between groups were tested using the Wilcoxon rank sum or chi-square tests.
RESULTS: The annual proportions of rifampicin-resistant (RR), isoniazid-resistant (INH-R) and multidrug-resistant (MDR) TB cases did not change significantly in Songjiang. In Wusheng, however, the percentage of total TB cases that were RR decreased from 13.2% in 2009 to 3.7% in 2020, the INH-R cases decreased from 16.5% to 7.3%, and the MDR cases decreased from 10.7% to 3.7%. In retreated cases, the percentage of drug resistance decreased in both Songjiang and Wusheng, suggesting improved treatment programs. Transmitted resistance accounted for more than two thirds of drug-resistant cases over the entire study periods, and in recent years this proportion has increased significantly in Songjiang.
CONCLUSION: In both urban Songjiang and rural Wusheng, drug-resistant TB is mostly the result of transmission of drug resistant strains and the percentage of transmitted resistance will likely increase with on-going improvements in the TB treatment programs. Reducing the prevalence of drug resistance depends principally upon decreasing transmission through the prompt diagnosis and effective treatment of drug-resistant TB cases.

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PMID: 38481653

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10. Inducing vulnerability to InhA inhibition restores isoniazid susceptibility in drug-resistant Mycobacterium tuberculosis.

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Of the approximately 10 million cases of Mycobacterium tuberculosis (Mtb) infections each year, over 10% are resistant to the frontline antibiotic isoniazid (INH). INH resistance is predominantly caused by mutations that decrease the activity of the bacterial enzyme KatG, which mediates the conversion of the pro-drug INH to its active form INH-NAD. We previously discovered an inhibitor of Mtb respiration, C10, that enhances the bactericidal activity of INH, prevents the emergence of INH-resistant mutants, and re-sensitizes a collection of INH-resistant mutants to INH through an unknown mechanism. To investigate the mechanism of action of C10, we exploited the toxicity of high concentrations of C10 to select for resistant mutants. We discovered two mutations that confer resistance to the disruption of energy metabolism and allow for the growth of Mtb in high C10 concentrations, indicating that growth inhibition by C10 is associated with inhibition of respiration. Using these mutants as well as direct inhibitors of the Mtb electron transport chain, we provide evidence that inhibition of energy metabolism by C10 is neither sufficient nor necessary to potentiate killing by INH. Instead, we find that C10 acts downstream of INH-NAD synthesis, causing Mtb to become particularly sensitive to inhibition of the INH-NAD target, InhA, without changing the concentration of INH-NAD or the activity of InhA, the two predominant mechanisms of potentiating INH. Our studies revealed that there exists a vulnerability in Mtb that can be exploited to render Mtb sensitive to

otherwise subinhibitory concentrations of InhA inhibitor.IMPORTANCEIsoniazid (INH) is a critical frontline antibiotic to treat Mycobacterium tuberculosis (Mtb) infections. INH efficacy is limited by its suboptimal penetration of the Mtb-containing lesion and by the prevalence of clinical INH resistance. We previously discovered a compound, C10, that enhances the bactericidal activity of INH, prevents the emergence of INH-resistant mutants, and re-sensitizes a set of INH-resistant mutants to INH. Resistance is typically mediated by katG mutations that decrease the activation of INH, which is required for INH to inhibit the essential enzyme InhA. Our current work demonstrates that C10 re-sensitizes INH-resistant katG-hypomorphs without enhancing the activation of INH. We furthermore show that C10 causes Mtb to become particularly vulnerable to InhA inhibition without compromising InhA activity on its own. Therefore, C10 represents a novel strategy to curtail the development of INH resistance and to sensitize Mtb to sub-lethal doses of INH, such as those achieved at the infection site.

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11. Second-line antituberculosis drug exposure thresholds predictive of adverse events in multidrug-resistant tuberculosis treatment.

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OBJECTIVES: This study aimed to investigate the association between drug exposure and adverse events (AEs) during the standardized multidrug-resistant tuberculosis (MDR-TB) treatment, as well as to identify predictive drug exposure thresholds.
METHODS: We conducted a prospective, observational multicenter study among participants receiving standardized MDR-TB treatment between 2016 and 2019 in China. AEs were monitored throughout the treatment and their relationships to drug exposure (e.g., the area under the drug concentration-time curve from 0 to 24 h, AUC0-24 h) were analyzed. The thresholds of pharmacokinetic predictors of observed AEs were identified by boosted classification and regression tree (CART) and further evaluated by external validation.
RESULTS: Of 197 study participants, 124 (62.9%) had at least one AE, and 15 (7.6%) experienced serious AEs. The association between drug exposure and AEs was observed including bedaquiline, its metabolite M2, moxifloxacin and QTcF prolongation (QTcF >450 ms), linezolid and mitochondrial toxicity, cycloserine and psychiatric AEs. The CART-derived thresholds of AUC0-24 h predictive of the respective AEs were 3.2 mg·h/l (bedaquiline M2); 49.3 mg·h/l (moxifloxacin); 119.3 mg·h/l (linezolid); 718.7 mg·h/l (cycloserine).
CONCLUSIONS: This study demonstrated the drug exposure thresholds predictive of AEs for key drugs against MDR-TB treatment. Using the derived thresholds will provide the knowledge base for further randomized clinical trials of dose adjustment to minimize the risk of AEs.

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12. Pharmacokinetics and Optimal Dosing of Levofloxacin in Children for Drug-Resistant Tuberculosis: An Individual Patient Data Meta-Analysis.

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BACKGROUND: Each year 25 000-32 000 children develop rifampicin- or multidrug-resistant tuberculosis (RR/MDR-TB), and many more require preventive treatment. Levofloxacin is a key component of RR/MDR-TB treatment and prevention, but the existing pharmacokinetic data in children have not yet been comprehensively summarized. We aimed to characterize levofloxacin pharmacokinetics through an individual patient data meta-analysis of available studies and to determine optimal dosing in children.
METHODS: Levofloxacin concentration and demographic data were pooled from 5 studies and analyzed using nonlinear mixed effects modeling. Simulations were performed using current World Health Organization (WHO)-recommended and model-informed optimized doses. Optimal levofloxacin doses were identified to target median adult area under the time-concentration curve (AUC)24 of 101 mg·h/L given current standard adult doses.
RESULTS: Data from 242 children (2.8 years [0.2-16.8] was used). Apparent clearance was 3.16 L/h for a 13-kg child. Age affected clearance, reaching 50% maturation at birth and 90% maturation at 8 months. Nondispersible tablets had 29% lower apparent oral bioavailability compared to dispersible tablets. Median

exposures at current WHO-recommended doses were below the AUC target for children weighing <24 kg and under <10 years, resulting in approximately half of the exposure in adults. Model-informed doses of 16-33 mg/kg for dispersible tablets or 16-50 mg/kg for nondispersible tablets were required to meet the AUC target without significantly exceeding the median adult Cmax.
CONCLUSIONS: Revised weight-band dosing guidelines with doses of >20 mg/kg are required to ensure adequate exposure. Further studies are needed to determine safety and tolerability of these higher doses.

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PMID: 38340060 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

13. Deep learning for precise diagnosis and subtype triage of drug-resistant tuberculosis on chest computed tomography.

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Deep learning, transforming input data into target prediction through intricate network structures, has inspired novel exploration in automated diagnosis based on medical images. The distinct morphological characteristics of chest

abnormalities between drug-resistant tuberculosis (DR-TB) and drug-sensitive tuberculosis (DS-TB) on chest computed tomography (CT) are of potential value in differential diagnosis, which is challenging in the clinic. Hence, based on 1176 chest CT volumes from the equal number of patients with tuberculosis (TB), we presented a Deep learning-based system for TB drug resistance identification and subtype classification (DeepTB), which could automatically diagnose DR-TB and classify crucial subtypes, including rifampicin-resistant tuberculosis, multidrug-resistant tuberculosis, and extensively drug-resistant tuberculosis. Moreover, chest lesions were manually annotated to endow the model with robust power to assist radiologists in image interpretation and the Circos revealed the relationship between chest abnormalities and specific types of DR-TB. Finally, DeepTB achieved an area under the curve (AUC) up to 0.930 for thoracic abnormality detection and 0.943 for DR-TB diagnosis. Notably, the system demonstrated instructive value in DR-TB subtype classification with AUCs ranging from 0.880 to 0.928. Meanwhile, class activation maps were generated to express a human-understandable visual concept. Together, showing a prominent performance, DeepTB would be impactful in clinical decision-making for DR-TB.

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PMID: 38469547

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14. Transmission dynamics and phylogeography of Mycobacterium tuberculosis in China based on whole-genome phylogenetic analysis.

Int J Infect Dis. 2024 Mar;140:124-131. doi: 10.1016/j.ijid.2023.10.015. Epub 2023 Oct 19.

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OBJECTIVES: This study aimed to describe the lineage-specific transmissibility and epidemiological migration of Mycobacterium tuberculosis in China.
METHODS: We curated a large set of whole-genome sequences from 3204 M. tuberculosis isolates, including thousands of newly sequenced genomes, and applied a series of metrics to compare the transmissibility of M. tuberculosis strains between lineages and sublineages. The countrywide transmission patterns of major lineages were explored.
RESULTS: We found that lineage 2 (L2) was the most prevalent lineage in China (85.7%), with the major sublineage 2.2.1 (80.9%), followed by lineage 4 (L4) (13.8%), which comprises major sublineages 4.2 (1.5%), 4.4 (6.2%) and 4.5 (5.8%). We showed evidence for frequent cross-regional spread and large cluster formation of L2.2.1 strains, whereas L4 strains were relatively geographically restricted in China. Next, we applied a series of genomic indices to evaluate M. tuberculosis strain transmissibility and uncovered higher transmissibility of L2.2.1 compared with the L2.2.2 and L4 sublineages. Phylogeographic analysis showed that southern, eastern, and northern China were highly connected regions for countrywide L2.2.1 strain spread.
CONCLUSIONS: The present study provides insights into the different transmission and migration patterns of the major M. tuberculosis lineages in China and highlights that transmissible L2.2.1 is a threat to tuberculosis control.

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15. Triple combination dry powder formulation of pretomanid, moxifloxacin, and pyrazinamide for treatment of multidrug-resistant tuberculosis.

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Both latent and multidrug-resistant tuberculosis (TB) have been causing significant concern worldwide. A novel drug, pretomanid (PA-824), has shown a potent bactericidal effect against both active and latent forms of Mycobacterium tuberculosis (MTb) and a synergistic effect when combined with pyrazinamide and moxifloxacin. This study aimed to develop triple combination spray dried inhalable formulations composed of antitubercular drugs, pretomanid, moxifloxacin, and pyrazinamide (1:2:8 w/w/w), alone (PaMP) and in combination with an aerosolization enhancer, L-leucine (20 % w/w, PaMPL). The formulation PaMPL consisted of hollow, spherical, dimpled particles (<5 μm) and showed good aerosolization behaviour with a fine particle fraction of 70 %. Solid-state characterization of formulations with and without L-leucine confirmed the amorphous nature of moxifloxacin and pretomanid and the crystalline nature of pyrazinamide with polymorphic transformation after the spray drying process. Further, the X-ray photoelectron spectroscopic analysis revealed the predominant surface composition of L-leucine on PaMPL dry powder particles. The dose-response cytotoxicity results showed pyrazinamide and moxifloxacin were non-toxic in both A549 and Calu-3 cell lines up to 150 μg/mL. However, the cell

viability gradually decreased to 50 % when the pretomanid concentration increased to 150 μg/mL. The in vitro efficacy studies demonstrated that the triple combination formulation had more prominent antibacterial activity with a minimum inhibitory concentration (MIC) of 1 μg/mL against the MTb H37Rv strain as compared to individual drugs. In conclusion, the triple combination of pretomanid, moxifloxacin, and pyrazinamide as an inhalable dry powder formulation will potentially improve treatment efficacy with fewer systemic side effects in patients suffering from latent and multidrug-resistant TB.

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16. Synergistic combination of antimicrobial peptide and isoniazid as inhalable dry powder formulation against multi-drug resistant tuberculosis.

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Multidrug-resistant tuberculosis (MDR-TB) has posed a serious threat to global public health, and antimicrobial peptides (AMPs) have emerged to be promising candidates to tackle this deadly infectious disease. Previous study has suggested that two AMPs, namely D-LAK120-A and D-LAK120-HP13, can potentiate the effect of isoniazid (INH) against mycobacteria. In this study, the strategy of combining INH and D-LAK peptide as a dry powder formulation for inhalation was explored. The antibacterial effect of INH and D-LAK combination was first evaluated on three MDR clinical isolates of Mycobacteria tuberculosis (Mtb). The minimum inhibitory concentrations (MICs) and fractional inhibitory concentration indexes (FICIs) were determined. The combination was synergistic against Mtb with FICIs ranged from 0.25 to 0.38. The INH and D-LAK peptide at 2:1 mole ratio (equivalent to 1: 10 mass ratio) was identified to be optimal. This ratio was adopted for the preparation of dry powder formulation for pulmonary delivery, with mannitol used as bulking excipient. Spherical particles with mass median aerodynamic diameter (MMAD) of around 5 μm were produced by spray drying. The aerosol performance of the spray dried powder was moderate, as evaluated by the Next Generation Impactor (NGI), with emitted fraction and fine particle fraction of above 70 % and 45 %, respectively. The circular dichroism spectra revealed that both D-LAK peptides retained their secondary structure after spray drying, and the antibacterial effect of the combination against the MDR Mtb clinical isolates was successfully preserved. The combination was found to be effective against MDR Mtb isolates with KatG or InhA mutations. Overall, the synergistic combination of INH with D-LAK peptide formulated as inhaled dry powder offers a new therapeutic approach against MDR-TB.

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17. The Safety and Tolerability of Linezolid in Novel Short-Course Regimens Containing Bedaquiline, Pretomanid, and Linezolid to Treat Rifampicin-Resistant Tuberculosis: An Individual Patient Data Meta-analysis.

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BACKGROUND: Effectiveness, safety, tolerability, and adherence are critical considerations in shifting to shorter tuberculosis (TB) regimens. Novel 6-month oral regimens that include bedaquiline (B), pretomanid (Pa), and linezolid (L), with or without a fourth drug, have been shown to be as or more effective than the established longer regimens for the treatment of multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB). We aimed to evaluate the safety and tolerability of linezolid in BPaL-containing regimens for the treatment of MDR/RR-TB among recently completed clinical trials.
METHODS: A review and meta-analysis was undertaken including published and unpublished data from clinical trials, conducted between 2010 and 2021, that evaluated regimens containing BPaL for the treatment of MDR/RR-TB. Individual patient data were obtained. For each BPaL-containing regimen, we evaluated the frequency and severity of treatment-related adverse events. The risk difference of adverse events for each regimen was calculated, in comparison to patients assigned to receiving the lowest cumulative exposure of linezolid.
RESULTS: Data from 3 clinical trials investigating 8 unique BPaL-containing regimens were included, comprising a total of 591 participants. Adverse events were more frequent in groups randomized to a higher cumulative linezolid dose. Among patients who were randomized to a daily dose of 1200 mg linezolid, 68 of 195 (35%) experienced a grade 3-4 adverse event versus 89 of 396 (22%) patients receiving BPaL-containing regimens containing 600 mg linezolid.
CONCLUSIONS: Regimens containing BPaL were relatively well tolerated when they included a daily linezolid dose of 600 mg. These novel regimens promise to improve the tolerability of treatment for MDR/RR-TB.

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18. Co-resistance to isoniazid and second-line anti-tuberculosis drugs in isoniazid-resistant tuberculosis at a tertiary care hospital in Thailand.

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Isoniazid-resistant tuberculosis (Hr-TB) is an important drug-resistant tuberculosis (TB). In addition to rifampicin, resistance to other medications for Hr-TB can impact the course of treatment; however, there are currently limited data in the literature. In this study, the drug susceptibility profiles of Hr-TB treatment and resistance-conferring mutations were investigated for Hr-TB clinical isolates from Thailand. Phenotypic drug susceptibility testing (pDST) and genotypic drug susceptibility testing (gDST) were retrospectively and prospectively investigated using the Mycobacterium Growth Indicator Tube (MGIT), the broth microdilution (BMD) method, and whole-genome sequencing (WGS)-based gDST. The prevalence of Hr-TB cases was 11.2% among patients with TB. Most Hr-TB cases (89.5%) were newly diagnosed patients with TB. In the pDST analysis, approximately 55.6% (60/108) of the tested Hr-TB clinical isolates exhibited high-level isoniazid resistance. In addition, the Hr-TB clinical isolates presented co-resistance to ethambutol (3/161, 1.9%), levofloxacin (2/96, 2.1%), and pyrazinamide (24/118, 20.3%). In 56 Hr-TB clinical isolates, WGS-based gDST predicted resistance to isoniazid [katG S315T (48.2%) and fabG1 c-15t (26.8%)], rifampicin [rpoB L430P and rpoB L452P (5.4%)], and fluoroquinolones [gyrA D94G (1.8%)], but no mutation for ethambutol was detected. The categorical agreement for the detection of resistance to isoniazid, rifampicin, ethambutol, and levofloxacin between WGS-based gDST and the MGIT or the BMD method ranged from 80.4% to 98.2% or 82.1% to 100%, respectively. pDST and gDST demonstrated a low co-resistance rate between isoniazid and second-line TB drugs in Hr-TB clinical isolates.
IMPORTANCE: The prevalence of isoniazid-resistant tuberculosis (Hr-TB) is the highest among other types of drug-resistant tuberculosis. Currently, the World Health Organization (WHO) guidelines recommend the treatment of Hr-TB with rifampicin, ethambutol, pyrazinamide, and levofloxacin for 6 months. The susceptibility profiles of Hr-TB clinical isolates, especially when they are co-resistant to second-line drugs, are critical in the selection of the appropriate treatment regimen to prevent treatment failure. This study highlights the susceptibility profiles of the WHO-recommended treatment regimen in Hr-TB clinical isolates from a tertiary care hospital in Thailand and the concordance and importance of using the phenotypic drug susceptibility testing or genotypic drug susceptibility testing for accurate and comprehensive interpretation of results.

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19. Spatial pattern of isoniazid-resistant tuberculosis and its associated factors among a population with migrants in China: a retrospective population-based study.

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BACKGROUND: Isoniazid-resistant, rifampicin-susceptible tuberculosis (Hr-TB) globally exhibits a high prevalence and serves as a potential precursor to multidrug-resistant tuberculosis (MDR-TB). Recognizing the spatial distribution of Hr-TB and identifying associated factors can provide strategic entry points for interventions aimed at early detection of Hr-TB and prevention of its progression to MDR-TB. This study aims to analyze spatial patterns and identify socioeconomic, demographic, and healthcare factors associated with Hr-TB in Shanghai at the county level.
METHOD: We conducted a retrospective study utilizing data from TB patients with available Drug Susceptible Test (DST) results in Shanghai from 2010 to 2016.

Spatial autocorrelation was explored using Global Moran's I and Getis-Ord Gi* statistics. A Bayesian hierarchical model with spatial effects was developed using the INLA package in R software to identify potential factors associated with Hr-TB at the county level.
RESULTS: A total of 8,865 TB patients with DST were included in this analysis. Among 758 Hr-TB patients, 622 (82.06%) were new cases without any previous treatment history. The drug-resistant rate of Hr-TB among new TB cases in Shanghai stood at 7.20% (622/8014), while for previously treated cases, the rate was 15.98% (136/851). Hotspot areas of Hr-TB were predominantly situated in southwestern Shanghai. Factors positively associated with Hr-TB included the percentage of older adult individuals (RR = 3.93, 95% Crl:1.93-8.03), the percentage of internal migrants (RR = 1.35, 95% Crl:1.15-1.35), and the number of healthcare institutions per 100 population (RR = 1.17, 95% Crl:1.02-1.34).
CONCLUSION: We observed a spatial heterogeneity of Hr-TB in Shanghai, with hotspots in the Songjiang and Minhang districts. Based on the results of the models, the internal migrant population and older adult individuals in Shanghai may be contributing factors to the emergence of areas with high Hr-TB notification rates. Given these insights, we advocate for targeted interventions, especially in identified high-risk hotspots and high-risk areas.

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20. Treatment outcomes and risk factors for an unsuccessful outcome among patients with highly drug-resistant tuberculosis in Ukraine.

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OBJECTIVES: To describe demographics, clinical features, and treatment outcomes of patients with highly drug-resistant tuberculosis (TB) in Ukraine, and to evaluate risk factors for an unsuccessful outcome.
METHODS: Data from patients with multi-, pre-extensively, or extensively drug-resistant TB were collected prospectively from TB dispensaries in 15 out of 24 Ukrainian oblasts (regions) from 2020 to 2021. Treatment outcomes were evaluated using WHO definitions. Risk factors for an unsuccessful outcome were identified using a multivariable logistic regression model.
RESULTS: Among 1748 patients, the overall proportion of successful outcomes was 58% (95% confidence interval [95% CI] 56-60) (n = 1015/1748), ranging from 65% (95% CI: 62-69) (n = 531/814) for multidrug-resistant TB to 54% (95% CI: 49-58) (n = 301/563) for pre-extensively drug-resistant TB and 49% (95% CI: 44-55) (n = 183/371) for extensively drug-resistant TB. Results were similar across oblasts, with few exceptions. The strongest risk factors for an unsuccessful outcome were extensively drug-resistant TB (adjusted OR [aOR] 3.23; 95% CI: 1.88-5.53), total serum protein below 62 g/L in adults and below 57 g/L for children and adolescents (aOR 2.79; 95% CI: 1.93-4.04), psychiatric illness (aOR 2.79; 95% CI: 1.46-5.33), age at TB diagnosis >65 years (aOR 2.50; 95% CI: 1.42-4.42), and alcohol misuse (aOR 2.48; 95% CI: 1.89-3.26).
DISCUSSION: The overall proportion of successful outcomes among Ukrainians treated for highly drug-resistant TB was 58%, notably better compared with previous years, but still low for extensively drug-resistant TB. Risk factors for unsuccessful outcomes highlight that addressing socioeconomic factors in TB management is crucial. Efforts in maintaining TB dispensaries during and following the ongoing war are highly warranted.

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21. Self-driven solutions and resilience adapted by people with drug-resistant tuberculosis and their caregivers in Bengaluru and Hyderabad, India: a qualitative study.

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BACKGROUND: One-fifth of people with drug-resistance tuberculosis (DR-TB) who were initiated on newer shorter treatment regimen (with injection) had unfavourable treatment outcomes in India as on 2020. Evidence on self-driven solutions and resilience adapted by people with DR-TB (PwDR-TB) towards their multi-dimensional disease and treatment challenges are scarce globally, which we aimed to understand.
METHODS: In this qualitative study using positive deviance framework, we conducted semi-structured in-depth interviews among consenting adult PwDR-TB (7 women, 13 men) who completed shorter treatment regimen (including injections) with maximum treatment adherence. The study was conducted in the southern districts of Bengaluru and Hyderabad, India between June 2020 and December 2022. Caregivers (14 women, 6 men) and health providers (8 men, 2 women) of PwDR-TB were also interviewed. Interviews were conducted in local language (Kannada, Tamil, Telugu, Urdu and Hindi) and inquired about practices, behaviours, experiences, perceptions and attributes which enabled maximum adherence and resilience of PwDR-TB. Interviews were audio recorded, transcribed, and translated to English and coded for thematic analysis using inductive approach.
FINDINGS: Distinctive themes explanatory of the self-driven solutions and resilience exhibited by PwDR-TB and their caregivers were identified: (i) Self-adaptation towards the biological consequences of drugs, by personalised nutritional and adjuvant practices, which helped to improve drug ingestion and therapeutic effects. Also home remedies and self-plans for ameliorating injection pain. (ii) Perceptual adaptation towards drugs aversion and fatigue, by their mind diversion practices, routinisation and normalisation of drug intake process. and constant reinforcement and re-interpretation of bodily signs of disease recovery (iii) Family caregivers intense and participatory care for PwDR-TB, by aiding their essential life activities and ensuring survival, learning and fulfilling special nutritional needs and goal oriented actions to

aid drug intake (iv) Health care providers care, marked by swift and timely risk mitigation of side-effects and crisis response (v) Acquired self-efficacy of PwDR-TB, by their decisive family concerns resulting in attitudinal change. Also being sensitised on the detrimental consequences of disease and being motivated through positive examples.
INTERPRETATION: Synthesised findings on self-driven solutions and resilience towards the multi-dimensional DR-TB challenges provides opportunity for developing and testing new interventions for its effectiveness in DR-TB care settings globally. Designing and testing personalised cognitive interventions for PwDR-TB: to inculcate attitudinal change and self-efficacy towards medication, developing cognitive reinforcements to address the perception burden of treatment, skill building and mainstreaming the role of family caregivers as therapeutic partners of PwDR-TB, curating self-adaptive behaviours and practices of PwDR-TB to normalise their drug consumptions experiences could be the way forward in building resilience towards DR-TB.
FUNDING: United States Agency for International Development (USAID) through Karnataka Health Promotion Trust (KHPT), Bengaluru, India.

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22. Particulate matter deposition and its impact on tuberculosis severity: A cross-sectional study in Taipei.

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The objective of this study was to examine the association between the lung lobe-deposited dose of inhaled fine particulate matter (PM2.5) and chest X-ray abnormalities in different lung lobes of pulmonary tuberculosis (TB), multidrug-resistant tuberculosis (MDR-TB), and non-tuberculosis mycobacteria infections (NTM). A cross-sectional study was conducted between 2014 and 2022, comprising 1073 patients who were recruited from chest department clinic in a tertial refer hospital in Taipei City, Taiwan. Ambient 1-, 7-, and 30-day PM2.5 exposure and the deposition of PM2.5 in different lung lobes were estimated in each subject. The β coefficient for PM2.5 and deposited PM2.5 in lungs with the outcome variables (pulmonary TB, MDR-TB, and NTM infection) was derived through regression analysis and adjusted for age, gender, BMI, smoking status, and family income. We observed that a 1 μg/m3 increase in ambient PM2.5 was associated with an increase of MDR-TB infections of 0.004 times (95%CI:

0.001-0.007). A 1 μg/m3 increase in 1-day and 7-day PM2.5 deposition in left upper lobe and left lower lobe was associated with an increase in chest X-ray abnormalities of 9.19 % and 1.18 % (95%CI: 0.87-17.51 and 95%CI: 0.08-2.28), and 4.52 % and 5.20 % (95%CI: 0.66-8.38 and 95%CI: 0.51-9.89) in left lung of TB patients, respectively. A 1 μg/m3 increase in 30-day PM2.5 deposition in alveolar region was associated with an increase in percent abnormality of 2.50 % (95%CI: 0.65-4.35) in left upper lobe and 3.33 % (95%CI: 0.65-6.01) in right middle lobe, while in total lung was 0.63 % (95%CI: 0.01-1.27) in right upper lobe and 0.37 % (95%CI, 0.06-0.81) in right lung of MDR-TB patients. Inhaled PM2.5 deposition in lungs was associated with an exacerbation of the radiographic severity of pulmonary TB, particularly in pulmonary MDR-TB patients in upper and middle lobes. Particulate air pollution may potentially exacerbate the radiographic severity and treatment resistance in individuals with pulmonary TB.

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23. Occurrence and predictors of adverse events associated with Linezolid in the treatment of patients with MDR-TB.

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24. Rapid detection of multidrug resistance in tuberculosis using nanopore-based targeted next-generation sequencing: a multicenter, double-blind study.

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BACKGROUND: Resistance to anti-tuberculous drugs is a major challenge in the treatment of tuberculosis (TB). We aimed to evaluate the clinical availability of nanopore-based targeted next-generation sequencing (NanoTNGS) for the diagnosis of drug-resistant tuberculosis (DR-TB).

METHODS: This study enrolled 253 patients with suspected DR-TB from six hospitals. The diagnostic efficacy of NanoTNGS for detecting Mycobacterium tuberculosis and its susceptibility or resistance to first- and second-line anti-tuberculosis drugs was assessed by comparing conventional phenotypic drug susceptibility testing (pDST) and Xpert MTB/RIF assays. NanoTNGS can be performed within 12 hours from DNA extraction to the result delivery.
RESULTS: NanoTNGS showed a remarkable concordance rate of 99.44% (179/180) with the culture assay for identifying the Mycobacterium tuberculosis complex. The sensitivity of NanoTNGS for detecting drug resistance was 93.53% for rifampicin, 89.72% for isoniazid, 85.45% for ethambutol, 74.00% for streptomycin, and 88.89% for fluoroquinolones. Specificities ranged from 83.33% to 100% for all drugs tested. Sensitivity for rifampicin-resistant tuberculosis using NanoTNGS increased by 9.73% compared to Xpert MTB/RIF. The most common mutations were S531L (codon in E. coli) in the rpoB gene, S315T in the katG gene, and M306V in the embB gene, conferring resistance to rifampicin, isoniazid, and ethambutol, respectively. In addition, mutations in the pncA gene, potentially contributing to pyrazinamide resistance, were detected in 32 patients. Other prevalent variants, including D94G in the gyrA gene and K43R in the rpsL gene, conferred resistance to fluoroquinolones and streptomycin, respectively. Furthermore, the rv0678 R94Q mutation was detected in one sample, indicating potential resistance to bedaquiline.
CONCLUSION: NanoTNGS rapidly and accurately identifies resistance or susceptibility to anti-TB drugs, outperforming traditional methods. Clinical implementation of the technique can recognize DR-TB in time and provide guidance for choosing appropriate antituberculosis agents.

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25. Knowledge, attitudes, and practices towards childhood tuberculosis among healthcare workers at two primary health facilities in Lusaka, Zambia.

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BACKGROUND: Zambia is among the 30 high-burden countries for tuberculosis (TB), Human Immunodeficiency Virus (HIV)-associated TB, and multi-drug resistant/rifampicin resistant TB with over 5000 children developing TB every year. However, at least 32% of the estimated children remain undiagnosed. We assessed healthcare workers' (HCWs) knowledge, attitudes, and practices (KAP) towards childhood TB and the factors associated with good KAP towards childhood TB.
METHODS: Data was collected at two primary healthcare facilities in Lusaka, Zambia from July to August 2020. Structured questionnaires were administered to HCWs that were selected through stratified random sampling. Descriptive analysis was done to determine KAP. A maximum knowledge, attitude, and practice scores for a participant were 44, 10, and 8 points respectively. The categorization as either "poor" or "good" KAP was determined based on the mean/ median. Logistic regression analysis was performed to assess the associations between participant characteristics and KAP at statistically significant level of 0.05%.
RESULTS: Among the 237 respondents, majority were under 30 years old (63.7%) and were female (72.6%). Half of the participants (50.6%) were from the outpatient department (OPD) and antiretroviral therapy (ART) clinic, 109 (46.0) had been working at the facility for less than 1 year, 134 (56.5%) reported no previous training in TB. The median/mean KAP scores were 28 (IQR 24.0-31.0), 7 (IQR = 6.0-8.0) and 5 points (SD = 1.9) respectively. Of the participants, 43.5% (103/237) had good knowledge, 48.1% (114/237) had a good attitude, and 54.4% (129/237) had good practice scores on childhood TB. In the multivariate analysis, clinical officers and individuals with 1-5 years' work experience at the facility had higher odds, 2.61 (95% CI = 1.18-5.80, p = 0.018) and 3.09 (95% CI = 1.69-5.65, p = 0.001) of having good attitude respectively, and medical doctors had 0.17 lower odds (95% CI = 0.18-5.80, p = 0.018) of good childhood TB practice. Other participant characteristics didn't show a significant association with the scores.
CONCLUSION: The study found suboptimal levels of knowledge, attitude, and practices regarding childhood TB among HCWs. Targeted programmatic support needs to be provided to address the above gaps.

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26. The prevalence, clinical reasoning and impact of non-standard anti-tuberculosis regimens at the initial prescription.

Sci Rep. 2024 Mar 7;14(1):5631. doi: 10.1038/s41598-024-55273-5.

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Regarding clinically-concerning non-standard initial anti-tuberculous (TB) regimens, few studies have examined their prevalence, risk factors and impacts. We recruited patients with drug susceptible TB and non-standard initial anti-TB regimens (NSTB group) and matched them with patients with standard initial regimens (STB group) in a 1:1 ratio. The risk factors and outcomes were analyzed. During the 11-year study period, we analyzed 50 (3.7%) patients with NSTB from a total set of 1337 patients with drug-susceptible TB. Pyrazinamide (60%) was the drug most commonly not prescribed in the NSTB group, followed by ethambutol (34%). Multivariable logistic regression identified independent risk factors as underlying eye disease (adjusted odds ratio [aOR]: 8.869; 95% CI 2.542-30.949; p = 0.001), gout/hyperuricemia (aOR: 4.012 [1.196-13.425]; p = 0.024), and liver disease (aOR: 12.790 [3.981-41.089]; p < 0.001). The NSTB group had longer treatment durations (281 ± 121 vs. 223 ± 63 days; p = 0.003) and more occurrences of treatment interruption (26% vs. 8%; p = 0.021) than the STB group. In conclusion, NSTB occurs in around 3.7% of patients and is associated with longer treatment and more treatment interruption. The risk factors might include underlying liver and eye diseases, and gout. Further studies to improve non-standard initial regimens and prevent negative outcomes

are warranted.

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

27. Sub-MIC levels of bedaquiline and clofazimine can select Mycobacterium tuberculosis mutants with increased MIC.

Antimicrob Agents Chemother. 2024 Mar 12:e0127523. doi: 10.1128/aac.01275-23. Online ahead of print.

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Multidrug-resistant tuberculosis (MDR-TB) patients not cured at the time of stopping treatment are exposed to Minimum Inhibitory Concentration (MIC) and sub-MIC levels for many months after discontinuing bedaquiline (BDQ) or clofazimine (CFZ) treatment. In vitro cultures treated with BDQ and CFZ sub-MIC concentrations clearly showed enrichment in the Rv0678 mutant population, demonstrating that pre-existing Rv0678 mutants can be selected by sub-MIC concentrations of BDQ and CFZ if not protected by an alternative MDR-TB treatment.

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28. Identification of genetic determinants of bedaquiline resistance in Mycobacterium tuberculosis in Ural region, Russia.

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Collecting data on rare Mycobacterium tuberculosis (Mtb) clinical isolates with resistance to the new anti-tuberculosis drug bedaquiline is an important task for improving antimicrobial susceptibility testing methods. Nanopore whole genome sequencing, the proportion method on Middlebrook 7H11 medium, and BACTEC MGIT 960 assays were used to analyze genotypic and phenotypic resistance to bedaquiline. We found four mutations: atpE I66M, atpE A63P, Rv0678 A36T, and Rv0678 S53P in five isolates with different levels of phenotypic bedaquiline resistance.
IMPORTANCE: Bedaquiline (BDQ) is a new anti-tuberculosis drug. The phenotypic and genotypic data describing the mechanism of drug resistance are critical for the design of rapid and accurate diagnostic tests. We consider that our work, which describes genotypic and phenotypic resistance to BDQ, can contribute to the standardization of drug susceptibility testing.

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PMID: 38345388 [Indexed for MEDLINE]

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29. Cost-effectiveness of improving patients' adherence to tuberculosis treatment in South Korea using discrete event simulation.

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BACKGROUND: Poor adherence to tuberculosis (TB) treatment is an obstacle to controlling the disease. The Korean government's national TB control plan includes a program on adherence to TB treatment to manage patients with TB. This study aimed to assess the cost-effectiveness of a national TB program for improving patient adherence.
METHODS: A discrete event simulation (DES) model was developed to estimate the costs and quality-adjusted life-years (QALYs) of adherent and non-adherent patients. In this model, we considered treatment completion, loss to follow-up, recurrence, death, and treatment changes from drug-susceptible to multidrug-resistant TB as clinical events. We obtained input parameters such as costs, probability of events, and time distributions for each event from the Korean National Health Insurance claims data. We estimated the costs and QALYs before implementation of the program (adherence rate = 79%) and at present (current adherence rate = 94%). The incremental cost-effectiveness ratio (ICER) was used to evaluate whether the program was cost-effective given the willingness-to-pay threshold.
RESULTS: In the simulation, the program increasing the proportion of adherent patients gained 0.018 QALY/patient while spending $162/patient. The ICER of the TB program was $8790/QALY. Given a willingness-to-pay threshold of $20,000, the national TB program was considered cost-effective.
CONCLUSION: Improvements in adherence to TB treatment through the current TB program were cost-effective. The DES model accurately reflected the real world. Commitment programs to improve patient adherence may help manage TB nationwide.

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Non-Open Access Pub Med

30. Contact investigation in multidrug-resistant tuberculosis: ethical challenges.

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Contact investigation is an evidence-based intervention of multidrug-resistant tuberculosis (MDR-TB) to protect public health by interrupting the chain of transmission. In pursuit of contact investigation, patients' MDR-TB status has to be disclosed to third parties (to the minimum necessary) for tracing the contacts. Nevertheless, disclosure to third parties often unintentionally leads the MDR-TB patients suffered from social discrimination and stigma. For this reason, patients are less inclined to reveal their MDR-TB status and becomes a significant issue in contact investigation. This issue certainly turns into a negative impact on the public interest. Tension between keeping MDR-TB status confidential and safeguarding public health arises in relation to this issue. Regarding MDR-TB management, patient compliance with treatment and contact investigation are equally important. Patients might fail to comply with anti-TB therapy and be reluctant to seek healthcare due to disclosure concerns. In order to have treatment adherence, MDRTB patients should not live through social discrimination and stigma arising from disclosure and TB team has a duty to support them as a mean of reciprocity. However, implementation of contact investigation as a public health policy can still be challenging even with promising reciprocal support to the patients because MDR-TB patients are living in different contexts and situations. There can be no straight forward settlement but an appropriate justification for each distinct context is needed to strike a balance between individual confidentiality and public interest.

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PMID: 38430345

31. Multidrug-resistant tuberculosis: latest opinions on epidemiology, rapid diagnosis and management.

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PURPOSE OF REVIEW: This review addresses the escalating global challenge of multidrug-resistant tuberculosis (MDR-TB) in Sub-Saharan Africa, with a focus on its complex comorbidity with HIV/AIDS. Emphasizing the urgency of the issue, the review aims to shed light on the unique healthcare landscape shaped by the convergence of high prevalence rates and intersecting complexities with HIV/AIDS in the region.
RECENT FINDINGS: A notable increase in MDR-TB cases across Sub-Saharan Africa is attributed to challenges in timely diagnoses, treatment initiation, and patient treatment defaulting. The literature underscores the critical need for proactive measures to address diagnostic and treatment gaps associated with MDR-TB, particularly concerning its comorbidity with HIV/AIDS.
SUMMARY: To effectively manage MDR-TB and its co-morbidity with HIV/AIDS, proactive screening programs are imperative. The review highlights the necessity of active follow-up strategies to ensure treatment adherence and reduce default rates, offering evidence-based insights for improved disease management in the region.

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PMID: 38488133

32. Updates in pulmonary drug-resistant tuberculosis pharmacotherapy: A focus on BPaL and BPaLM.

Pharmacotherapy. 2024 Mar;44(3):268-282. doi: 10.1002/phar.2909. Epub 2024 Jan 25.

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Drug-resistant tuberculosis (TB) is a major public health concern and contributes to high morbidity and mortality. New evidence supports the use of shorter duration, all-oral regimens, which represent an encouraging treatment strategy for drug-resistant TB. As a result, the landscape of drug-resistant TB pharmacotherapy has drastically evolved regarding treatment principles and preferred agents. This narrative review focuses on the key updates of drug-resistant TB treatment, including the use of short-duration all-oral regimens, while calling attention to current gaps in knowledge that may be addressed in future observational studies.

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PMID: 38270468 [Indexed for MEDLINE]

33. Pre-extensively drug-resistant and extensively drug-resistant tuberculosis in Latin America and the Caribbean: A systematic review and meta-analysis.

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BACKGROUND: The growing threat from pre-extensively drug-resistant tuberculosis

(pre-XDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) poses a major public health concern in Latin America and the Caribbean (LAC). Therefore, this study aimed to summarize the available evidence on the prevalence of pre-XDR-TB and XDR-TB among patients with multidrug-resistant tuberculosis in LAC.
METHODS: A systematic review was conducted in the following databases on June 3, 2023: PubMed, Scopus, Ovid Medline, Web of Science, Scielo and LILACS. We estimated pooled proportions using a random effects model (Dersimonian and Laird). The 95% confidence intervals (95% CI) were calculated using the binomial exact method (Clopper-Pearson Method). Subgroup (by time period and country) and sensitivity analyses were performed.
RESULTS: Twenty-nine studies were eligible for qualitative synthesis and 27 for meta-analysis (n = 15,565). The pooled prevalence of XDR-TB in the study participants was 5% (95% CI: 3%-6%), while that of pre-XDR-TB was 10% (95% CI 7%-14%). Cuba (6%, 95% CI 0%-17%) and Peru (6%, 95% CI 5%-7%) had the highest pooled prevalence of XDR-TB. Regarding pre-XDR-TB, Brazil (16%, 95% CI 11%-22%) and Peru (13%, 95% CI: 9%-16%) showed the highest prevalence.
CONCLUSIONS: The pooled prevalence of pre-XDR-TB and XDR-TB in LAC was 10% and 5%, respectively. Governments should strengthen drug-resistance surveillance and TB programs.

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PMID: 38061402 [Indexed for MEDLINE]

34. Unlocking InhA: Novel approaches to inhibit Mycobacterium tuberculosis.

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Multidrug-resistant tuberculosis continues to pose a health security risk and remains a public health emergency. Antimicrobial resistance result from

treatment regimens that are both insufficient and incomplete leading to the emergence of multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis and totally drug-resistant tuberculosis. The impact of tuberculosis on the people suffering from HIV (Human immunodeficiency virus infection) have resulted in the increased research efforts in designing and discovery of novel antitubercular drugs that may result in decreasing treatment duration, minimising the need for multiple drug intake, minimising cytotoxicity and enhancing the mechanism of action of drug. While many drugs are available to treat tuberculosis, a precise and timely cure is still absent. Consequently, further investigation is needed to identify more recent molecular equivalents that have the potential to swiftly remove this disease. Isoniazid (INH), a treatment for tuberculosis (TB), targets the enzyme InhA (mycobacterium enoyl acyl carrier protein reductase), the Mycobacterium tuberculosis enoyl-acyl carrier protein (ACP) reductase, most common INH resistance is circumvented by InhA inhibitors that do not require KatG (catalase-peroxidase) activation, as a result, researchers are trying to work in the area of development of InhA inhibitors which could help in eradicating the era of tuberculosis from the world.

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PMID: 38460337

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35. Associations of residential greenness exposure and ambient air pollutants with newly-diagnosed drug-resistant tuberculosis cases.

Environ Sci Pollut Res Int. 2024 Mar 20. doi: 10.1007/s11356-024-32913-x. Online ahead of print.

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Growing evidence has found the health protective effects of greenness exposure on tuberculosis (TB) and the impact of ambient air pollutants on TB drug-resistance. However, it remains unclear whether residential greenness is also beneficial to reduce TB drug-resistance, and whether air pollution modify the greenness-TB resistance relationship. We enrolled 5006 newly-diagnosed TB patients from Shandong, China, during 2014 to 2021. Normalized Difference Vegetation Index (NDVI) in 250 m and 500 m buffer around individuals' residential zone was used to assess greenness exposure. All patients were divided by quartiles of NDVI250-m and NDVI500-m (from low to high: Q1, Q2, Q3, Q4) respectively. Six logistic regression models (NDVI, NDVI + PM2.5/PM10/SO2/NO2/O3) were used to estimate the association of NDVI and TB drug-resistance when adjusting different air pollutants or not. All models were adjusted for age, gender, body mass index, complications, smoking, drinking, population density, nighttime light index, road density. Compared with participants in NDVI250-m Q1 and NDVI500-m Q1, other groups had lower rates of MDR-TB, PDR-TB, RFP-resistance, SM-resistance, RFP + SM resistance, INH + RFP + EMB + SM resistance. NDVI500-m reduced the risk of multidrug resistant tuberculosis (MDR-TB) and the adjusted odds ratio (aOR, 95% confidence interval, CI) compared with NDVI500-m Q1 were 0.736 (0.547-0.991) in NDVI + PM10 model, 0.733 (0.544-0.986) in NDVI + PM2.5 model, 0.735(0.546-0.99) in NDVI + SO2 model, 0.736 (0.546-0.991) in NDVI + NO2 model, respectively,

P < 0.05. NDVI500-m contributed to a decreased risk of streptomycin (SM)-resistance. The aOR of rifampicin (RFP) + SM resistance were 0.132 (NDVI250-m, Q4 vs Q1, 95% CI: 0.03-0.578), 0.199 (NDVI500-m, Q3 vs. Q1, 95% CI: 0.057-0.688) and 0.264 (NDVI500-m, Q4 vs. Q1, 95% CI: 0.087-0.799). The adjusted ORs (Q2 vs. Q1, 95% CI) of isoniazid (INH) + RFP + ethambutol (EMB) + SM resistance in 500 m buffer were 0.276 (0.119-0.639) in NDVI model, 0.279 (0.11-0.705) in NDVI + PM10 model, 0.281 (0.111-0.713) in NDVI + PM2.5 model, 0.279 (0.11-0.709) in NDVI + SO2 model, 0.296 (0.117-0.754) in NDVI + NO2 model, 0.294 (0.116-0.748) in NDVI + O3 model, respectively. The study showed, for the first time, that residential greenness exposure in 500 m buffer is beneficial for reducing newly-diagnosed DR-TB (including PDR-RB, MDR-TB, MR-TB), and ambient air pollutants may partially mediate this association.

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PMID: 38509309

36. Pharmacokinetics and pharmacodynamics of high-dose isoniazid for the treatment of rifampicin- or multidrug-resistant tuberculosis in Indonesia.

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BACKGROUND: Pharmacokinetic data on high-dose isoniazid for the treatment of rifampicin-/multidrug-resistant tuberculosis (RR/MDR-TB) are limited. We aimed to describe the pharmacokinetics of high-dose isoniazid, estimate exposure target attainment, identify predictors of exposures, and explore exposure-response relationships in RR/MDR-TB patients.
METHODS: We performed an observational pharmacokinetic study, with exploratory pharmacokinetic/pharmacodynamic analyses, in Indonesian adults aged 18-65 years treated for pulmonary RR/MDR-TB with standardized regimens containing high-dose isoniazid (10-15 mg/kg/day) for 9-11 months. Intensive pharmacokinetic sampling was performed after ≥2 weeks of treatment. Total plasma drug exposure (AUC0-24) and peak concentration (Cmax) were assessed using non-compartmental analyses. AUC0-24/MIC ratio of 85 and Cmax/MIC ratio of 17.5 were used as exposure targets. Multivariable linear and logistic regression analyses were used to identify predictors of drug exposures and responses, respectively.
RESULTS: We consecutively enrolled 40 patients (median age 37.5 years). The geometric mean isoniazid AUC0-24 and Cmax were 35.4 h·mg/L and 8.5 mg/L, respectively. Lower AUC0-24 and Cmax values were associated ($P < 0.05$) with non-slow acetylator phenotype, and lower Cmax values were associated with male sex. Of the 26 patients with MIC data, less than 25% achieved the proposed targets for isoniazid AUC0-24/MIC (n = 6/26) and Cmax/MIC (n = 5/26). Lower isoniazid AUC0-24 values were associated with delayed sputum culture conversion (>2 months of treatment) [adjusted OR 0.18 (95% CI 0.04-0.89)].
CONCLUSIONS: Isoniazid exposures below targets were observed in most patients, and certain risk groups for low isoniazid exposures may require dose adjustment. The effect of low isoniazid exposures on delayed culture conversion deserves attention.

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PMID: 38459759

37. The occurrence rate of Haarlem and Beijing genotypes among Middle Eastern isolates of multi drug resistant Mycobacterium tuberculosis: A systematic review and meta-analysis.

Respir Investig. 2024 Mar;62(2):296-304. doi: 10.1016/j.resinv.2024.01.010. Epub 2024 Jan 31.

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Antibiotic resistance is a serious problem that poses a major challenge to tuberculosis control worldwide. Many developing countries still struggle with this infection in term of various aspects as it remains a major health concern. A number of developing countries are located in the Middle East, one of the world's most important regions. The control of this infection remains largely suboptimal despite intensive research in the field, and the mechanisms that lead to its progression have not yet been fully understood. Therefore, TB control must be amended through the identification of new strategies. For this reason, monitoring genetic characterizations of TB strains by molecular typing methods in different geographical regions can be important to setting local programs and global strategies to control TB infection. It is important to know the genotype of Mycobacterium tuberculosis strains to evaluate the occurrence of outbreaks and the transmission of this disease. Beijing and Haarlem genotypes are the most prevalent and, in these families, there is greater association with drug resistance, resulting in more severe forms of TB and higher levels of treatment failure than in other families. The current study is planned to systematically conduct a review using a meta-analysis to show the prevalence of Beijing and Haarlem genotypes in the Middle Eastern MDR-TB cases. M. tuberculosis strains pose particular epidemiological and clinical concerns as they can endanger tuberculosis control programs.

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38. Antitubercular drugs: possible role of natural products acting as antituberculosis medication in overcoming drug resistance and drug-induced hepatotoxicity.

Naunyn Schmiedebergs Arch Pharmacol. 2024 Mar;397(3):1251-1273. doi: 10.1007/s00210-023-02679-z. Epub 2023 Sep 4.

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Mycobacterium tuberculosis (Mtb) is a pathogenic bacterium which causes tuberculosis (TB). TB control programmes are facing threats from drug resistance. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) Mtb strains need longer and more expensive treatment with many medications resulting in more adverse effects and decreased chances of treatment outcomes. The World Health Organization (WHO) has emphasised the development of not just new individual anti-TB drugs, but also novel medication regimens as an alternative treatment option for the drug-resistant Mtb strains. Many plants, as well as marine creatures (sponge; Haliclona sp.) and fungi, have been continuously used to treat TB in various traditional treatment systems around the world, providing an almost limitless supply of active components. Natural products, in addition to their anti-mycobacterial action, can be used as adjuvant therapy to increase the efficacy of conventional anti-mycobacterial medications, reduce their side effects, and reverse MDR Mtb strain due to Mycobacterium's genetic flexibility and environmental adaptation. Several natural compounds such as quercetin, ursolic acid, berberine, thymoquinone, curcumin, phloretin, and propolis have shown potential anti-mycobacterial efficacy and are still being explored in preclinical and clinical investigations for confirmation of their efficacy and safety as anti-TB medication. However, more high-level randomized clinical trials are desperately required. The current review provides an overview of drug-resistant TB along with the latest anti-TB medications, drug-induced hepatotoxicity and oxidative stress. Further, the role and mechanisms of action of first and second-line anti-TB drugs and new drugs have been highlighted.

Finally, the role of natural compounds as anti-TB medication and hepatoprotectants have been described and their mechanisms discussed.

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PMID: 37665346 [Indexed for MEDLINE]

39. Emergence of bedaquiline-resistant tuberculosis and of multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis strains with rpoB Ile491Phe mutation not detected by Xpert MTB/RIF in Mozambique: a retrospective observational study.

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BACKGROUND: In 2021, an estimated 4800 people developed rifampicin-resistant tuberculosis in Mozambique, 75% of which went undiagnosed. Detailed molecular data on rifampicin-resistant and multidrug-resistant (MDR) tuberculosis are not available. Here, we aimed at gaining precise data on the determinants of rifampicin-resistant and MDR tuberculosis in Mozambique.
METHODS: In this retrospective observational study, we performed whole-genome sequencing of 704 rifampicin-resistant Mycobacterium tuberculosis complex (Mtbc) strains submitted to the National Tuberculosis Reference Laboratory (NTRL) in Maputo, Mozambique, between 2015 and 2021. Phylogenetic strain classification, genomic resistance prediction, and cluster analysis were performed.
FINDINGS: Between Jan 1, 2015, and July 31, 2021, 2606 Mtbc isolates with an isoniazid or rifampicin resistance were identified in the NTRL biobank, of which, 1483 (56·9%) were from men, 1114 (42·7%) from women, and nine (0·4%) were unknown. Genome-based drug-resistant prediction classified 704 Mtbc strains as rifampicin resistant. 628 (89%) of the 704 Mtbc strains were classified MDR; of those, 146 (23%) were pre-extensively drug resistant (pre-XDR; additional fluoroquinolone resistance), and 24 (4%) extensively drug resistant (XDR; combined fluoroquinolone and bedaquiline resistance). Overall, 61 (9%) of 704 strains revealed resistance to bedaquiline: five (7%) of 76 rifampicin resistant plus bedaquiline resistant, 32 (7%) of 458 MDR plus bedaquiline resistant, and 24 (100%) of 24 XDR. Prevalence of bedaquiline resistance increased from 3% in 2016 to 14% in 2021. The cluster rate (12 single-nucleotide polymorphism threshold) was 42% for rifampicin-resistant strains, 78% for MDR strains, 94% for pre-XDR strains, and 96% for XDR Mtbc strains. 31 (4%) of 704 Mtbc strains, belonging to a diagnostic escape outbreak strain previously described in Eswatini (group_56), had an rpoB Ile491Phe mutation which is not detected by Xpert MTB/RIF (no other rpoB mutation). Of these, 23 (74%) showed additional resistance to bedaquiline, 13 (42%) had bedaquiline and fluoroquinolone resistance, and two (6%) were bedaquiline, fluoroquinolone, and delamanid resistant.
INTERPRETATION: Pre-XDR resistance is highly prevalent among MDR Mtbc strains in Mozambique and so is bedaquiline resistance; and the frequency of bedaquiline resistance quadrupled over time and was found even in Mtbc strains without fluoroquinolone resistance. Importantly, strains with Ile491Phe mutation were frequent, accounting for 31% (n=10) of MDR plus bedaquiline-resistant strains and 54% (n=13) of XDR Mtbc strains. Given the current diagnostic algorithms and treatment regimens, both the emergence of rifampicin resistance due to Ile491Phe and bedaquiline resistance might jeopardise MDR tuberculosis prevention and care unless sequencing-based technology is rolled out. The potential cross border spread of diagnostic escape strains needs further investigation.
FUNDING: The German Ministry of Health through the Seq_MDRTB-Net project, the Deutsche Forschungsgemeinschaft under Germany's Excellence Strategy Precision Medicine in Inflammation and the Research Training Group 2501 TransEvo, the Leibniz Science Campus Evolutionary Medicine of the Lung, and the German

Ministry of Education and Research via the German Center for Infection Research.

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40. Characteristic SNPs defining the major multidrug-resistant Mycobacterium tuberculosis clusters identified by EuSeqMyTB to support routine surveillance, EU/EEA, 2017 to 2019.

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BackgroundThe EUSeqMyTB project, conducted in 2020, used whole genome sequencing (WGS) for surveillance of drug-resistant Mycobacterium tuberculosis in the European Union/European Economic Area (EU/EEA) and identified 56 internationally clustered multidrug-resistant (MDR) tuberculosis (TB) clones.AimWe aimed to define and establish a rapid and computationally simple screening method to identify probable members of the main cross-border MDR-TB clusters in WGS data to facilitate their identification and track their future spread.MethodsWe screened 34 of the larger cross-border clusters identified in the EuSeqMyTB pilot study (2017-19) for characteristic single nucleotide polymorphism (SNP) signatures that could identify and define members of each cluster. We also linked this analysis with published clusters identified in previous studies and identified more distant genetic relationships between some of the current clusters.ResultsA panel of 30 characteristic SNPs is presented that can be used as an initial (routine) screen for members of each cluster. For four of the clusters, no unique defining SNP could be identified; three of these are closely related (within approximately 20 SNPs) to one or more other clusters and likely represent a single established MDR-TB clade composed of multiple recent

subclusters derived from the previously described ECDC0002 cluster.ConclusionThe identified SNP signatures can be integrated into routine pipelines and contribute to the more effective monitoring, rapid and widespread screening for TB. This SNP panel will also support accurate communication between laboratories about previously identified internationally transmitted MDR-TB genotypes.

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PMID: 38516788

41. In vitro and ex vivo activity of the fluoroquinolone DC-159a against mycobacteria.

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Antimicrobial resistance is a global health problem. In 2021, it was estimated almost half a million of multidrug-resistant tuberculosis (MDR-TB) cases. Besides, non-tuberculous mycobacteria (NTM) are highly resistant to several drugs and the emergence of fluoroquinolone (FQ) resistant M. tuberculosis (Mtb) is also a global concern making treatments difficult and with variable outcome. The aim of this study was to evaluate the activity of the FQ, DC-159a, against Mtb and NTM and to explore the cross-resistance with the currently used FQs.A total of 12 pre-extensively drug-resistant (XDR) Mtb, 2 XDR, 36 fully drug susceptible strains and 41 NTM isolates were included to estimate the in vitro activity of DC-159a, moxifloxacin (MOX) and levofloxacin (LX), using minimal inhibitory and bactericidal concentration (MIC and MBC). The activity inside the human macrophages and pulmonary epithelial cells were also determined.DC-159a was active in vitro and ex vivo against mycobacteria. Besides, it was more active than MOX/LX. Moreover, no cross-resistance was evidenced between DC-159a and LX/MOX as DC-159a could inhibit Mtb and MAC strains that were already resistant to LX/MOX.DC-159a could be a possible candidate in new therapeutic regimens for MDR/ XDR-TB and mycobacterioses cases.

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PMID: 38438500

42. Global Burden of Tuberculosis in Adolescents and Young Adults: 1990-2019.

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OBJECTIVE: Tuberculosis (TB) is a major health threat in adolescents and young adults. However, its burden in this population remains unclear. This study aimed to assess TB burden and changing trends in individuals aged 10 to 24 years from 1990 to 2019.
METHODS: All data were obtained from the Global Burden of Disease Study 2019. We calculated the percentage of relative changes in incident cases, deaths, and disability-adjusted life years (DALYs). The temporal trends of the incidence, mortality, and DALYs were assessed using estimated annual percentage changes (EAPCs).
RESULTS: At global level, TB incidence (per 100 000 population) decreased from 144.12 in 1990 to 97.56 in 2019, with average 1.28% (95% confidence interval [CI]: 1.36%-1.19%) of decline per year. Similar decreasing trends occurred across sex, age, sociodemographic index regions, and in most Global Burden of Disease study regions and countries. TB incidence in female adolescents decreased faster than that in male. However, there was an increasing trend in the incidence of extensively drug-resistant TB (EAPC = 11.23, 95% CI: 8.22-14.33) and multidrug-resistant TB without extensive drug resistance (EAPC = 3.28, 95% CI: 1.73-4.86). South Africa had the highest increase in TB incidence (EAPC = 3.51, 95% CI: 3.11-3.92).
CONCLUSIONS: Global TB incidence, mortality, and DALYs in adolescents and young adults decreased from 1990 to 2019. However, the incidence of drug-resistant TB increased. TB remains a threat in adolescents and young adults worldwide, especially in low- and middle-income countries.

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PMID: 38482587

Conflict of interest statement: CONFLICT OF INTEREST DISCLOSURES: The authors have no conflicts of interest relevant to this article to disclose.

43. Molecular Detection of Multidrug Resistance and Characterizations of Mutations in Mycobacterium Tuberculosis Using Polycarbonate Track-Etched Membrane Based DNA Bio-Chip.

Indian J Microbiol. 2024 Mar;64(1):92-99. doi: 10.1007/s12088-023-01116-2. Epub 2023 Nov 24.

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With the widespread use of rifampicin (RMP) and isoniazid (INH), multidrug resistance (MDR) in Mycobacterium tuberculosis (M.tb) poses a threat to the success of tuberculosis (TB) control programs. We have developed a new polycarbonate track-etched membranes (PC-TEM) based DNA bio-chip designed for rapid detection of mutations conferring MDR in M.tb culture isolates. Bio-chips were designed to contain 14 specific probes for wild type and mutated allele of selected codons within 80 bp rifampicin resistance determining region of rpoB gene, katG gene and mabA-inhA regulatory region. RMP-resistance-associated gene mutation points rpoB 516, 526, 531 and 533, and the INH-resistance-associated gene mutation points katG315 and inhA-15 were targeted. Bio-chip signal was detected using enhanced chemiluminescence. A total of 50 culture isolates that were sensitive or resistant to RMP and/or INH were analyzed by bio-chip. The results of culture-based drug susceptibility testing (DST) were used as the gold standard and gene sequencing was performed to resolve the discordance. Amongst 50 culture isolates, we have detected 18 MDR, 9 RMP mono-resistant, 6 INH mono-resistant, and 17 fully susceptible isolates. The developed DNA bio-chip has a sensitivity of 90% for RMP and MDR and 100% for INH resistance. The bio-chip has a specificity of 100% for RMP and MDR and 88.8% for INH detection. The identification of mutations using the DNA bio-chip was 100% concordant with the sequencing data for the probes covered by the bio-chip. The detection of rpoB, katG and inhA gene mutation points by a DNA bio-chip may be used as a rapid, accurate, and economical, clinical detection method for MDR detection in M.tb. This is very valuable for the control of TB epidemics.

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PMID: 38468745

Conflict of interest statement: Conflict of interestAll the authors declare that they have no conflict of interest.

44. T-wave morphology abnormalities in the STREAM stage 1 trial.

Expert Opin Drug Saf. 2024 Mar 10:1-8. doi: 10.1080/14740338.2024.2322116. Online ahead of print.

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BACKGROUND: Shorter regimens for drug-resistant tuberculosis (DR-TB) have non-inferior efficacy compared with longer regimens, but QT prolongation is a concern. T-wave morphology abnormalities may be a predictor of QT prolongation.
RESEARCH DESIGN AND METHODS: STREAM Stage 1 was a randomized controlled trial in rifampicin-resistant TB, comparing short and long regimens. All participants had regular ECGs. QT/QTcF prolongation (≥500 ms or increase in ≥60 ms from baseline) was more common on the short regimen which contained high-dose moxifloxacin and clofazimine. Blinded ECGs were selected from the baseline, early (weeks 1-4), and late (weeks 12-36) time points. T-wave morphology was categorized as normal or abnormal (notched, asymmetric, flat-wave, flat peak, or broad). Differences between groups were assessed using Chi-Square tests (paired/unpaired, as appropriate).

RESULTS: Two-hundred participants with available ECGs at relevant times were analyzed (QT prolongation group n = 82; non-prolongation group n = 118). At baseline, 23% (45/200) of participants displayed abnormal T-waves, increasing to 45% (90/200, p < 0.001) at the late time point. Abnormalities were more common in participants allocated the Short regimen (75/117, 64%) than the Long (14/38, 36.8%, p = 0.003); these occurred prior to QT/QTcF ≥500 ms in 53% of the participants (Long 2/5; Short 14/25).
CONCLUSIONS: T-wave abnormalities may help identify patients at risk of QT prolongation on DR-TB treatment.
TRIAL REGISTRATION: The trial is registered at ClinicalTrials.gov (CT.gov identifier: NCT02409290). Current Controlled Trial number, ISRCTN78372190.

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45. Bioactives from medicinal herb against bedaquiline resistant tuberculosis: removing the dark clouds from the horizon.

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Tuberculosis is a contagious bacterial ailment that primarily affects the lungs and is brought on by the bacterium Mycobacterium tuberculosis (MTB). An antimycobacterial medication called bedaquiline (BQ) is specified to treat multidrug-resistant tuberculosis (MDR-TB). Despite its contemporary use in clinical practice, the mutations (D32 A/G/N/V/P) constrain the potential of BQ by causing transitions in the structural conformation of the atpE subunit-c after binding. In this study, we have taken the benzylisoquinoline alkaloids from thalictrum foliolosum due to its antimicrobial activity reported in prior literature. We used an efficient and optimized structure-based strategy to examine the wild type (WT) and mutated protein upon molecule binding. Our

results emphasize the drastic decline in BQ binding affinity of mutant and WT atpE subunit-c complexes compared to thalirugidine (top hit) from thalictrum foliolosum. The decrease in BQ binding free energy is due to electrostatic energy because nearly every atom in a macromolecule harbors a partial charge, and molecules taking part in molecular recognition will interact electrostatically. Similarly, the high potential mean force of thalirugidine than BQ in WT and mutant complexes demonstrated the remarkable ability to eradicate mycobacteria efficiently. Furthermore, the Alamar blue cell viability and ATP determination assay were performed to validate the computational outcomes in search of novel antimycobacterial. Upon closer examination of the ATP determination assay, it became apparent that both BQ and thalirugidine showed similar reductions in ATP levels at their respective MICs, presenting a potential common mechanism of action.

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46. Increased expression of Mycobacterium tuberculosis Rv3737 gene associated with low-level amikacin resistance.

J Infect Chemother. 2024 Mar;30(3):208-212. doi: 10.1016/j.jiac.2023.10.006. Epub 2023 Nov 25.

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INTRODUCTION: As an infectious disease, tuberculosis (TB) poses a serious threat to public health. Although amikacin (AMK) is an important antibiotic for the

treatment of drug-resistant TB, its resistance mechanisms are not fully understood.
METHODS: To investigate the role of Rv3737 gene on AMK drug susceptibility, a Mycobacterium tuberculosis (M.tb) Rv3737 knockout strain (H37Rv△Rv3737) and a Mycobacterium smegmatis (M.sm) Rv3737 overexpressing strain (Msm/pMV261-Rv3737) were used to detect their minimal inhibitory concentrations (MICs) in this study.
RESULTS: The AMK MICs of Rv3737 knockout and overexpressing strains were 4-fold lower and 2-fold higher than those of the wild-type and empty plasmid strains, respectively. The results of clinical isolates showed that no Rv3737 gene mutation was found to be associated with AMK susceptibility, while the rrs A1401G mutation remained the main mechanism of high level of AMK resistance (MIC>32 μg/ml). There was a positive correlation between Rv3737 mRNA expression level and AMK MIC. In the isolates with low-level AMK resistance (MIC = 4 μg/ml) without rrs A1401G mutation, the expression level of Rv3737 gene was significantly higher than those of susceptible isolates.
CONCLUSIONS: In this study, the Rv3737 gene was reported for the first time for its effect on AMK susceptibility in M.tb. Although the rrs A1401G mutation remains the main reason of high-level AMK resistance, high expression of the Rv3737 gene was associated with low-level AMK resistance in clinical isolates.

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PMID: 38012984 [Indexed for MEDLINE]

47. Diagnosing osteoarticular tuberculosis and detecting rifampicin resistance: A comparative analysis of Truenat MTB Plus vs GeneXpert Ultra.

Tuberculosis (Edinb). 2024 Mar;145:102483. doi: 10.1016/j.tube.2024.102483. Epub 2024 Feb 1.

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SETTING: Diagnosing osteoarticular tuberculosis (OATB) and detecting drug resistance is a challenge in an endemic country like India.
OBJECTIVE: Truenat MTB Plus assay (TruPlus), a chip-based portable machine, was compared with GeneXpert Ultra (GxUltra) for diagnosing drug-resistant OATB.
DESIGN: 115 synovial fluid and pus specimens [22 culture-positive confirmed, 58 culture-negative clinically-suspected, 35 non-TB controls] processed between 2017 and 2023 were subjected to TruPlus, GxUltra and multiplex-PCR for diagnosing OATB. They were further screened for rifampicin resistance using TruRif chip. The performance was evaluated against composite reference standard, phenotypic drug susceptibility testing and rpoB gene sequencing.
RESULTS: TruPlus, GxUltra and MPCR detected 77.5 %, 71.25 %, and 83.75 %, cases of OATB, respectively. TruPlus detected five additional cases missed by GxUltra. The performance of TruPlus was comparable to GxUltra ($p = 0.074$) and to MPCR ($p = 0.074$), while performance of GxUltra was significantly inferior to MPCR ($p = 0.004$). The overall agreement with reference standard was substantial for TruPlus and MPCR and moderate for GxUltra. Both TruRif and GxUltra reported 4 cases as rifampicin resistant.
CONCLUSION: TruPlus along with TruRif offers better sensitivity than GxUltra. Its compact and portable platform allows wider application in peripheral settings, thus making it a pragmatic solution for diagnosing OATB and its drug resistance.

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48. The structure of Mycobacterium thermoresistibile MmpS5 reveals a conserved disulfide bond across mycobacteria.

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The tuberculosis (TB) emergency has been a pressing health threat for decades. With the emergence of drug-resistant TB and complications from the COVID-19 pandemic, the TB health crisis is more serious than ever. Mycobacterium tuberculosis (Mtb), the causative agent of TB, requires iron for its survival. Thus, Mtb has evolved several mechanisms to acquire iron from the host. Mtb produces two siderophores, mycobactin and carboxymycobactin, which scavenge for host iron. Mtb siderophore-dependent iron acquisition requires the export of apo-siderophores from the cytosol to the host environment and import of iron-bound siderophores. The export of Mtb apo-siderophores across the inner membrane is facilitated by two mycobacterial inner membrane proteins with their cognate periplasmic accessory proteins, designated MmpL4/MmpS4 and MmpL5/MmpS5. Notably, the Mtb MmpL4/MmpS4 and MmpL5/MmpS5 complexes have also been implicated in the efflux of anti-TB drugs. Herein, we solved the crystal structure of M. thermoresistibile MmpS5. The MmpS5 structure reveals a previously uncharacterized, biologically relevant disulfide bond that appears to be conserved across the Mycobacterium MmpS4/S5 homologs, and comparison with structural homologs suggests that MmpS5 may be dimeric.

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PMID: 38425033 [Indexed for MEDLINE]

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49. Indole Propionic Acid Disturbs the Normal Function of Tryptophanyl-tRNA Synthetase in Mycobacterium tuberculosis.

ACS Infect Dis. 2024 Mar 8. doi: 10.1021/acsinfecdis.3c00585. Online ahead of print.

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Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis and the second-most contagious killer after COVID-19. The emergence of drug-resistant TB has caused a great need to identify and develop new anti-TB drugs with novel targets. Indole propionic acid (IPA), a structural analog of tryptophan (Trp), is active against M. tuberculosis in vitro and in vivo. It has been verified that IPA exerts its antimicrobial effect by mimicking Trp as an allosteric inhibitor of TrpE, which is the first enzyme in the Trp synthesis pathway of M. tuberculosis. However, other Trp structural analogs, such as indolmycin, also target tryptophanyl-tRNA synthetase (TrpRS), which has two functions in bacteria: synthesis of tryptophanyl-AMP by catalyzing ATP + Trp and producing Trp-tRNATrp by transferring Trp to tRNATrp. So, we speculate that IPA may also target TrpRS. In this study, we found that IPA can dock into the Trp binding pocket of M. tuberculosis TrpRS (TrpRSMtb), which was further confirmed by isothermal titration calorimetry (ITC) assay. The biochemical analysis proved that TrpRS can catalyze the reaction between IPA and ATP to generate pyrophosphate (PPi) without Trp as a substrate. Overexpression of wild-type trpS in M. tuberculosis increased the MIC of IPA to 32-fold, and knock-down trpS in Mycolicibacterium smegmatis made it more sensitive to IPA. The supplementation of Trp in the medium abrogated the inhibition of M. tuberculosis by IPA. We demonstrated that IPA can interfere with the function of TrpRS by mimicking Trp, thereby impeding protein synthesis and exerting its anti-TB effect.

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PMID: 38457660

50. Unravelling the potential of Triflusal as an anti-TB repurposed drug by targeting replication protein DciA.

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The increasing prevalence of drug-resistant Tuberculosis (TB) is imposing extreme difficulties in controlling the TB infection rate globally, making treatment critically challenging. To combat the prevailing situation, it is crucial to explore new anti-TB drugs with a novel mechanism of action and high efficacy. The Mycobacterium tuberculosis (M.tb)DciA is an essential protein involved in bacterial replication and regulates its growth. DciA interacts with DNA and provides critical help in binding other replication machinery proteins to the DNA. Moreover, the lack of any structural homology of M.tb DciA with human proteins makes it an appropriate target for drug development. In this study, FDA-approved drugs were virtually screened against M.tb DciA to identify potential inhibitors. Four drugs namely Lanreotide, Risedronate, Triflusal, and Zoledronic acid showed higher molecular docking scores. Further, molecular dynamics simulations analysis of DciA-drugs complexes reported stable interaction, more compactness, and reduced atomic motion. The anti-TB activity of drugs was further evaluated under in vitro and ex vivo conditions where Triflusal was observed to have the best possible activity with the MIC of

25 µg/ml. Our findings present novel DciA inhibitors and anti-TB activity of Triflusal. Further investigations on the use of Triflusal may lead to the discovery of a new anti-TB drug.

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PMID: 38145750 [Indexed for MEDLINE]

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

51. Identification of Genes Encoded Toxin-Antitoxin System in Mycobacterium Tuberculosis Strains from Clinical Sample.

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BACKGROUND: The toxin-antitoxin system is a genetic element that is highly present in Mycobacterium tuberculosis (MTB), the causative agent of tuberculosis. The toxin-antitoxin sys-tem comprises toxin protein and antitoxin protein or non-encoded RNA interacting with each other and inhibiting toxin activity. M. Tuberculosis has more classes of TA loci than non-tubercle bacilli and other microbes, including VapBC, HigBA, MazEF, ParDE, RelBE, MbcTA, PemIK, DarTG, MenTA, one tripartite type II TAC chaperone system, and hypothetical proteins.
AIMS: The study aims to demonstrate the genes encoded toxin-antitoxin system in mycobacterium tuberculosis strains from clinical samples.
MATERIALS AND METHODS: The pulmonary and extra-pulmonary tuberculosis clinical samples were collected, and smear microscopy (Ziehl-Neelsen staining) was performed for the detection of high bacilli (3+) count, followed by nucleic acid amplification assay. Bacterial culture and growth assay, genomic DNA extraction, and polymerase chain reaction were also carried out.

RESULTS: The positive PTB and EPTB samples were determined by 3+ in microscopy smear [20], and the total count of tubercle bacilli determined by NAAT assay was 8.0×1005 in sputum and 1.3×1004 CFU/ml in tissue abscess. Moreover, the genomic DNA was extracted from culture, and the amplification of Rv1044 and Rv1045 genes in 624 and 412 base pairs (between 600-700 and 400-500 in ladder), respectively, in the H37Rv and clinical samples was observed.
CONCLUSION: It has been found that Rv1044 and Rv1045 are hypothetical proteins with 624 and 882 base pairs belonging to the AbiEi/AbiEii family of toxin-antitoxin loci. Moreover, the signifi-cant identification of TA-encoded loci genes may allow for the investigation of multidrug-resistant and extensively drug-resistant tuberculosis.

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PMID: 38486387

52. A novel synergistic enzyme-antibiotic therapy with immobilization of mycobacteriophage Lysin B enzyme onto Rif@UiO-66 nanocomposite for enhanced inhaled anti-TB therapy; Nanoenzybiotics approach.

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The emergence of antibiotic-resistant and phage-resistant strains of Mycobacterium tuberculosis (M. tuberculosis) necessitates improving new therapeutic plans. The objective of the current work was to ensure the effectiveness of rifampicin and the mycobacteriophage LysB D29 (LysB)enzyme in

the treatment of multi-drug resistant tuberculosis (MDR-TB) infection, where new and safe metal-organic framework (MOF) nanoparticles were used in combination. UiO-66 nanoparticles were synthesized under mild conditions in which the antimycobacterial agent (rifampicin) was loaded (Rif@UiO-66) and LysB D29 enzyme immobilized onto Rif@UiO-66, which were further characterized. Subsequently, the antibacterial activity of different ratios of Rif@UiO-66 and LysB/Rif@uio-66 against the nonpathogenic tuberculosis model Mycobacterium smegmatis (M. smegmatis) was evaluated by minimum inhibitory concentration (MIC) tests. Impressively, the MIC of LysB/Rif@uio-66 was 16-fold lower than that of pure rifampicin. In vitro and in vivo toxicity studies proved that LysB/Rif@UiO-66 is a highly biocompatible therapy for pulmonary infection. A biodistribution assay showed that LysB/Rif@UiO-66 showed a 5.31-fold higher drug concentration in the lungs than free rifampicin. A synergistic interaction between UiO-66, rifampicin and the mycobacteriophage lysB D29 enzyme was shown in the computational method (docking). Therefore, all results indicated that the LysB/Rif@UiO-66 nanocomposite exhibited promising innovative enzyme-antibiotic therapy for tuberculosis treatment.

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53. Minimising the threat of bedaquiline-resistant tuberculosis: better diagnosis as prevention.

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54. Pancreatitis delays the absorption of first-line anti-TB drugs.

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55. NK-derived exosome miR-1249-3p inhibits Mycobacterium tuberculosis survival in macrophages by targeting SKOR1.

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Murine Natural Killer cells were cultivated in vitro to isolate NK-derived

exosomes. Subsequent quantification via qPCR confirmed enrichment of miR-1249-3p. Ana-1 murine macrophages were cultured in vitro and subsequently inoculated with Mycobacterium tuberculosis (MTB) strain H37Rv. NK-exo and NK-exo miR-1249-3p were separately applied to the infection model, followed by immunological assays conducted post-48-hour co-culture. Western blot analyses corroborated that NK-exo exhibited exosomal marker proteins Granzyme A (GzmA), Granzyme B (GzmB), and Perforin (PFN), alongside a notable enrichment of miR-1249-3p. Functionally, NK-exo augmented the expression levels of Caspase-9,-8, and -3, as well as PARP, while attenuating the expression of NLRP3, ASC, and Cleaved-Caspase-1. Furthermore, qPCR demonstrated an up-regulation of Caspase-9, -8, and -3, along with pro-apoptotic factors Bax and Bid, and a concomitant down-regulation of the anti-apoptotic factor Bcl-2. The expression levels of inflammatory markers ASC, NLRP3, Cleaved-Caspase-1, and IL-1β were concomitantly decreased. ELISA findings indicated diminished levels of TNF-α and ROS secretion. NK-exo miR-1249-3p specifically targeted and attenuated the expression of SKOR-1, engendering up-regulation of apoptosis-associated proteins and down-regulation of inflammation-related proteins, consequently affecting cellular fate.Our empirical evidence substantiates that NK-exo induces macrophage apoptosis, thereby mitigating MTB survival. Furthermore, NK-exo miR-1249-3p directly targets and inhibits SKOR-1 expression, leading to macrophage apoptosis and consequently hampering the proliferation of MTB. The data implicate the potential therapeutic relevance of NK-exo and miR-1249-3p in managing drug-resistant tuberculosis.

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56. Tuberculosis in people of Ukrainian origin in the European Union and the European Economic Area, 2019 to 2022.

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Approximately five million Ukrainians were displaced to the EU/EEA following the Russian invasion of Ukraine. While tuberculosis (TB) notification rates per 100,000 Ukrainians in the EU/EEA remained stable, the number of notified TB cases in Ukrainians increased almost fourfold (mean 2019-2021: 201; 2022: 780). In 2022, 71% cases were notified in three countries, and almost 20% of drug-resistant TB cases were of Ukrainian origin. Targeted healthcare services for Ukrainians are vital for early diagnosis and treatment, and preventing transmission.

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PMID: 38516786

57. Inhalable porous particles as dual micro-nano carriers demonstrating efficient lung drug delivery for treatment of tuberculosis.

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Inhalation therapy treating severe infectious disease is among the more complex and emerging topics in controlled drug release. Micron-sized carriers are needed to deposit drugs into the lower airways, while nano-sized carriers are of preference for cell targeting. Here, we present a novel and versatile strategy using micron-sized spherical particles with an excellent aerodynamic profile that dissolve in the lung fluid to ultimately generate nanoparticles enabling to enhance both extra- and intra-cellular drug delivery (i.e., dual micro-nano inhalation strategy). The spherical particles are synthesised through the condensation of nano-size amorphous silicon dioxide resulting in high surface area, disordered mesoporous silica particles (MSPs) with monodispersed size of 2.43 µm. Clofazimine (CLZ), a drug shown to be effective against multidrug-resistant tuberculosis, was encapsulated in the MSPs obtaining a dry powder formulation with high respirable fraction (F.P.F. <5 µm of 50%) without the need of additional excipients. DSC, XRPD, and Nitrogen adsorption/desorption indicate that the drug was fully amorphous when confined in the nano-sized pores (9-10 nm) of the MSPs (shelf-life of 20 months at 4 °C). Once deposited in the lung, the CLZ-MSPs exhibited a dual action. Firstly, the nanoconfinement within the MSPs enabled a drastic dissolution enhancement of CLZ in simulated lung fluid (i.e., 16-fold higher than the free drug), increasing mycobacterial killing than CLZ alone ($p = 0.0262$) and reaching concentrations above the minimum bactericidal concentration (MBC) against biofilms of M. tuberculosis (i.e., targeting extracellular bacteria). The released CLZ permeated but was highly retained in a Calu-3 respiratory epithelium model, suggesting a high local drug concentration within the lung tissue minimizing risk for systemic side effects. Secondly, the micron-sized drug carriers spontaneously dissolve in simulated lung fluid into nano-sized drug carriers (shown by Nano-FTIR), delivering high CLZ cargo inside macrophages and drastically decreasing the mycobacterial burden inside macrophages (i.e., targeting intracellular bacteria). Safety studies showed neither measurable toxicity on macrophages or Calu-3 cells, nor impaired epithelial integrity. The dissolved MSPs also did not show haemolytic effect on human erythrocytes. In a nutshell, this study presents a low-cost, stable and non-invasive dried powder formulation based on a dual micro-nano carrier to efficiently deliver drug to the lungs overcoming technological and practical challenges for global healthcare.

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Conflict of interest statement: Declaration of competing interest Nanologica AB (Södertälje) is a biotech company manufacturing porous silica particles for chromatography and drug delivery applications. Iconovo AB (Medicon Village, Lund) develops inhalation products, inhaler devices and dry powder formulation.

58. Exploring rhodanine linked enamine-carbohydrazide derivatives as mycobacterial carbonic anhydrase inhibitors: Design, synthesis, biological evaluation, and molecular docking studies.

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With the rise of multidrug-resistant tuberculosis, the imperative for an alternative and superior treatment regimen, incorporating novel mechanisms of action, has become crucial. In pursuit of this goal, we have developed and synthesized a new series of rhodanine-linked enamine-carbohydrazide derivatives, exploring their potential as inhibitors of mycobacterial carbonic anhydrase. The findings reveal their efficacy, displaying notable selectivity toward the mycobacterial carbonic anhydrase 2 (mtCA 2) enzyme. While exhibiting moderate activity against human carbonic anhydrase isoforms, this series demonstrates promising selectivity, positioning these compounds as potential antitubercular agents. Compound 6d was the best one from the series with a Ki value of 9.5 μM toward mtCA 2. Most of the compounds displayed moderate to good inhibition against the Mtb H37Rv strain; compound 11k showed a minimum inhibitory concentration of 1 μg/mL. Molecular docking studies revealed that compounds 6d and 11k show metal coordination with the zinc ion, like classical CA inhibitors.

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