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1. Genomic epidemiology analysis of extremely drug-resistant tuberculosis in Shanghai, China.

Emerg Microbes Infect. 2025 Dec;14(1):2521842. doi:
10.1080/22221751.2025.2521842. Epub 2025 Jul 4.

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Tuberculosis (TB), particularly extremely drug-resistant TB (EDR-TB), remains a significant public health concern worldwide. Understanding the transmission patterns and epidemiological characteristics of EDR-TB is vital for effective disease control. Between 1 January 2006 and 31 December 2018, we collected clinical M. tuberculosis strains in Shanghai, with whole-genome sequencing performed on 58 identified clinical EDR-TB strains. We analyzed EDR-related genetic mutations, conducted phylogenetic analyses, and examined bacterial and epidemiological factors that influence their transmission. Among these 58 EDR patients, 43.1% (25/58) were aged 45-64 years, with a median age of 51 years (interquartile range, IQR, 29-59 years). About two-thirds of the EDR-TB patients were residents. We observed a clustering rate of 44.8% (26/58) among EDR strains. Logistic regression analysis indicated a higher risk of recent EDR-TB transmission among the strains with the drug-resistant compensatory mutations. The primary mode of EDR-TB transmission in the study setting was recent, direct person-to-person spread of drug-resistant strains, as evidenced by high clustering rates and the presence of identical resistance mutations among clustered cases.

DOI: 10.1080/22221751.2025.2521842
PMCID: PMC12231322
PMID: 40548454 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

2. Mixed infections and heteroresistance of Mycobacterium tuberculosis among multidrug-resistant tuberculosis in China: a genomic epidemiology study.

Emerg Microbes Infect. 2025 Dec;14(1):2534656. doi:
10.1080/22221751.2025.2534656. Epub 2025 Aug 1.

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Mixed infection refers to the presence of multiple Mycobacterium tuberculosis strains within one host, while heteroresistance denotes the coexistence of drug-susceptible and drug-resistant strains or genotypes. Mixed infections and heteroresistance with Mycobacterium tuberculosis can complicate drug resistance diagnosis, treatment options, and transmission inference. We conducted a population-based genomic epidemiological study of multidrug-resistant tuberculosis (MDR-TB) in Shanghai, China, between January 1, 2005, and December 31, 2018, to evaluate the prevalence and impact of mixed infection and heteroresistance on MDR-TB diagnosis and treatment outcomes. Demographic, clinical, and laboratory data were collected, and factors associated with mixed infections and heteroresistance were identified with multivariable logistic regression analysis. Among the 936 MDR-TB patients in our study, 10.8% (101/936) had mixed infections and 16.5% (154/936) exhibited heteroresistance, which was more frequent with second-line anti-TB drugs ($P < 0.01$). There was a higher risk of heteroresistance in older patients (≥60 years: aOR 1.91, 95% CI 1.02-3.57), patients with diabetes (2.59, 1.36-4.91), and mixed infections (2.85, 1.67-4.88). Mixed infections and heteroresistance accounted for 22.6% (58/257) of the strains with discrepancies between phenotypic and genotypic drug susceptibility testing (DST). Strains with heteroresistance to EMB had a higher discordance rate than those without (29.1% VS 17.2%, $P < 0.05$). Isolates that were phenotypically susceptible but genotypically resistant harboured minority or low-frequency resistance mutations and were more common in patients with mixed infections and heteroresistance. In summary, mixed infections are significantly associated with heteroresistance, and both mixed infections and heteroresistance can lead to discrepancies between phenotypic and genotypic DST.

DOI: 10.1080/22221751.2025.2534656
PMCID: PMC12320256
PMID: 40748858 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the authors.

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3. Novel Pharmacological Approaches for Multidrug-Resistant Tuberculosis: Review.

Adv Pharmacol Pharm Sci. 2025 Nov 29;2025:8849786. doi: 10.1155/adpp/8849786. eCollection 2025.

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BACKGROUND: Due to its resistance to common anti-TB drugs, multidrug-resistant tuberculosis (MDR-TB) presents substantial treatment problems. Optimizing therapeutic outcomes requires individualized treatment plans that take into account patient comorbidities, medication susceptibility profiles, and past treatment history. The significance of individualized medication in the treatment of MDR-TB is emphasized in this study.
METHODS OF REVIEW: Current research on tailored treatment plans for MDR-TB is summarized in this review. It highlights how pharmacogenomics, medication sensitivity testing, and patient-centered care can be used to customize

treatment plans. The utilization of combination therapies, monitoring and adaptation techniques, and novel treatment options-such as adjuvant therapy and newer agents-are also covered in the review.
FINDINGS: Important findings show that thorough medication susceptibility testing is essential for directing wise treatment decisions. Dosage modifications based on individual metabolic responses can be informed by pharmacogenomic data. Treatment regimen adherence is improved when patients participate in decision-making. Combination therapy involving new drugs has demonstrated potential for increasing therapeutic effectiveness while reducing the emergence of resistance. Frequent monitoring makes it possible to promptly modify therapy in response to the patient response.
CONCLUSIONS: Treatment for MDR-TB must be individualized and comprehensive due to its complexity. For individuals with MDR-TB, therapy outcomes can be greatly enhanced while lowering the risk of further resistance by combining host-directed therapies, pharmacological breakthroughs, and continuous patient monitoring. Enhancing customized care solutions in this difficult field of infectious illness management requires ongoing research and innovation.

DOI: 10.1155/adpp/8849786
PMCID: PMC12664762
PMID: 41328075

Conflict of interest statement: The authors declare no conflicts of interest.

5.Decentralising drug-resistant TB treatment initiation services.

IJTLD Open. 2025 Dec 10;2(12):757-762. doi: 10.5588/ijtldopen.25.0412. eCollection 2025 Dec.

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BACKGROUND: Drug-resistant TB (DR-TB) care coordination in Nigeria remains largely centralised, negatively impacting pre-treatment loss-to-follow-up (PTLTFU) and time-to-treatment initiation. We piloted a multi-faceted intervention and documented how the decentralisation of DR-TB services affected treatment enrolment and time-to-treatment initiation.
METHODS: A quasi-experimental study was conducted in Southern Nigeria. Multi-level intervention consisting of eight components was implemented in the intervention states over a 15-month period. Data were collected using desk review proformas and analysed.
RESULTS: At baseline, comparable proportions of people with DR-TB initiated treatment (χ2 = 3.150, P = 0.076). Following decentralisation, a higher proportion (79.1%) of diagnosed persons with DR-TB in the intervention states were enrolled into treatment compared with the control states, 66.0% (χ2 = 15.232, P < 0.001). There was a significant reduction in PTLTFU in the intervention states from 39.5% to 20.9% (P < 0.001) while PTLTFU increased from 31.9% to 34.0% (P = 0.689) in the control states. The median time-to-treatment initiation decreased from 17 days (interquartile range [IQR]: 10.0-32.0) at baseline to 14 days (IQR: 9.0-25.2) post-intervention. In the control states, median time-to-treatment initiation decreased from 21 days (IQR: 13.0-35.3) at baseline to 15 days (8.0-36.0) post-intervention.
CONCLUSION: Decentralising DR-TB services significantly reduced the diagnosis-enrolment gap and time-to-treatment initiation. Our findings provide contextual evidence for the expansion of decentralised services in Nigeria.

DOI: 10.5588/ijtldopen.25.0412
PMCID: PMC12699969
PMID: 41395326

Conflict of interest statement: Conflicts of interest: none declared.

6. Scutellarin suppresses Mycobacterium tuberculosis-induced pyroptosis in macrophages by inhibiting the HIF-1α-mediated Warburg effect.

Redox Rep. 2025 Dec;30(1):2565861. doi: 10.1080/13510002.2025.2565861. Epub 2025 Oct 6.

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BACKGROUND: Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), remains a major global health threat due to prolonged treatment and drug-resistant strains. Host-directed therapy (HDT), which modulates host-pathogen interactions, offers potential to shorten treatment and limit resistance. This study investigates the effects of Scutellarin (SCU), a flavonoid from Scutellaria baicalensis, on Mtb-infected macrophages within the HDT framework.
METHODS: Anti-pyroptotic and anti-inflammatory effects of SCU were assessed in Mtb-infected THP-1 and J774A.1 macrophages, and in a lipopolysaccharide (LPS)-induced acute lung injury (ALI) mouse model. Mitochondrial function was evaluated by oxygen consumption rate(OCR), membrane potential, and superoxide levels; glycolytic activity was measured by proton efflux rate (GlycoPER). Expression of inflammasome-related markers was analyzed by Western blot, qPCR, ELISA, immunofluorescence, and flow cytometry. The role of hypoxia-inducible factor 1-alpha (HIF-1α) was examined via siRNA knockdown.
RESULTS: SCU inhibited NLRP3 inflammasome activation, reduced IL-1β and IL-18 secretion, and attenuating pyroptosis. It restored mitochondrial integrity by regulating p-DRP1, MFN2, and Cytochrome C expression, and suppressed HIF-1α-mediated glycolytic reprogramming. Silencing of HIF-1α confirmed its role in SCU's mechanism. In vivo, SCU reduced pulmonary inflammation and cytokine release in LPS-induced ALI.
CONCLUSION: SCU alleviates Mtb-induced pyroptosis and inflammation in macrophages by inhibiting the HIF-1α-mediated Warburg effect.

DOI: 10.1080/13510002.2025.2565861
PMCID: PMC12502121
PMID: 41051976 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

7. Policy analysis on drug-resistant tuberculosis in ASEAN member countries using a governance framework approach: a scoping review.

BMJ Glob Health. 2025 Nov 29;10(11):e016346. doi: 10.1136/bmjgh-2024-016346.

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Drug-resistant tuberculosis (DR-TB) heavily contributes to the global challenge of antimicrobial resistance (AMR), resulting in increased morbidity among tuberculosis cases. The Association of Southeast Asian Nations is home to approximately 10% of the world's population, accounting for almost 15% of the annual global TB incidence. Thus, this study aimed to evaluate the existing national policies on DR-TB in the region using the governance framework approach for AMR and the WHO Health System Building Blocks. A thorough search for DR-TB-related national policies was performed on the websites of official health ministries and international health organisations. A total of 118 policy documents were identified after the systematic searches, and 38 policy documents were included in the data analysis. Utilising the governance framework approach, we found that the least frequently addressed domains were antimicrobial research, equity and medicine regulation for monitoring and evaluation, policy design and implementation tools, respectively. While health workforce strategies were often detailed in these national policies, we found that financing schemes were the least frequently addressed health system building blocks. The findings of our study support the need to establish a comprehensive and consolidated policy development system following the governance framework approach and to strengthen the health system building blocks in order to achieve integrated care for patients with DR-TB as espoused by the principles of universal healthcare.

DOI: 10.1136/bmjgh-2024-016346
PMCID: PMC12666106
PMID: 41320198 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

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8. Care-seeking and treatment pathways of multidrug-resistant tuberculosis patients: an analysis of real-world data from regional health information system in Ningbo City in Eastern China.

Ann Med. 2025 Dec;57(1):2496405. doi: 10.1080/07853890.2025.2496405. Epub 2025 Apr 21.

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OBJECTIVES: The patient pathway of multidrug-resistant tuberculosis (MDR-TB) in China is an essential but not well-studied area. This study aimed to understand

the alignment between patient-initiated care-seeking demands for MDR-TB and the availability of diagnostic and treatment services in Ningbo, a city in eastern China, using patient pathway analysis (PPA).
METHODS: We collected the diagnostic and treatment data of 240 patients with MDR-TB in Ningbo from 2015 to 2019. Using patient pathway analysis, we matched the medical data of patients from different medical institutions and mapped their care pathways to illustrate their access to medical services.
RESULT: Our study indicated that the proportion of patients with MDR-TB who chose non-TB-designated medical institutions (55%) was higher than those who chose TB-designated medical institutions (45%) at their initial visit. An estimated 69% of patients with MDR-TB patients received initial TB screening services during their first visit. In this study, 47% of patients needed to visit 4-7 medical institutions to be diagnosed with MDR-TB. Overall, 80% (n = 192) of patients were diagnosed with MDR-TB within four visits, while 13% (n = 30), 4% (n = 10), and 3% (n = 8) of patients were not diagnosed at the fourth visit and remained at level 2, 1, and 0 medical institutions, respectively.
CONCLUSION: The care-seeking pathway of patients with MDR-TB in Ningbo is complex. This indicates room for improvement in local diagnosis and referral services. There is a need to promote the deployment of MDR-TB screening, diagnosis, and treatment services at lower-level institutions.

DOI: 10.1080/07853890.2025.2496405
PMCID: PMC12016273
PMID: 40259579 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

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9. Predominance of gram-negative multidrug-resistant pathogens causing lower respiratory tract infections among gene X-pert negative presumptive tuberculosis patients in Dar Es Salaam, Tanzania.

Ann Med. 2025 Dec;57(1):2550577. doi: 10.1080/07853890.2025.2550577. Epub 2025 Aug 23.

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BACKGROUND: Lower respiratory tract infections (LTRIs) represent a significant global health burden. The clinical presentation of pulmonary tuberculosis (PTB) and other LRTIs often overlap, making it difficult to differentiate based on clinical features only. This study aims to investigate the role of other bacteria pathogens in LRTIs among presumptive TB patients and antibiotic susceptibility patterns for appropriate patient management.
MATERIALS AND METHODS: We conducted a cross-sectional study among patients with symptoms and signs suggestive of PTB at Muhimbili National Hospital and Infectious Diseases Centre in Dar es Salaam, Tanzania. Sputum samples collected for TB diagnosis using the original GeneXpert system were investigated for other causes of LRTIs. The sputum samples were assessed for quality based on the Bartlett criteria before culture. We performed descriptive statistics to summarize the data.
RESULTS: We assessed 470 sputum samples, of which 317(67.4%) were of good quality. Of 317 samples, 21(6.6%) were Mycobacterium tuberculosis (MTB) positive by GeneXpert, while 126(39.7%) had 138 significant bacterial isolates other than MTB. Pseudomonas aeruginosa 44/99(44.4%) was the prominent Gram-negative bacteria isolated, followed by Klebsiella pneumoniae 22/99(22.2%). High rates of resistance was detected towards ampicillin (98%), penicillin (92%), and amoxicillin-clavulanic acid (65%). A high proportion of isolates, 71/138(51.4%) were multidrug resistant (MDR).
CONCLUSION: This study revealed a high prevalence of LRTIs caused by non-TB pathogens, particularly MDR strains in presumptive TB. MTB was detected only in high-quality sputum samples. The high resistance rate to commonly prescribed antibiotics for LRTIs called for further large-scale studies to guide and/or refine treatment guidelines and optimize patient care.

DOI: 10.1080/07853890.2025.2550577
PMCID: PMC12377089
PMID: 40847889 [Indexed for MEDLINE]

Conflict of interest statement: All authors declare no commercial or other associations that may pose a conflict of interest.

10. The time is now: making the case for compassionate use/pre-approval access to new TB drugs.

IJTLD Open. 2025 Dec 10;2(12):701-704. doi: 10.5588/ijtldopen.25.0644.
eCollection 2025 Dec.

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Although the majority of people with multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) can now be successfully treated with all-oral shorter regimens, rising rates of resistance to the components in these regimens are a growing global challenge. The drug development pipeline for TB has more novel compounds in phase 2 trials than ever before, and accessing these agents through systematic compassionate use programmes is an ethical and public health imperative. There is more than a decade of successful experience with compassionate use for MDR/RR-TB, resulting in benefits for people with MDR/RR-TB, novel chemical entity developers, providers, and programmes. Although there are some arguments for delaying access to the new TB drugs in the pipeline, we present reasons why such access should be an urgent priority for all TB stakeholders.

DOI: 10.5588/ijtldopen.25.0644

PMCID: PMC12699964
PMID: 41395317

11. Effectiveness and safety of the BPaL regimen in the Philippines.

J Clin Tuberc Other Mycobact Dis. 2025 Oct 13;41:100567. doi: 10.1016/j.jctube.2025.100567. eCollection 2025 Dec.

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BACKGROUND: Treatment success among multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) patients in the Philippines increased with the introduction of a 9-month all-oral treatment regimen; however, this remained sub-optimal, and patients continued to endure the burdensome and toxic effects of component medicines. In 2022, the World Health Organization recommended a 6-month MDR-TB regimen (bedaquiline, pretomanid, and linezolid or BPaL given for 26 weeks).
METHOD: Operational research was conducted in 12 TB treatment centers in 10 regions in the Philippines using the BPaL regimen. From June 2021 to December 2022, patients with pre-extensively drug-resistant TB or MDR/RR-TB that was treatment intolerant or nonresponsive to a previous MDR-TB regimen were enrolled. Linezolid was started daily at either 1200 mg or 600 mg.
RESULTS: A total of 103 patients received the BPaL regimen; 96 patients were included in the cohort analysis. Despite fluoroquinolone resistance in 42 %, cavitary TB 31 %, diabetes mellitus 42 %, and HIV coinfection 8 %, treatment

success was 98 %, with 1 (1 %) death and 1 (1 %) patient not evaluated. Sputum culture conversion was 78 % at month 1 of treatment, and 96 % by month 4. Sustained success at 6 and 12 months post-treatment were 92 % and 90 %, respectively, with the remainder attributable to patients not returning for post-treatment follow-up.Adverse events were mostly grade 1-2, which fully resolved in almost all patients. Linezolid dose modifications, and BPaL regimen interruption occurred in 66 % and 18 %, respectively.
CONCLUSION: The BPaL regimen had a remarkably high treatment success, rapid culture conversion, and a manageable safety profile among MDR/RR-TB patients in this study despite fluoroquinolone resistance and comorbidities.

DOI: 10.1016/j.jctube.2025.100567
PMCID: PMC12554217
PMID: 41146647

Conflict of interest statement: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors report financial support and equipment, drugs, or supplies were provided by Korea International Cooperation Agency, The Alliance for TB Drug Development, Inc (TB Alliance) and the Global Fund to Fight TB, HIV/AIDS and Malaria. All authors report financial article publishing charges were provided by TB Alliance. All authors report article statistical analysis, and writing assistance were provided by KNCV Tuberculosis Foundation. Maria Imelda Quelapio reports a relationship with The Global Alliance for TB Drug Development Inc that includes: consulting or advisory. Salah Foraida reports a relationship with The Global Alliance for TB Drug Development Inc that includes: employment. Maria Diachenko reports a relationship with The Global Alliance for TB Drug Development Inc that includes: employment. Sandeep Juneja reports a relationship with The Global Alliance for TB Drug Development Inc that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

12. Epidemiology and Outcomes of Pediatric Multidrug-resistant Tuberculosis in Namibia: A Retrospective Review of National Registry Data From 2013 to 2023.

Pediatr Infect Dis J. 2025 Dec 1;44(12):1159-1165. doi: 10.1097/INF.0000000000004933. Epub 2025 Aug 6.

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BACKGROUND: Multidrug-resistant (MDR) and rifampin-resistant (RR) tuberculosis (TB) is challenging the national response to tuberculosis in Namibia. The recent introduction of Xpert MTB/RIF (Cepheid, Sunnyvale, CA) and the use of new and repurposed drugs have the potential to improve both management and outcomes.
METHODS: Retrospective review of Namibian national registry data from 2013 to 2023 of children 0-14 years with MDR/RR-TB. National census data were used to estimate annual case notification rates (aCNRs).
RESULTS: Totally 205 episodes were available for analysis. The median age was 4 years [interquartile range (IQR) 1-10]. Ninety (43.9%) were female and 20 (9.8%) were living with HIV. The aCNR increased by two-thirds from 1.2 in 2013 to 2.0 per 100,000 population in 2023. One region, Ojotzondjupa, notified 58 (28.3%) of all cases with a median aCNR of 7.1 per 100,000 population while the national median aCNR was 1.8 per 100,000 population. Ninety individuals (58.1%) received a treatment regimen containing injectables, whereas 65 (41.9.6%) received an all-oral treatment regimen containing two or more World Health Organization class A drugs and/or delamanid. Outcome was unfavorable in 46 (24.1%) individuals, and 18 (9.4%) died. No decrease in the proportion of children with unfavorable outcomes was observed over the study period.
CONCLUSION: The epidemiology and outcome of children with MDR/RR-TB in Namibia are in keeping with the limited international data available; however, the geographical distribution of children with MDR/RR-TB poses a major challenge to the national TB response.

DOI: 10.1097/INF.0000000000004933
PMCID: PMC12594123

PMID: 40829018 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no funding or conflicts of interest to disclose.

13. The epidemiology and gene mutation characteristics of pyrazinamide-resistant Mycobacterium tuberculosis clinical isolates in Southern China.

Emerg Microbes Infect. 2025 Dec;14(1):2447607. doi:
10.1080/22221751.2024.2447607. Epub 2025 Jan 8.

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This study investigates the epidemic trend of pyrazinamide (PZA)-resistant tuberculosis in Southern China over 11 years (2012-2022) and evaluates the mutation characteristics of PZA resistance-related genes (pncA, rpsA, and panD) in clinical Mycobacterium tuberculosis (M. tuberculosis) isolates. To fulfil these goals, we analyzed the phenotypic PZA resistance characteristics of 14,927 clinical isolates for which Bactec MGIT 960 PZA drug susceptibility testing (DST) results were available, revealing that 2,054 (13.76%) isolates were resistant to PZA. After evaluating the annual variation in the PZA resistance rate among tuberculosis cases in this region, it was observed that it decreased from 37.21% to 6.45% throughout the initial 7 years (2012-2018) and then increased from 8.01% to 12.12% over the subsequent 4 years (2019-2022). Sequences of pncA were obtained from 402 clinical M. tuberculosis complex isolates. For rpsA and panD, sequences were obtained from 360 clinical M.

tuberculosis complex isolates. Mutations in pncA were found in 8 out of 223 PZA-sensitive isolates (3.59%) and 105 of 179 (58.66%) PZA-resistant isolates. Conversely, non-synonymous mutations in rpsA were identified in 5 of 137 (3.65%) PZA-resistant isolates, whereas the mutation ratio of rpsA among PZA-sensitive isolates was high at 14.03% (31/221). This difference in the rpsA mutation rate was statistically significant (P = 0.001, chi-square test). No panD mutations were observed in the 137 PZA-resistant isolates, whereas two PZA-sensitive isolates harboured point mutations in panD, including one nonsense mutation (C433 T) and another C-69 T mutation. These findings indicate that rpsA and panD may not significantly contribute to the development of PZA resistance in clinical M. tuberculosis isolates.

DOI: 10.1080/22221751.2024.2447607
PMCID: PMC11721771
PMID: 39745172 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

14. Patterns of compensatory mutations in rpoA/B/C genes of multidrug resistant M. tuberculosis in Uganda.

PLoS One. 2025 Dec 4;20(12):e0328957. doi: 10.1371/journal.pone.0328957. eCollection 2025.

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Update of
bioRxiv. 2025 Jul 11:2025.07.11.664293. doi: 10.1101/2025.07.11.664293.

Mutations in rpoB, a gene that encodes the bacterial RNA polymerase (RNAP) beta-subunit, can cause high-level resistance to rifampicin. Approximately 95% of rifampicin-resistant Mycobacterium tuberculosis clinical isolates harbour mutations in an 81-base pair rpoB region referred to as the rifampicin-resistance-determining region (rpoB/RRDR). Also, rifampicin-resistant M. tuberculosis clinical isolates carry multiple mutations in RNAP genes (i.e., rpoA, rpoB, rpoC, rpoD), particularly rpoA and rpoC, which encode the alpha- (α2) and beta'- (β') subunits, respectively. Such secondary mutations offset the fitness cost associated with acquisition of rifampicin-resistance mutations in M. tuberculosis, resulting in resistant strains that are as fit as the wild-type drug-susceptible strains. To analyse the patterns of compensatory mutations in RNAP encoding genes of rifampicin-resistant M. tuberculosis clinical isolates in Uganda, whole genome sequencing and Sanger DNA sequencing were performed on 52 M. tuberculosis clinical isolates - 20 drug-susceptible and 32 multidrug resistant (MDR). A total of 24 (75%) MDR-TB isolates had high-level rifampicin-resistance-conferring mutations in rpoB/RRDR, i.e., Ser531Leu (31%); His526Asp (6%); His526Leu (3%); His526Tyr (3%); His526Arg (3%); His526Gly (3%); Asp516Tyr (13%); Asp516Val (6%); Glu513Lys (3%); Leu511Pro (3%); Leu492Leu (3%); Gln490Arg (3%). Further, two putative compensatory mutations (Gln490Arg & Lys1025Glu) outside the RRDR and not resistance-conferring were found in rpoB. Altogether, 15 (63%, 15/24) MDR-TB isolates with rpoB/RRDR resistance-conferring mutations had non-synonymous mutations in rpoC of the following patterns Leu39Phe (3%); Tyr61His (3%); Asp271Gly (3%); Ser377Ala (3%); Pro481Thr (3%); Val483Ala (6%); Leu516Pro (3%); Ala521Asp (3%); Gly594Glu (13%); Asn698Ser (3%); Leu823Pro (3%). In conclusion, putative compensatory mutations are prevalent in rifampicin-resistant M. tuberculosis clinical isolates in Uganda, with rpoC/Gly594Glu and rpoC/Val483Ala as the most frequent. Further studies will determine their association with strain genetic background, fitness and transmission in an endemic setting with a high burden of HIV-TB coinfection.

DOI: 10.1371/journal.pone.0328957
PMCID: PMC12677784
PMID: 41343595 [Indexed for MEDLINE]

Conflict of interest statement: The authors have declared that no competing interests exist.

15. Non-tuberculous mycobacterial infections in mainland China and Taiwan: a systematic review and meta-analysis of epidemiology, species distribution, and drug resistance (2013-2024).

Front Public Health. 2025 Dec 5;13:1676715. doi: 10.3389/fpubh.2025.1676715.
eCollection 2025.

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INTRODUCTION: Non-tuberculous mycobacteria (NTM) represent an emerging public health threat in China. Despite evidence of rising NTM prevalence and significant regional variation, comprehensive and up-to-date nationwide data on epidemiology, species distribution, and drug resistance patterns have been lacking. This study aimed to systematically evaluate the prevalence, geographical and temporal trends, species composition, and antimicrobial resistance of NTM in mainland China and Taiwan from 2013 to 2024.
METHODS: Adhering to PRISMA guidelines, this systematic review and meta-analysis (PROSPERO: CRD42024540102) included 43 studies (2013-2024) encompassing 17,959 NTM isolates from 225,733 suspected TB patients. Stata software was used for meta-analysis with a random-effects model; publication bias was assessed via Egger's test and funnel plots.
RESULTS: The pooled NTM prevalence among suspected tuberculosis patients was 11.27% (95% CI: 9.89-12.65%), with marked geographic variation: highest in northeast (24.18%) and southeast coastal regions (12.83%), and lowest in southwest (2.30%). Slowly growing mycobacteria accounted for 68.07% of isolates, dominated by Mycobacterium avium complex (especially M. intracellulare); rapidly growing mycobacteria (26.57%) were more prevalent in southern provinces, with M. abscessus predominant. An overall upward trend in NTM isolation was observed from 2009-2021, followed by a decline in 2022-2023. Widespread resistance to first-line antituberculosis drugs was universal, whereas clarithromycin, amikacin, linezolid, and clofazimine retained good activity.
CONCLUSION: NTM prevalence in China has continued to rise over the past decade and now exceeds many global estimates, with pronounced coastal-southern predominance. The persistently high resistance to standard antituberculosis drugs underscores the urgent need for standardized diagnostic protocols, mandatory NTM reporting, enhanced surveillance networks, and region-tailored treatment guidelines.
SYSTEMATIC REVIEW REGISTRATION: https://www.crd.york.ac.uk/prospero/, identifier CRD42024540102.

DOI: 10.3389/fpubh.2025.1676715

PMCID: PMC12714956
PMID: 41426698 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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16. Transforming tuberculosis diagnosis with clinical metagenomics: progress and Roadblocks.

J Clin Microbiol. 2025 Dec 17;63(12):e0053725. doi: 10.1128/jcm.00537-25. Epub 2025 Sep 19.

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Tuberculosis (TB) remains a leading global infectious killer, yet traditional diagnostic methods are inadequate. Acid-fast staining suffers from low sensitivity, and mycobacterial culture requires prolonged incubation because of the slow growth of Mycobacterium tuberculosis. PCR-based molecular assays allow rapid detection, but their capacity for resistance profiling is limited to a narrow set of mutations. Metagenomic next-generation sequencing (mNGS) has emerged as a promising culture-independent tool for TB detection, enabling broad-spectrum pathogen identification and offering added value in complex scenarios including extra-pulmonary disease, mixed infections, and infections in immunocompromised or pediatric populations. Clinical studies indicate that mNGS achieves moderate to high sensitivity and excellent specificity in the diagnosis of tuberculosis. However, its diagnostic performance is often constrained by low mycobacterial read counts, interference from abundant host nucleic acids, and the inability to distinguish active from latent infection. In addition, the accuracy of drug resistance prediction using mNGS remains limited, and the World Health Organization currently endorses targeted NGS as the preferred sequencing-based approach for resistance profiling. Despite these challenges,

mNGS has facilitated novel diagnostic strategies that combine pathogen detection with host-response data, thereby broadening its potential clinical utility. Nevertheless, practical barriers such as high cost, complex laboratory workflows, and difficulties in data interpretation continue to restrict widespread adoption in routine practice. Future efforts should prioritize technical optimization, standardized protocols, and integration with conventional diagnostics to establish cost-effective and clinically meaningful roles for mNGS in TB diagnosis and management.

DOI: 10.1128/jcm.00537-25
PMCID: PMC12710363
PMID: 40970697 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

17. Retreatment TB is a risk factor for multidrug-resistant TB among people with HIV in rural eastern Uganda: A nested case-control study.

J Clin Tuberc Other Mycobact Dis. 2025 Sep 12;41:100562. doi: 10.1016/j.jctube.2025.100562. eCollection 2025 Dec.

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RATIONALE: People with human immunodeficiency virus (PWH) have an increased risk of multidrug-resistant TB (MDR-TB) compared to those without HIV.
OBJECTIVE: To investigate the risk factors for MDR-TB among PWH in rural eastern Uganda.
METHODS: We conducted a nested case-control study at Soroti Regional Referral Hospital in rural eastern Uganda. TB records from January 2017 to May 2024 were retrospectively reviewed to identify all PWH. MDR-TB was defined as resistance to at least both Isoniazid and Rifampicin following GeneXpert Mycobacterium TB and Rifampicin assay and culture-based drug-susceptible testing. Cases were PWH with MDR-TB, while controls were a random sample of PWH without MDR-TB, in a 1:3 ratio. Multivariable binary logistic regression was used to identify factors independently associated with being a case rather than a control. Adjusted odds

ratios (aORs) and 95% confidence intervals (CIs) were reported.
RESULTS: We included 37 cases and 111 controls, and found retreatment TB was associated with being a case rather than a control (aOR 6.97; 95% CI 2.65-19.46). Male sex (aOR: 1.59; 95% CI: 0.67-3.93), clinically diagnosed pulmonary TB (aOR: 0.38; 95% CI: 0.10-1.23) or extrapulmonary TB (aOR: 0.37; 95% CI: 0.05-1.62), and recent anti-retroviral therapy initiation (aOR: 2.07; 95% CI: 0.83-5.28) were insignificantly associated with being a case.
CONCLUSION: This study showed that retreatment TB is associated with a higher likelihood of MDR-TB among PWH in a referral hospital in rural eastern Uganda. These findings underscore the need for intensified drug resistance surveillance and adherence support among PWH with prior TB treatment.

DOI: 10.1016/j.jctube.2025.100562
PMCID: PMC12478262
PMID: 41031316

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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18. Tuberculosis infection control in MDR-TB designated hospitals in Jiangsu Province, China.

J Clin Tuberc Other Mycobact Dis. 2025 Jul 29;41:100555. doi: 10.1016/j.jctube.2025.100555. eCollection 2025 Dec.

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BACKGROUND: Hospital-acquired Tuberculosis (TB) infections among healthcare workers (HCWs) and patients present a significant challenge due to the increased risk of TB infection within healthcare settings.
METHODS: A standardized assessment tool was applied for the evaluation, which involved direct observation, document review, and interviews with facility heads. A baseline evaluation of TB infection control (TBIC) measures in TB outpatient and inpatient departments, as well as laboratories, was completed by January 2019. Based on the results, a comprehensive intervention package was implemented, incorporating a three-tiered hierarchy of controls: administrative control (AC), environmental control (EC), and respiratory protection (RP). Subsequent monitoring was conducted quarterly, with corrective actions accordingly. More than two years of follow-up data were collected, with the collaboration of local hospitals, the municipality Centers for Disease Control and Prevention (CDC), and the Jiangsu Provincial CDC, concluding on August 31, 2021.
RESULTS: At baseline, the average implementation rates of AC, EC and RP were 57.3 %, 59.2 %, and 66.6 %, respectively. After the intervention, significant improvements were observed in key infection control measures. A triage process for cough patients was established, mechanical ventilation systems were installed, and the use of masks was improved. In addition, ultraviolet (UV) and upper-room ultraviolet germicidal irradiation (UVGI) systems were installed where required. As a result, the average implementation rates of AC, EC and RP significantly increased to 86.3 %, 87.4 %, and 98.4 % ($P < 0.05$), respectively. However, at the study's conclusion, Suzhou Fifth People's Hospital reported a lower AC implementation rate of 70.7 %, while Changzhou Third People's Hospital had an EC implementation rate of 68.1 %. These discrepancies were primarily attributed to suboptimal architectural designs that hindered proper ventilation in the wards.
CONCLUSIONS: This study demonstrates that designated hospitals still face persistent gaps in tuberculosis infection control (TBIC). However, over the course of one and a half years of targeted and standardized interventions, substantial improvements in TBIC practices were achieved across most participating institutions. Despite the suboptimal availability of dedicated TB wards, strengthening TBIC measures remains crucial to reducing TB transmission among healthcare workers and non-TB patients. This approach is both practical and scalable, particularly in high-burden TB settings. Nevertheless, the long-term efficacy and sustainability of these TBIC practices warrant ongoing evaluation.

DOI: 10.1016/j.jctube.2025.100555
PMCID: PMC12340389
PMID: 40809299

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

19. Variability in intrinsic drug tolerance in Mycobacterium tuberculosis corresponds with phylogenetic lineage.

Antimicrob Agents Chemother. 2025 Dec 10;69(12):e0099625. doi: 10.1128/aac.00996-25. Epub 2025 Oct 21.

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Drug tolerance allows bacteria to survive extended exposure to bactericidal drugs and is thought to play a role in drug resistance evolution. In Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), multidrug-resistant TB outbreaks are frequently caused by strains belonging to two phylogenetic lineages of the human-adapted strains of the Mtb complex, namely, lineages (L) 2 and L4. We hypothesized that members of L2 and L4 are more intrinsically drug tolerant and, as such, more readily evolve drug resistance. To explore this, we devised a high-throughput in vitro assay to measure drug tolerance in Mtb. We selected a cohort of strains representative of the globally most frequent lineages, L1-L4. We measured tolerance to rifampicin and bedaquiline and found L3 and L4 strains to have higher tolerance compared to L1 and L2 strains. In addition, phylogenetically closely related strains exhibited similar levels of tolerance, suggesting that tolerance is heritable. Finally, we explored genes previously reported to be associated with tolerance in Mtb and found significant enrichment in mutations in genes involved in cell wall and cell processes, intermediary metabolism and respiration, as well as lipid metabolism in high-tolerance strains.

DOI: 10.1128/aac.00996-25
PMCID: PMC12691649

PMID: 41118320 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

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20. Mycobacterium tuberculosis complex lineages and drug resistance patterns among tuberculosis patients with or without diabetes mellitus in southern Ghana.

PLoS One. 2025 Dec 15;20(12):e0338498. doi: 10.1371/journal.pone.0338498. eCollection 2025.

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Drug-resistant (DR) tuberculosis (TB) and diabetes mellitus (DM) are intersecting epidemics that complicate management of both diseases and worsen patient outcomes. We conducted a prospective cohort study of 758 GeneXpert-confirmed pulmonary TB patients, of whom 75 had DM. Demographic, clinical, radiographic, and anthropometric data were collected at baseline. Sputum samples were cultured for mycobacterial isolation, and the obtained isolates were characterized for Mycobacterium tuberculosis complex (MTBC) lineage and drug-susceptibility testing using spoligotyping and microplate alamar blue assay. The TB-diabetes (TB-DM) comorbid cohort was older [TB-DM: 53/75 (70.7%) vs. 241/683 (35.3%) aged 41-60 years) ($p < 0.001$), included a higher proportion of females [TB-DM: 31/75 (41.3%) vs. TB-only: 150/683 (22.0%), $p < 0.001$], and had greater mean BMI (TB-DM: 23.36 ± 0.99 vs. TB-only: 19.97 ± 0.45 kg/m², $p = 0.003$). Analysis of 501 (TB-only: 448, TB-DM: 53) MTBC isolates revealed that TB-DM patients are more likely to get TB caused by L6 [TB-DM: 10/53 (18.9%) vs. TB-only: 37/448 (8.3%), $p = 0.022$] compared to the general TB population Lineage 4 [TB-DM: 36/53 (67.9%) vs. TB-only: 362/448 (80.8%), $p = 0.046$], Mycobacterial strains from TB-DM exhibited higher isoniazid mono-resistance [TB-DM: 15/50 (30.0%) vs. 42/288 (14.6%), $p = 0.012$] and harbored more multidrug-resistant TB [TB-DM: 5/50 (10.0%) vs. TB-only: 16/288 (5.6%), $p = 0.215$] although this did not reach statistical significance. These findings indicate that DM not only predisposes individuals to TB but may also shift the spectrum of infecting lineages and promotes the emergence of DR strains. Integrated TB-DM screening, lineage-aware diagnostics, and tailored treatment protocols are urgently needed in high-burden settings to address this dual threat.

DOI: 10.1371/journal.pone.0338498
PMCID: PMC12704858
PMID: 41397019 [Indexed for MEDLINE]

Conflict of interest statement: The authors have declared that no competing interests exist.

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21. Impact of drug-resistance diagnosis based on whole-genome sequencing on the treatment adequacy of patients with drug-resistant pulmonary tuberculosis in the state of São Paulo, Brazil: a protocol for a non-randomised controlled trial (Gen-TB PróCura).

BMJ Open. 2025 Nov 29;15(11):e098861. doi: 10.1136/bmjopen-2025-098861.

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INTRODUCTION: Since 2018, WHO has endorsed the use of whole-genome sequencing (WGS) of Mycobacterium tuberculosis complex isolates to detect drug-resistant tuberculosis (DR-TB). This endorsement was based on the assumption that a faster and more detailed description of the resistance profile would improve treatment prescription for DR-TB by healthcare providers, and hence the treatment outcomes of patients. Nonetheless, this assumption has not been tested in routine clinical practice and different scenarios. In Brazil, WGS is not routinely used for the diagnosis of DR-TB, having been carried out in only a few centres for research purposes. With this trial, we will evaluate whether a WGS-based drug-resistance report improves treatment adequacy in patients with pulmonary DR-TB, compared with the current standard-of-care diagnostic methods used in the state of São Paulo, Brazil.

METHODS AND ANALYSIS: We will conduct a non-randomised controlled clinical trial with two arms to compare the intervention group (ie, individuals receiving a WGS-based report) with a historical control group (i.e., individuals who received resistance diagnostics based on the standard of care of conventional genotyping and phenotyping techniques). The primary outcome will be the proportion of patients whose treatment scheme was adequate based on complete resistance profile determined by WGS and/or phenotypic drug-susceptibility testing (pDST). Other secondary outcomes will also be considered. The target sample size is 88 eligible patients per group. The intervention group will be prospectively recruited over 18 months and the control group will be composed of patients diagnosed with pulmonary DR-TB up to 2 years before the start of the trial. To ensure comparability, isolates from the control group will undergo WGS retrospectively, and pDST will be performed retrospectively in both groups. This clinical trial will take place in six medical centres for the treatment of DR-TB in the state of São Paulo. This study is intended to support the implementation of the WGS in the routine diagnosis of DR-TB in the state of São Paulo.

ETHICS AND DISSEMINATION: Ethical approval was obtained from the Human Research

Committee of the Institute of Biomedical Sciences, University of São Paulo, Brazil (CAAE: 79497924.1.1001.5467). Study results will be published in peer-reviewed journals and disseminated to policymakers and stakeholders.
TRIAL REGISTRATION NUMBER: U1111-1308-4669.

DOI: 10.1136/bmjopen-2025-098861
PMCID: PMC12666065
PMID: 41320215 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

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22. Dysregulation of the JNK signaling pathway in tuberculosis: mechanisms and therapeutic strategies.

Front Cell Infect Microbiol. 2025 Nov 26;15:1663992. doi: 10.3389/fcimb.2025.1663992. eCollection 2025.

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Tuberculosis (TB), which is caused by Mycobacterium tuberculosis (Mtb), remains a major infectious disease worldwide. Despite the availability of anti-TB drugs, the emergence of drug resistance, the need for prolonged treatment duration and the occurrence of side effects highlight the urgent need for new therapeutic strategies. The c-Jun N-terminal kinase (JNK) signaling pathway, which is an important member of the mitogen-activated protein kinase (MAPK) family, plays a crucial role in regulating cellular stress responses, inflammation, apoptosis, autophagy, and ferroptosis. Excessive JNK activation can induce uncontrolled inflammation, tissue damage, and chronic immune activation. In contrast, insufficient activation may impair the host's defense, facilitating Mtb immune evasion and persistence. Such alterations disrupt the delicate immune equilibrium essential for effective pathogen clearance and host protection. This review summarizes the molecular mechanisms through which Mtb manipulates the JNK signaling pathway to disrupt host immunity, emphasizing its roles in metabolic reprogramming, apoptosis, autophagy, and ferroptosis. In addition, this review discusses potential therapeutic strategies targeting the JNK pathway, including the development of selective JNK inhibitors, with a focus on their prospects in TB treatment. Progress has been made in elucidating the role of JNK signaling pathway in TB, but further research is required to clarify its specific mechanisms and evaluate the safety and efficacy of JNK-targeted interventions. Continued exploration of this pathway may provide new targets and strategies for TB therapy.

DOI: 10.3389/fcimb.2025.1663992
PMCID: PMC12689912
PMID: 41383846 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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23. All-Oral Shorter Treatment Regimens for Multidrug- and Rifampicin-Resistant Tuberculosis: Evaluating Their Effectiveness, Safety, and Impact on the Quality of Life of Patients in Lao PDR.

Trop Med Int Health. 2025 Dec;30(12):1340-1353. doi: 10.1111/tmi.70041. Epub 2025 Sep 25.

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BACKGROUND: Drug-resistant tuberculosis remains a major public health challenge in Lao PDR, with low second-line treatment uptake and suboptimal outcomes. To improve effectiveness, safety, and tolerability, a shorter all-oral regimen for

multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) was introduced under the TDR Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis (ShORRT) initiative.
METHODS: A retrospective and prospective comparative cohort study was conducted across five drug-resistant tuberculosis treatment centres from January 2020 to December 2023. Two programmatic cohorts were analysed during partially overlapping calendar periods: a standard injectable-containing regimen cohort and an all-oral regimen cohort. Outcomes were assessed at the end of treatment and 12 months post-treatment. Safety was evaluated through adverse events, including serious adverse events and adverse events of special interest. Health-related quality of life was measured using EQ-5D-5L and EQ-VAS tools.
RESULTS: Among 126 participants, 65 received the all-oral regimen and 61 the standard regimen. Treatment success was higher in the all-oral group (90.8% vs. 80.3%), with lower mortality (7.5% vs. 16.4%) and fewer serious adverse events (12.3% vs. 19.7%). Anaemia was more common in the all-oral group (46.2%), while hepatotoxicity and QTcF prolongation were more frequent in the standard group. Both groups showed improvements in health-related quality of life, but greater recovery in mobility, daily activities, and anxiety reduction was observed in the all-oral group. Between group differences did not reach statistical significance. No cases of tuberculosis recurrence were reported at 12-month follow-up in either group.
CONCLUSION: In this programmatic setting, the all-oral, bedaquiline and linezolid-based regimen demonstrated high effectiveness and acceptable safety. Non-significant trends favoured the all-oral regimen for treatment success, mortality, and quality of life, consistent with but not definitive for improved outcomes. These findings support the transition to all-oral regimens as the preferred approach for drug-resistant tuberculosis care, while acknowledging the observational design and limited power.

DOI: 10.1111/tmi.70041
PMCID: PMC12675319
PMID: 40998747 [Indexed for MEDLINE]

Conflict of interest statement: Philipp du Cros works at the Burnet Institute, which is currently receiving funding from TB Alliance to support the roll‐out of the BPaL/M regimen. Philipp du Cros was on the steering committee for the TB‐PRACTECAL RCT.

24. Analysis of influencing factors and construction of prediction model for multidrug-resistant tuberculosis in Nanning area.

Front Public Health. 2025 Dec 3;13:1599578. doi: 10.3389/fpubh.2025.1599578.
eCollection 2025.

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OBJECTIVE: This study aims to analyze the characteristics of multidrug-resistant Mycobacterium tuberculosis isolates and to identify the factors influencing multidrug resistance in the Nanning area.
METHODS: This study retrospectively analyzed all sputum specimens from pulmonary tuberculosis patients collected at the Fourth People's Hospital of Nanning from January 2021 to June 2022, including a total of 337 strains of Mycobacterium tuberculosis. Univariate analysis and binary logistics regression analysis were used to identify factors influencing multidrug resistance. A predictive model was constructed with SPSS software, and the predictive value of the model was evaluated with the Receiver Operating Characteristic (ROC) curve.
RESULTS: The results of binary logistics regression analysis indicated that treatment status and high-risk population were independent factors influencing multidrug resistance ($p < 0.05$). According to the logistics regression analysis results, the model was constructed as follows:
$\mathrm{Logit}(P) = -1.874 + (1.187X1) + (0.837X2)$. ROC analysis showed that the area under the curve (AUC) of the model was 0.936. In the validation group, the AUC was 0.853.
CONCLUSION: This study results provide a basis for precise prevention and control of multidrug-resistant tuberculosis bacteria in Nanning, help reduce the risk of transmission, and ensure public health safety of local and surrounding populations.

DOI: 10.3389/fpubh.2025.1599578
PMCID: PMC12708887
PMID: 41415255 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

25. Epidemiological trends and burden of mortality from HIV/AIDS and multidrug-resistant tuberculosis without extensive drug-resistance across Africa: A global burden of disease analysis (1990-2021).

J Clin Tuberc Other Mycobact Dis. 2025 Sep 20;41:100564. doi: 10.1016/j.jctube.2025.100564. eCollection 2025 Dec.

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BACKGROUND: HIV/AIDS and multidrug-resistant tuberculosis (MDR-TB, non-extensively drug-resistant) together cause significant mortality in Africa, home to 67% of the 39 million people living with HIV globally and 2.5 million TB cases in 2022. This study analyzes Global Burden of Disease (GBD) 2021 data to quantify temporal trends and mortality burdens of HIV/AIDS and MDR-TB across African subregions from 1990 to 2021, focusing on regional and gender-specific patterns.
METHODS: Age-standardized mortality rates (ASMR) per 100,000 population for HIV/AIDS and MDR-TB were extracted from GBD 2021 for the African Union (Central, Eastern, Northern, Southern, Western subregions), stratified by gender. Joinpoint regression (Joinpoint Regression Program, version 5.0.2) calculated Annual Percent Change (APC) and Average Annual Percent Change (AAPC) with 95 % CIs and p-values ($p < 0.05$ for significance). Weighted Bayesian Information Criterion and permutation testing identified up to six joinpoints. This method fits piecewise log-linear models, pinpointing inflection points (joinpoints) where statistically significant changes occur. Sensitivity analyses ensured robustness, adhering to GBD protocols.
RESULTS: From 1990 to 2021, the African Union exhibited varied trends in age-standardized mortality rates (ASMR) for HIV/AIDS and multidrug-resistant tuberculosis (MDR-TB). Overall, mortality trends showed a non-significant average annual percent change (AAPC) of 1.9526 % (95 % CI: -1.7682, 6.3941; $p = 0.278344$), reflecting a complex epidemic trajectory. Early in the period (1990-1999), mortality surged dramatically, with annual percent changes (APCs) peaking at 99.81 % (1990-1992) due to limited treatment access. A turning point emerged around 2003, with declines becoming prominent from 2006 onward. The most substantial reductions occurred between 2006 and 2014, with an APC of (-10.3478 %; 95 % CI: -11.0939, -9.8873; $p < 0.000001$), driven by expanded antiretroviral therapy (ART) and improved diagnostics. Gender-specific patterns revealed steeper declines for females, particularly in Southern Africa

(2007-2014, APC: -12.97 %), compared to males (2007-2013, APC: -11.36 %), highlighting the impact of targeted interventions for women. Regionally, Southern Africa bore the highest burden, with early increases (1990-1993, APC: 105.55 %) but significant declines post-2007 (APC: -11.95 %). Central Africa saw notable reductions after 2016 (APC: -15.75 %), while Northern Africa experienced a rising trend: AAPC 3.5641 % (95 % CI: 0.6866, 7.0452; p = 0.014397); driven by early spikes (1990-1992, APC: 38.89 %). Eastern and Western Africa showed modest declines, with APCs of -10.98 % (2004-2008) and -9.21 % (2006-2014), respectively.
CONCLUSIONS: The study highlights significant progress in reducing HIV/AIDS and MDR-TB mortality across Africa from 1990 to 2021, largely due to expanded access to antiretroviral therapy (ART), advanced diagnostics like GeneXpert, and global health initiatives such as PEPFAR and the Global Fund. However, persistent regional disparities, with Northern Africa showing rising mortality trends and Southern Africa bearing the highest burden, underscore the need for tailored interventions. Females experienced more pronounced mortality declines in certain periods, particularly in Southern Africa, likely due to targeted interventions like PMTCT, while males showed slightly less progress overall, potentially due to factors like occupational exposures or lower ART adherence. Limitations include reliance on modeled GBD data and lack of subnational granularity.

DOI: 10.1016/j.jctube.2025.100564
PMCID: PMC12510036
PMID: 41079943

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

26. Improving the efficiency of drug resistant tuberculosis treatment trials: a time-to-event alternative marker for bacteriological response and adaptive minimization for randomization.

BMC Med Res Methodol. 2025 Nov 25;25(1):265. doi: 10.1186/s12874-025-02697-w.

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BACKGROUND: Establishing the efficacy of new treatments for rifampicin-resistant tuberculosis (RR-TB) is challenging due to the long-term clinical endpoints of two-year relapse-free survival. This study aimed to evaluate the effect of an alternative indicator of treatment response on sample size requirements and the use of a minimization strategy for randomization.
METHODS: Sample size estimates were compared when based on the commonly used endpoint of the proportion of patients achieving stable culture conversion (SCC) at 12 weeks versus a novel but corresponding indicator of treatment response based on a model of changes in mycobacterial load (MBL) over time. The non-linear mixed effects model, calibrated using data from a RR-TB cohort in the same setting, included a longitudinal MBL decline, a probabilistic component for mycobacteria presence in sputum, and a time-to-event model for culture positivity. Data were simulated for a prespecified treatment effect to compare the power of detecting the treatment effect for various sample sizes when using the commonly used endpoint and alternative indicator of treatment response. Additionally, the impact of random patient allocation versus a minimization strategy for randomization on covariate imbalance was assessed.
RESULTS: To achieve 80% power, 410 individuals were needed using the commonly used endpoint versus 110 participants when using the non-linear mixed effects model, corresponding to a 73% reduction in sample size. A small sample size results in high baseline covariate imbalance with random treatment group allocation, with a median relative imbalance of 0.104 for 110 participants versus 0.053 for 410 participants. This imbalance was reduced to 0.036 for 110 participants when an adaptive minimization procedure was implemented.
CONCLUSION: Using a model of mycobacterial burden changes over time as an alternative indicator of treatment response, combined with a minimization procedure during the randomization process, significantly reduced the sample size which could, if validated, enhance the efficiency of RR-TB clinical trial design.

DOI: 10.1186/s12874-025-02697-w
PMCID: PMC12649012
PMID: 41291526 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The SMARTT trial received ethical approval from the ethics committees of the University of the Free State Health Sciences Research Ethics Committee (UFS-HSD2019/0364/2004), Stellenbosch University Health Research Ethics Committee (N19/07/100), and the University of Antwerp (21/18/239). Written, informed consent to participate was obtained from all piloting participants. The EXIT-RIF study was approved by the Human Research Ethics Committee of the University of the Witwatersrand in South Africa (M111139) and the Institutional Review Board of the University of North Carolina at Chapel Hill in the United States (11-2273) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Approval of study activities was obtained from relevant health authorities. Participants gave verbal consent by phone (recorded). Waiver of consent was obtained for patients who had died or were LTFU from TB care prior to study enrolment and could not be contacted despite multiple attempts. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

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27. Mathematical model analysis of drug resistance TB dynamics with immigrants and impact of media efficiency.

Sci Rep. 2025 Nov 27;15(1):42375. doi: 10.1038/s41598-025-26270-z.

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Tuberculosis (TB) is a deadly and contagious disease that can be found all over the world. The purpose of this research is to analyze the dynamics of drug-resistant tuberculosis (DR-TB) involving infected individuals and media efficacy. Moreover, the study investigates the impact of media efficiency and immigration on TB disease transmission, as well as the role of early treatment and immunity enhancement in controlling the spread of the disease. In this paper, well-posedness (the boundedness and positivity) of the solutions of the mathematical model is verified to make the mathematical model biologically meaningful. To characterize the stability of the disease locally and globally, both TB-free and endemic equilibrium points were computed. The basic reproduction number of the model is constructed to reveal the dynamics of TB distribution and to help public health officials design effective strategies to control and prevent both the DS-TB and DR-TB epidemics. The local stability (at both disease-free and endemic equilibrium points) of the mathematical model was also verified by using the Routh-Hurwitz criterion. The local stability of the TB-free and endemic equilibrium points indicates that a bifurcation has occurred, and we have verified its existence using the Castillo-Chavez and Song theorem. The optimal control problem was analyzed using Pontryagin's maximum principle to characterize the protection control, first-line treatment control, and second-line treatment control. We compared our model with and without optimal control and found that the model with control strategies significantly reduced the disease. Sensitivity analysis is also performed to identify the most sensitive parameters, such as the transmission rate [Formula: see text] and media efficiency (m). Numerical simulations are conducted to identify effective combinations of control strategies, demonstrating that the disease can be controlled through these interventions. The study also examined the impacts of media efficiency and migration on TB transmission. Finally, the research concludes with a discussion and summary of the findings.

DOI: 10.1038/s41598-025-26270-z
PMCID: PMC12660975
PMID: 41309726 [Indexed for MEDLINE]

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

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28. Impact of tuberculosis on median survival time and years of potential life lost in patients: A scoping review.

J Clin Tuberc Other Mycobact Dis. 2025 Oct 16;41:100568. doi: 10.1016/j.jctube.2025.100568. eCollection 2025 Dec.

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OBJECTIVE: Tuberculosis significantly affects human health and longevity. We aimed to systematically synthesize studies to summarize the median survival time range and years of potential life lost (YPLL) among tuberculosis patients.
METHODS: We searched Web of Science, PubMed, China National Knowledge Infrastructure, and Wanfang Data from inception to October 1, 2024. Studies reporting median survival time or YPLL in patients with drug-susceptible or drug-resistant tuberculosis were included, mostly involving adult participants. Two reviewers independently screened studies and extracted data. Any disagreements were resolved by consensus or by arbitration from a third reviewer.
RESULTS: A total of 22 studies were incorporated into this analysis. Patients with multidrug resistant tuberculosis (MDR -TB) had a median survival of 1.9-7.6 years (indexed from diagnosis), compared with 2.9-6.5 years for extensively drug-resistant tuberculosis (XDR-TB) and 2.0-8.0 years for Non- MDR -TB. Notably, untreated MDR -TB patients presented with particularly unfavorable survival outcomes. Patients coinfected with HIV and tuberculosis (TB/HIV) consistently showed very short survival times, whereas individuals with pneumoconiosis but without tuberculosis had substantially longer survival compared to those with both conditions. Life expectancy estimates revealed that TB/HIV coinfection reduced life expectancy at age 30 to between 4.2 and 21.6 years, in stark contrast to over 35.0 years in individuals with HIV but without tuberculosis. Years of potential life lost analyses indicated that patients with active tuberculosis lost 4.9-15.8 years of potential life, compared to 1.3 years for those with latent tuberculosis infection (LTBI). TB/HIV coinfection further amplified this burden, with losses reaching up to 16.3 years. Using a fixed age cut-off of 69 years, patients with tuberculosis lost an average of 39.1 years of potential life compared with 24.5 years among non-TB controls.
CONCLUSION: Most studies suggest that tuberculosis shortens survival and increases potential years of life lost, particularly in patients with drug-resistant tuberculosis, TB/HIV coinfection, or untreated tuberculosis, although there is important variation by patient group and study method. Early diagnosis and appropriate treatment may help reduce life loss and improve life expectancy.

DOI: 10.1016/j.jctube.2025.100568

PMCID: PMC12554181
PMID: 41146646

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

29. Active case finding for tuberculosis among Ukrainian soldiers by German armed Forces.

Eur Respir J. 2025 Dec 18;66(6):2500728. doi: 10.1183/13993003.00728-2025. Print 2025 Dec.

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Estimated TB incidence rate was 168/100 000. Our screening approach still underestimates incidence. Majority did not present with symptoms. WGS is helpful in confirming phenotypic DST, guiding successful treatment decisions, and to exclude transmission. https://bit.ly/47beg0z

Tuberculosis (TB) remains a public health threat in Ukraine, with 20 991 persons with TB reported in 2023, and an estimated incidence of 112 per 100 000 persons [1, 2]. Drug-resistant TB (DR-TB) is of concern: 27% of newly diagnosed TB infections in Ukraine were caused by Mycobacterium tuberculosis carrying resistance to rifampicin, or rifampicin and isoniazid (multidrug-resistant TB (MDR-TB)). Additionally, 27% of these isolates exhibited additional resistance to fluoroquinolones (pre-XDR-TB) or combined fluoroquinolone and bedaquiline and/or linezolid resistance, thus classified as extensively drug-resistant TB (XDR-TB) [1].

DOI: 10.1183/13993003.00728-2025
PMCID: PMC12713385
PMID: 41198397

Conflict of interest statement: Conflict of interest: The authors have no potential conflicts of interest to disclose.

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30. Real-world safety profile of novel anti-multidrug-resistant tuberculosis drugs: a disproportionality analysis based on the FAERS database.

BMJ Open. 2025 Dec 7;15(12):e096515. doi: 10.1136/bmjopen-2024-096515.

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OBJECTIVES: Bedaquiline (BDQ), delamanid (DLM) and pretomanid (Pa) were widely used in recent years. This study aimed to analyse adverse drug event (ADE) reports associated with them based on the Food and Drug Administration Adverse Event Reporting System (FAERS) database, to explore the signals of ADEs and provide reference for clinical use.
DESIGN: A retrospective pharmacovigilance study.
SETTING: The FAERS database was extracted from 2015 to 2023, and the ADE reports about BDQ, DLM, and Pa were collected.
MAIN OUTCOME MEASURES: Data mining was carried out on relevant reports of BDQ, DLM, and Pa using the reporting odds ratio (ROR), proportional reporting ratio (PRR), medicines and healthcare products regulatory agency (MHRA) and the information component (IC).
RESULTS: A total of 4010 ADE reports were included: 2477 for BDQ, 1360 for DLM and 173 for Pa. Combined with disproportionality analysis in different backgrounds, the salient risks of three target drugs varied. In the entire dataset, prolonged ECG QT (BDQ: ROR=42.57; DLM: ROR=28.00; Pa: ROR=20.45), hepatitis toxic (BDQ: ROR=28.65; DLM: ROR=21.42; Pa: ROR=90.67), bilirubin conjugated increased (BDQ: ROR=14.40; DLM: ROR=14.56; Pa: ROR=53.95), increased aspartate aminotransferase (BDQ: ROR=9.10; DLM: ROR=8.83; Pa: ROR=7.77), increased alanine aminotransferase (BDQ: ROR=5.68; DLM: ROR=5.54; Pa: ROR=8.92), drug-induced liver injury (BDQ: ROR=6.51; DLM: ROR=6.24; Pa: ROR=3.61) and anaemia (BDQ: ROR=6.54; DLM: ROR=5.75; Pa: ROR=4.83) remained common risks for them. However, in the other two contexts, only decreased haemoglobin (tuberculosis dataset: ROR=2.15; target dataset: ROR=1.03), which was more pronounced associated with DLM and prolonged ECG QT (tuberculosis dataset: ROR=2.46; target dataset: ROR=1.23), hepatotoxicity (tuberculosis dataset: ROR=1.74; target dataset: ROR=4.03) was more pronounced associated with BDQ, while other ADEs, like pancreatitis (tuberculosis dataset: ROR=4.54; target dataset: ROR=7.36), death (tuberculosis dataset: ROR=5.71; target dataset: ROR=2.47) and multiple organ dysfunction syndrome (tuberculosis dataset: ROR=1.46; target dataset: ROR=2.76), were worthy of attention associated with Pa apart from the common ADEs. The combination of linezolid (LZD) with the target drugs elevated risk signals for hepatotoxicity, haematologic toxicity and neurotoxicity. Subgroup analyses revealed that <45 years exhibit a higher relative risk of hepatotoxicity (increased aspartate aminotransferase, aminotransferase increased, bilirubin conjugated increased and drug-induced liver injury), whereas peripheral neuropathy and decreased haemoglobin were observed in three target drugs. While ≥45 years are at a higher risk of prolonged ECG QT, females exhibited slightly higher signal strengths for hepatitis toxic, anaemia, and acute cardiac failure compared with males. While males aged ≥45 years receiving Pa may be at increased risk for pancreatitis.
CONCLUSION: Our study highlights the differences in common ADEs of BDQ, DLM and Pa, as well as the differences in these ADEs among genders and age groups, providing valuable insights for clinical application.

DOI: 10.1136/bmjopen-2024-096515
PMCID: PMC12684222
PMID: 41360462 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

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31. Clinical evaluation of the diagnostic performances and treatment monitoring of the new PATHFAST TB LAM Ag assay in sputum specimens of patients with tuberculosis or with nontuberculous mycobacteria pulmonary disease.

J Clin Microbiol. 2025 Dec 17;63(12):e0126925. doi: 10.1128/jcm.01269-25. Epub 2025 Nov 26.

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Diagnosing pulmonary tuberculosis (TB) and monitoring treatment remain challenging. New tools such as the PATHFAST TB LAM assay (PHC Corporation, formerly LSI Medience Corporation, Tokyo, Japan; distributed by BioSynex, France; PF-LAM) may complement microscopy, culture, and NAAT. PF-LAM is an immunoassay quantifying lipoarabinomannan (LAM), a mycobacterial cell wall component, in sputum within 1 hour using an automated chemiluminescent reader. Diagnostic performance was first assessed on 100 sputum samples: 40 culture-positive for Mycobacterium tuberculosis complex (MTBC), 40 culture-positive for nontuberculous mycobacteria (NTM), and 20 culture-negative for both. We then tested 61 longitudinal sputum samples from 19 pulmonary TB patients under treatment. Four additional samples from one patient with NTM pulmonary disease (NTM-PD) were also tested. PF-LAM showed 75% sensitivity for MTBC detection, with a strong correlation between LAM concentration and culture time-to-positivity (Spearman $\rho = 0.915$, $P < 0.0001$). Specificity was 95% on

culture-negative specimens. The test was also positive for 26/40 (65%) NTM-culture-positive samples. Notably, 19 of these 26 samples were obtained from NTM-PD patients, yielding 73% sensitivity for NTM-PD detection. The assay's potential for treatment monitoring was demonstrated by significant negative correlations between LAM concentration and (a) treatment duration (ρ=-0.434, P = 0.0012) and (b) time to positive culture (ρ=-0.665, P < 0.0001). PF-LAM is a rapid and easy-to-use test for diagnosing pulmonary TB. While NTM cross-reactivity reduces specificity, it may provide diagnostic value for NTM-PD. Results on monitoring TB treatment are promising as no test is currently available for this indication.
IMPORTANCE: Effective monitoring of the treatment response is essential for successful tuberculosis (TB) management as prolonged therapies require accurate evaluation to prevent relapse, treatment failure, or drug resistance. This study highlights the diagnostic and treatment-monitoring potential of the PATHFAST TB LAM Ag assay, which quantifies lipoarabinomannan (LAM) concentrations in sputum samples and correlates with bacterial load. For the first time, we also demonstrate the assay's applicability for detecting and monitoring nontuberculous mycobacterial (NTM) pulmonary diseases, which are increasingly prevalent in industrialized countries. The semi-automated, rapid format (<17 minutes) of the PATHFAST TB LAM Ag assay provides a simple and reliable approach for assessing bacillary load during treatment, representing a promising tool for improving patient management and diagnostic efficiency in both TB and NTM-PD.

DOI: 10.1128/jcm.01269-25
PMCID: PMC12710305
PMID: 41294343 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

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32. Description of bacterial RNA transcripts detected in Mycobacterium tuberculosis - infected cells from peripheral human granulomas.

Virulence. 2025 Dec;16(1):2547326. doi: 10.1080/21505594.2025.2547326. Epub 2025 Aug 25.

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Update of
bioRxiv. 2024 Aug 20:2024.08.20.608852. doi: 10.1101/2024.08.20.608852.

Mycobacterium tuberculosis (Mtb) remains a global human health threat. However, understanding effects of the microbe on cellular interactions in infected tissue has been hindered by inability to discriminate between infected versus un-infected cells. We included the H37Rv Mtb reference genome when assembling scRNA seq libraries from fine needle aspirate samples of peripheral nodal TB patients. Using the 10X Genomics Cell Ranger tool to align sequencing reads, we consistently detected bacterial small and large ribosomal subunit RNA sequences. We interpret Mtb reads associated with a cell's UMI and transcriptome to indicate infection of that individual host cell. This provides a new window into the status of infected cells in the context of the bystander cells in the infected tissue. We investigated these Mtb transcripts to explore their clinical utility. The Mtb transcripts showed frequent sequence variation from the reference genome, with greater than 90% of the rrs or rrl reads from many clinical samples having at least one sequence difference. The highly conserved nature of the rrs and rrl gene sequences limited the ability to assign bacterial lineage based solely transcriptome analysis. However, rapid improvements in sequencing depth may soon allow transcriptome analysis of infecting microbes and improved certainty regarding their lineage, drug resistance, and virulence factors.

DOI: 10.1080/21505594.2025.2547326
PMCID: PMC12380210
PMID: 40817758 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the authors.

33. ACA kills Mycobacterium tuberculosis and M. bovis by targeting cell wall core assembling protein CpsA.

Commun Biol. 2025 Nov 26;8(1):1706. doi: 10.1038/s42003-025-09107-3.

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Tuberculosis (TB), caused by Mycobacterium tuberculosis, still globally threatens human health. With the emergence of multidrug-resistant strains, there is an imperative need to discover new anti-TB agents and identify novel drug targets. Here, we report that the compound ACA, namely 3-azidothiophene-2-carboxylic acid, can kill M. tuberculosis by targeting the bacterial cell wall core assembling process. Whole-genome sequencing of spontaneous ACA-resistant mutants identified single-nucleotide variants in the cpsA2 ligase gene responsible for the covalent attachment of arabinogalactan and peptidoglycan. The cell wall of cpsA2 or its homolog cpsA1-deleted mutant H37Ra strains show increased permeability and drug sensitivity, which is similar to the ACA-treated mycobacteria. Both cpsA1 and cpsA2 could reverse the resistant phenotype of ACA-resistant mutants and the growth defects of the ΔcpsA1 H37Ra strain. ACA can directly bind CpsA1 and CpsA2 to inhibit significantly the pyrophosphatase activity of CpsA1 and CpsA2. Our results suggest that ACA may disturb the cell wall core assembling process and kill M. tuberculosis by targeting CpsA1 and CpsA2, which provide potential candidate drug target for controlling drug-resistant TB.

DOI: 10.1038/s42003-025-09107-3
PMCID: PMC12658130
PMID: 41299017 [Indexed for MEDLINE]

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

34. Person-centred care for people with tuberculosis-associated comorbidities: a multi-country qualitative study.

BMJ Open. 2025 Nov 28;15(11):e106529. doi: 10.1136/bmjopen-2025-106529.

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INTRODUCTION: To contribute to the development of a people-centred global framework for collaborative action on tuberculosis (TB) and comorbidities, a rapid qualitative study on the perspectives of people with lived experience of TB and its associated comorbidities was undertaken.
METHODS: From August to October 2021, TB survivors from high-burden countries, who encountered at least one comorbidity during TB treatment, were interviewed to explore their healthcare experiences and priorities. Thematic analysis drew on a healthcare acceptability model.
RESULTS: Participants (n=24, 13 women) were treated for drug-susceptible (n=13) or drug-resistant (n=11) TB between 2015 and 2021. They faced diverse comorbidities (mental health and substance use disorders, diabetes, Hepatitis C, lupus and HIV); half of whom reported more than one comorbidity, and all faced socioeconomic hardships. TB diagnosis and treatment exacerbated participants' comorbidities and, in the absence of integrated support, precipitated mental health challenges. Four healthcare priorities for addressing TB-associated comorbidities were identified: (1) disclosure and early identification of comorbidities, (2) timely and affordable access to care for comorbidities, (3) tailored counselling and peer support and (4) coordinated and consolidated care for TB and comorbidities.
CONCLUSION: The syndemic manifestation of comorbidities in people affected by TB calls for a people-centred approach to care that facilitates building of trust with multiple care providers, timely linkages to non-TB programmes, access to integrated diagnosis and treatment, allaying intersecting stigmas and self-shame, and care coordination approaches that correspond to people's needs and preferences. These healthcare priorities were included in the WHO's Framework for collaborative action on TB and comorbidities.

DOI: 10.1136/bmjopen-2025-106529
PMCID: PMC12666104
PMID: 41314841 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

35. Impact of HIV and hospitalization on the incidence of subsequent rifampicin-resistant tuberculosis after initiation of first-line tuberculosis treatment: a retrospective cohort study in South Africa.

EClinicalMedicine. 2025 Oct 30;90:103603. doi: 10.1016/j.eclinm.2025.103603. eCollection 2025 Dec.

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BACKGROUND: People living with human immunodeficiency virus (PLHIV) may have a higher risk of acquired rifampicin-resistance during first-line tuberculosis (TB) treatment, potentially driving the multi-drug or rifampicin-resistant tuberculosis (MDR/RR-TB) epidemic. Nosocomial transmission may further elevate MDR/RR-TB risk. We assessed the impact of HIV and hospitalization on subsequent MDR/RR-TB diagnosis among individuals starting first-line TB treatment.
METHODS: The retrospective cohort included individuals with laboratory-confirmed rifampicin-susceptible TB (RS-TB), who started TB treatment (2013-2021). Subsequent TB diagnoses (MDR/RR-TB and RS-TB) over 2 years' follow-up from TB treatment initiation were assessed. Routine health service data utilized.
FINDINGS: A total of 190,945 individuals were included; median age 34.0

(interquartile range (IQR), 25.5-44.9); 79,160 (42%) female and 69,636 (37%) PLHIV. Overall, 6870 (9.9%) PLHIV and 9342 (7.7%) HIV-negative individuals were diagnosed with recurrent TB within 24 months. Rifampicin drug susceptibility testing was available for 5354 (77.9%) and 8154 (87.3%) PLHIV and HIV-negative individuals, respectively. PLHIV with advanced HIV (cluster of differentiation 4 (CD4) <200 cells/μl) (adjusted-hazard ratio (HR) 2.86, 95% confidence interval (CI), 2.60-3.15) and individuals hospitalized (adjusted-HR 2.76, 95% CI, 2.50-3.05) for ≥1 week had significantly increased MDR/RR-TB risk compared to HIV-negative and non-hospitalized individuals, respectively. PLHIV had a higher risk of MDR/RR-TB relative to all other recurrent TB, regardless of CD4.
INTERPRETATION: This study suggests that PLHIV may have an increased risk of both acquiring rifampicin-resistance during TB treatment and re- or super-infection with already resistant Mycobacterium tuberculosis strain during hospitalization. While not causal, these data suggest the need for improved TB treatment for PLHIV including tailored drug regimens, potentially with increased rifampicin dosages, and emphasize the importance of TB infection control in healthcare settings.
FUNDING: The study received no funding.

DOI: 10.1016/j.eclinm.2025.103603
PMCID: PMC12613042
PMID: 41245538

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

36. Structural isomerisation affects the antitubercular activity of adamantyl-isoxyl Adducts.

J Enzyme Inhib Med Chem. 2025 Dec;40(1):2502600. doi: 10.1080/14756366.2025.2502600. Epub 2025 May 21.

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Despite efforts to discover effective treatments to eradicate tuberculosis (TB), it remains a global threat. The increase in drug-resistant bacterial species has made the discovery of new drugs highly coveted. The utilisation of previous efficacious structures is one approach that can be employed to developing novel series of compounds to combat this ever-growing problem. This study sought to re-examine two such compounds, isoxyl (ISO) and SQ109, previously shown to be efficacious in TB treatment. SQ109-ISO hybrid compounds were shown to have demonstrable activity against both drug-sensitive and drug-resistant Mtb whilst displaying limited toxicity in vitro in comparison to other antitubercular agents. Indications from our genetic and biochemical studies suggest that these structurally similar pharmacophores bind to different proteins within Mtb, highlighting the need for careful consideration when producing regioisomeric analogues and that the utilisation of previous efficacious structures is a valid approach to developing promising novel drugs against Mtb.

DOI: 10.1080/14756366.2025.2502600
PMCID: PMC12096669
PMID: 40396606 [Indexed for MEDLINE]

Conflict of interest statement: The authors report no conflicts of interest.

37. An assessment of video-observed treatment as an adherence support tool for patients with drug-resistant TB.

IJTLD Open. 2025 Dec 10;2(12):763-768. doi: 10.5588/ijtldopen.25.0370. eCollection 2025 Dec.

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BACKGROUND: In 2017, WHO endorsed digital adherence technologies, including video-observed treatment (VOT), to support TB treatment adherence. In 2021, Eswatini implemented VOT to support adherence for drug-resistant TB (DR-TB) patients nationwide, although limited evidence exists regarding its feasibility and acceptability in low-resource settings.
METHODS: We conducted 33 in-depth interviews with DR-TB patients and health care providers (HCPs), across all four regions of Eswatini to explore their experiences with VOT.
RESULTS: The findings indicated broad acceptance of VOT among both HCPs and patients. HCPs reported that VOT strengthened their connection with patients, facilitated adherence, and increased their confidence in treatment outcomes. While most patients found VOT user-friendly and appreciated the independence and privacy it offered, elderly patients faced challenges using smartphones, which sometimes resulted in poor-quality video submissions.
CONCLUSION: VOT is feasible and acceptable among HCPs and patients in Eswatini. Further research is needed to evaluate the impact of VOT on treatment outcomes in high-burden and low-resource settings to inform the scale-up of similar digital health interventions in comparable contexts. Strengthening digital infrastructure and providing tailored support for elderly patients could further enhance VOT effectiveness and equity.

DOI: 10.5588/ijtldopen.25.0370
PMCID: PMC12699967
PMID: 41395321

Conflict of interest statement: Conflicts of interest: none declared.

38. Evaluation of T-NGS, Xpert Ultra, and Line Probe Assay on Clinical Samples for the Diagnosis of Drug-Resistant Pulmonary Tuberculosis in Rio de Janeiro.

Rev Soc Bras Med Trop. 2025 Dec 15;58:e03582025. doi: 10.1590/0037-8682-0358-2025. eCollection 2025.

Bhering M, Ribeiro EP, Silveira AK, Lalucha C, Ribeiro EO, Igreja T, Pôrto LC, Secco D, Silva PEAD, Viveiros M, Oliveira M, Kritski A.

BACKGROUND: The rapid detection of drug resistance in Mycobacterium tuberculosis is essential for managing drug-resistant tuberculosis (DR-TB). This study evaluated the performance of molecular assays compared to phenotypic drug

susceptibility testing (pDST) and targeted next-generation sequencing (T-NGS).
METHODS: We retrospectively analyzed 40 presumptive pulmonary DR-TB cases in Rio de Janeiro from 2018 to 2022. Xpert MTB/RIF Ultra (Xpert Ultra) and Line Probe Assay (LPA; MTBDRplus = LPA-1, MTBDRsl = LPA-2) were performed directly on clinical respiratory specimens, with pDST serving as the reference standard. T-NGS was used to identify resistance mutations and clarify discordant results.
RESULTS: Most samples (92.5%) were smear-positive. Xpert Ultra and LPA-1 demonstrated high sensitivity for detecting resistance to rifampicin (91.7% and 89.3%, respectively). However, LPA-1 exhibited lower sensitivity for isoniazid (81.5%). The performance of LPA-1 decreased in samples with cycle threshold (Ct) values ≥16, indicating low bacterial load ($p = 0.001$). T-NGS detected resistance to fluoroquinolones (22.5%) and injectables (15-20%) that was missed by LPA-2 and MGIT. Mixed infections were identified in 17.5% of samples and accounted for 27.8% of discordant results. Isoniazid heteroresistance was detected in 32.5% of samples by LPA-1 and in 7.5% by T-NGS.
CONCLUSIONS: Xpert Ultra and LPA-1 are effective for the rapid detection of rifampicin resistance but have limitations for isoniazid and second-line drugs. T-NGS improved the detection of low-level resistance, heteroresistance, and mixed infections, supporting its implementation in reference laboratories for comprehensive DR-TB diagnosis.

DOI: 10.1590/0037-8682-0358-2025
PMCID: PMC12707747
PMID: 41417345 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflicts of interest.

39. Effect of Isoniazid Resistance on Treatment Outcome Among People With Pulmonary Tuberculosis in Korea.

J Korean Med Sci. 2025 Dec 8;40(47):e313. doi: 10.3346/jkms.2025.40.e313.

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BACKGROUND: Isoniazid resistance is the most common type of ant-tuberculosis drug resistance, which is often neglected in clinical practice. This study aimed to evaluate the impact of isoniazid mono-resistant tuberculosis (Hr-TB) on the treatment outcomes of people with pulmonary tuberculosis.
METHODS: People with pulmonary tuberculosis were enrolled from the Korea Tuberculosis Cohort (KTBC) registry and the multicenter prospective cohort study of pulmonary tuberculosis (COSMOTB). Isoniazid resistance was confirmed using drug susceptibility test results. The primary outcome was an unfavorable outcome, which defined as comprising death, failure, loss-to-follow-up, still-on-treatment, and not-evaluated. Logistic regression analysis was conducted to evaluate effect of isoniazid resistance on treatment outcomes. We also compared 2-month sputum negative culture conversion rate and incidence of adverse events between Hr-TB and drug-susceptible tuberculosis.
RESULTS: From the KTBC and COSMOTB databases, 10,482 and 758 participants were included, respectively. Compared to drug-susceptible tuberculosis, Hr-TB had higher rates of unfavorable outcome in the KTBC (45.8% vs. 37.0%, $P < 0.001$) and COSMOTB (31.5% vs. 17.9%, $P = 0.014$). Multivariable logistic regression analysis showed significant association between isoniazid resistance and unfavorable outcome in the KTBC (adjusted odds ratio [aOR], 1.43; 95% confidence interval [CI], 1.24-1.65) and in the COSMOTB (aOR, 1.98; 95% CI, 1.02-3.85). Additional analyses on COSMOTB data showed that Hr-TB had more serious adverse drug reactions, while 2-month sputum culture conversion rates did not differ significantly.
CONCLUSION: Isoniazid resistance is significantly associated with unfavorable clinical outcomes.

DOI: 10.3346/jkms.2025.40.e313
PMCID: PMC12685575
PMID: 41365553 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no potential conflicts of interest to disclose.

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40. Actively Targeted Nanoparticles for Enhanced Diagnosis, Treatment, and Vaccination of Tuberculosis: A Systematic Review.

Int J Nanomedicine. 2025 Dec 2;20:14343-14374. doi: 10.2147/IJN.S557784. eCollection 2025.

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Tuberculosis (TB) remains a leading cause of morbidity and mortality worldwide, hampered by prolonged, toxic treatment regimens that lead to poor patient adherence and drug resistance, as well as diagnostic tools that lack sensitivity and specificity. This systematic review evaluates recent advancement in actively targeted nanoparticle (NP) systems designed to improve TB diagnosis, treatment, and vaccination. Peer-reviewed studies published after 2015 focusing on NPs with active targeting capabilities were analyzed. The findings show that: ligand-functionalized NPs achieve precise, receptor-mediated targeting of infected cells, enhancing therapeutic efficacy; integrating diagnostic elements into these platforms enables rapid, sensitive biomarker detection; and antigen-loaded NPs effectively modulate immune responses, showing significant promise for novel vaccine development. Therefore, actively targeted NPs represent a transformative platform to overcome critical limitations in TB care by offering a unified strategy to improve diagnostic accuracy, therapeutic outcomes, and vaccine-induced immunity.

DOI: 10.2147/IJN.S557784
PMCID: PMC12681205
PMID: 41356707 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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41. Symptom-Based Active Tuberculosis Screening in Two Nigerian Correctional Facilities: A Cross-Sectional Study.

Infez Med. 2025 Dec 1;33(4):382-390. doi: 10.53854/liim-3304-3. eCollection 2025.

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BACKGROUND: Tuberculosis (TB) remains a pressing health challenge in Nigerian correctional facilities, where the prevalence can be ten times higher than in the general population. Many facilities rely on passive TB case detection, often missing asymptomatic TB cases. This study evaluated a systematic active case-finding (ACF) approach using symptom-based screening followed by GeneXpert MTB/RIF testing across two high-volume Nigerian correctional facilities in Lagos and Ogun States.
METHODS: Between April and September 2021, 2,244 inmates underwent standardized TB symptom screening (e.g., cough ≥2 weeks, weight loss, fever). Individuals with presumptive symptoms of TB provided sputum for GeneXpert analysis. The intervention comprised three strategies: (1) outreach screening in awaiting-trial mass cells, (2) cell-to-cell active case search, and (3) contact tracing of confirmed TB cases. Collected data were analysed to determine detection rates per 100,000 inmates and the overall positivity yield. Ethical clearance was obtained from the Lagos and Ogun State Ministries of Health, with formal permission granted by authorities of correctional facilities.
RESULTS: Of the 2,244 inmates screened, 678 were identified as presumptive and tested, 45 were confirmed TB cases with estimated prevalence of 0.5% (approximately 489 per 100,000 inmates). The estimated prevalence is more than double the national prevalence 0.2% (219 per 100,000). The overall TB positivity rate among presumptive inmates was 7%. Inmates from Lagos recorded a TB point prevalence of 500 per 100,000, while prevalence in Ogun state was 458 per 100,000. A targeted outreach in one facility achieved a 32% TB yield. All detected TB cases were rifampicin-sensitive, and no drug-resistant strains was found in this cohort.

CONCLUSIONS: These findings highlight the effectiveness of symptom-based GeneXpert screening within correctional facilities which was substantially higher that conventional passive TB detection rates. All confirmed TB cases (n = 45) were rifampicin-sensitive, and no MDR or XDR strains were identified, an important observation in the prison environment. Regular, systematic ACF, especially in overcrowded and high-turnover environments, can significantly enhance early TB diagnosis and treatment initiation. Policymakers should institutionalize routine ACF in correctional facilities through universal entry screening for all new admissions and at least annual facility-wide screening, with symptom checklists plus rapid molecular testi. Where feasible, this should be combined with portable digital CXR/CAD triage alongside improvement in living conditions and post-release linkage to DOTS.

DOI: 10.53854/liim-3304-3
PMCID: PMC12695161
PMID: 41384160

Conflict of interest statement: Conflict of interest: There is no conflict of interest.

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42. Triple-synergy bactericidal action: a mannose-decorated bioinspired coating on silver-mesoporous silica for eradicating multidrug-resistant Mycobacterium Tuberculosis.

RSC Adv. 2025 Nov 24;15(54):46266-46276. doi: 10.1039/d5ra07047c. eCollection 2025 Nov 24.

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Tuberculosis, the world's leading cause of death from a single infectious agent in 2023, is exacerbated by the rising prevalence of multidrug-resistant (MDR) Mycobacterium tuberculosis, underscoring an urgent need for novel therapeutic agents. In this study, we developed a green in situ synthesis strategy for silver nanoparticles (Ag NPs) utilizing polydopamine (PDA) as a biomimetic reducing and coating agent on mesoporous silica (SBA-15). The material was further co-coated with the antimicrobial polymer epsilon-poly-l-lysine (EPL) and functionalized with mannose via a Schiff-base reaction. The resulting composite, denoted as Ag@SBA-15/Man-PDA-EPL, was comprehensively characterized by physicochemical techniques and exhibited low cytotoxicity. Mycobacterium tuberculosis (H37Rv and MDR) was used for the evaluation of the prepared nanocomposites in which the components (Ag@SBA-15/PDA and EPL) exhibited synergistic effect towards MDR. The mannose-grafted composite (Ag@SBA-15/Man-PDA-EPL) exhibited significantly enhanced anti-tubercular efficacy compared to its non-functionalized counterpart (Ag@SBA-15/PDA-EPL), an improvement attributed to the antibacterial capability conferred by the Schiff-base formation. Transmission electron microscopy (TEM) imaging confirmed extensive cellular damage in mycobacteria treated with Ag@SBA-15/Man-PDA-EPL. This study validates a rational combination strategy integrating silver nanoparticles, EPL, and ligand-specific targeting via a Schiff-base moiety into a unified nanoplatform, offering a promising approach to combat drug-resistant tuberculosis and mitigate nosocomial infections.

DOI: 10.1039/d5ra07047c
PMCID: PMC12643096
PMID: 41293293

Conflict of interest statement: The authors declare no conflict of interest.

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43. Laboratory strengthening strategies to advance drug susceptibility testing for BPaL regimens in TB treatment.

Public Health Action. 2025 Dec 3;15(4):145-148. doi: 10.5588/pha.25.0014. eCollection 2025 Dec.

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BACKGROUND: To support BPaL (bedaquiline [Bdq], pretomanid [Pa] and linezolid [Lzd]) rollout, countries require ongoing technical and policy support for standardized drug susceptibility testing (DST).

METHODS: The Leveraging Innovation for the Faster Treatment of Tuberculosis (LIFT-TB) operational research project aimed to strengthen laboratory capacity for DST in 7 countries (the Philippines, Myanmar, Indonesia, Vietnam, Uzbekistan, Kyrgyzstan and Ukraine) through needs assessments, reagent and equipment support, quality control and training.
RESULTS: During the project, we trained 157 professionals in phenotypic and molecular DST, enhancing quality assurance and implementation. We found there was variable DST capacity and resistance patterns.
CONCLUSION: Our study highlights the need for continued investment in training and infrastructure to integrate DST into routine diagnostics and to support scale-up of BPaL regimens in high TB-burden settings.

DOI: 10.5588/pha.25.0014
PMCID: PMC12687124
PMID: 41376683

Conflict of interest statement: Conflicts of interest: none declared.

44.Clinical standards for antimicrobial stewardship in TB care.

IJTLD Open. 2025 Dec 10;2(12):716-726. doi: 10.5588/ijtldopen.25.0522. eCollection 2025 Dec.

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BACKGROUND: While antimicrobial stewardship (AMS) is essential for combating antimicrobial resistance (AMR), TB-specific AMS strategies remain poorly defined.
METHODS: An international panel of 62 experts participated in a Delphi process. Using a 5-point Likert scale (5 = strong agreement; 1 = strong disagreement), participants evaluated 10 draft clinical standards developed by a core coordination team. A standard was adopted if ≥90% of respondents rated it three or higher, according to a predefined consensus threshold.
RESULTS: All 10 standards reached the consensus threshold and were adopted: Standard 1, integration of TB into national AMR action plans; Standard 2, implementation of TB surveillance systems; Standard 3, education of health care providers, individuals affected by TB, and the public; Standard 4, integration of TB into AMS activities; Standard 5, establishment of expert consultation services; Standard 6, targeted testing and preventive treatment for individuals at risk for TB; Standard 7, access to timely and comprehensive drug susceptibility testing; Standard 8, prioritisation of efficacy, safety, and resistance prevention in TB treatment regimens; Standard 9, clinical and microbiological monitoring of treatment response; and Standard 10, assessment of adherence, drug exposure, and resistance in treatment failure.
CONCLUSION: These clinical standards aim to support clinicians, programme managers, and public health authorities in implementing effective, TB-specific AMS strategies.

DOI: 10.5588/ijtldopen.25.0522
PMCID: PMC12699960
PMID: 41395320

Conflict of interest statement: Conflicts of interest: OWA serves as Secretary of Assembly 10 of the European Respiratory Society (unpaid role). DMC reports honoraria from Roche, Germany (2025), and receipt of LAM tests from SD Biosensor for a trial in Italy. RD serves as Chair of Assembly 10 of the European Respiratory Society (unpaid role). JSF serves as President-elect of the European Society for Clinical Microbiology and Infectious Diseases and as a non-executive Board member of the UK Health Security Agency. SHG serves on the Data Safety Monitoring Board for the TB Alliance. EG is former President of the Board of Médecins Sans Frontières (MSF) Norway and is a Board member of the Operational Centre Brussels (MSF). OK received free registration for the ERS Congress 2025 (Amsterdam) and is expected to have registration covered for the ERS Respiratory Infections 2025 course. She serves as unpaid Chair of the ERS 10.2 Group on Tuberculosis and Non-Tuberculous Mycobacterial Diseases. CL provided consultancy services to Insmed, a company producing liposomal amikacin as an inhalative suspension for the treatment of NTM-PD. He received speakers' honoraria from Insmed, Gilead, AstraZeneca, and GSK. CL is a member of the Data Safety Monitoring Board for trials conducted by Médecins Sans Frontières. TL serves as unpaid President of the European Society of Mycobacteriology and holds bound pension funds. LNQV provided consultancy to the Stop TB Partnership for TB REACH proposal review and received travel support from the World Health Organization and the Stop TB Partnership for meeting attendance. He serves as President of the Freundeskreis für Internationale Tuberkulosehilfe and as Treasurer of the International Union Against Tuberculosis and Lung Disease. LNQV is an individual shareholder of Johnson & Johnson. GBM serves as Board member and President of the International Union Against Tuberculosis and Lung Disease. MM received fees from the Combating Antibiotic Resistant Bacteria (CARB-X) initiative for review committee work on applications relating to rapid diagnostic tests. He serves as an unpaid member of the Scientific Advisory Board for the Global Antibiotic Research and Development Partnership (GARDP) and for the Vivli Open AMR Register. CM received honoraria for lectures or presentations from Insmed Inc. and Menarini Hellas. He received travel support from Menarini Hellas and Ariti S.A. DW received consulting fees from Pfizer for participation in the Hospital NTM Virtual Advisory Board (2022) and travel support from Publi CREATIONS S.A.M. through an unrestricted grant from Insmed for the MAC PaLTO Consensus Conference, Milan, 2023. J-JY serves as a member of the Data Safety Monitoring Board for the PanACEA–DECODE study sponsored by LigaChem Biosciences, Inc. (since 24 September 2020) and for the CTP-QTP101-003 study sponsored by Quratis (since 21 May 2024). VC is a shareholder of Johnson & Johnson. IE-W is an employee and stockholder of Johnson & Johnson. Johnson & Johnson holds patents for the anti-tuberculosis medication bedaquiline. SHP serves as an unpaid Board member of the Israeli Society for Tuberculosis and Mycobacterial Diseases. CR received speaker honoraria from BD, bioMérieux, and Cepheid. DJS serves on the Data and Safety Monitoring Board for RID-TB, a study on diagnosis and treatment of latent TB infection run by University College London, and on the Clinical and

Ethical Advisory Board for EUSAT-RCS, a consortium on TB diagnosis and treatment in Peru led from Radboudumc in the Netherlands. Both roles are unpaid. ST is an unpaid member of the conference steering committee of the International Union Against Tuberculosis and Lung Disease (The Union). He is a shareholder and employee of GSK. JvI received a lecture honorarium from Insmed, Inc., paid to his institution. He is an inventor on a patent for tigecycline inhalation held by his institution. JvI serves on the advisory board for MannKind.

45. A rapid systematic scoping review of the levels of bacterial antimicrobial resistance and antibiotic use among people in contact with the criminal justice System.

JAC Antimicrob Resist. 2025 Dec 4;7(6):dlaf222. doi: 10.1093/jacamr/dlaf222. eCollection 2025 Dec.

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BACKGROUND: Antimicrobial resistance (AMR) poses a significant public health threat. Individuals in contact with the criminal justice system, including individuals in custody, prisons, jails or youth offending institutions, may be particularly vulnerable due to living conditions, behaviours and pre-existing health issues. This review assesses bacterial AMR and antibiotic use in this population.
METHODS: A rapid systematic scoping review was conducted (OSF: https://doi.org/10.17605/OSF.IO/XHCFJ). Embase, Medline and Scopus were searched for studies published between 1 January 2010 and 28 September 2023. One author screened all records, with 10% dual screened. Included studies examined AMR bacteria or antibiotic use among people in contact with the criminal justice system (including people in custody, prisons, jails or youth offending institutes). Study quality was assessed using the Newcastle-Ottawa Scale and STROBE AMS checklist. Findings were synthesized narratively as evidence was limited and heterogeneous, which prohibited planned meta-analyses.
RESULTS: Sixteen papers met inclusion criteria; eight were at lower risk of bias. Three studies examined antibiotic use, reporting common inappropriate prescribing (n = 1) and associations between recent antibiotic use and resistant infections (n = 2). Fourteen papers reported AMR findings, most with a focus on Mycobacterium tuberculosis and Staphylococcus aureus. Drug-resistant TB prevalence in prison populations ranged from 5.2% to 37% (n = 4). Methicillin resistant Staphylococcus aureus colonization ranged from 8.1% to 8.8% (n = 4). Other bacteria examined included Salmonella spp., Acinetobacter spp., Group A

Streptococcus, and Mycoplasma genitalium.
CONCLUSIONS: People in contact with the criminal justice system face heightened risks of resistant bacterial infections. However, with only three studies addressing antibiotic use, evidence is limited. Addressing AMR in this group requires collaborative and targeted public health interventions.

DOI: 10.1093/jacamr/dlaf222
PMCID: PMC12676007
PMID: 41356143

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46. Experience with Linezolid for the Treatment of Rifampin-Susceptible Tuberculosis in San Francisco.

Open Forum Infect Dis. 2025 Nov 26;12(12):ofaf714. doi: 10.1093/ofid/ofaf714. eCollection 2025 Dec.

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Linezolid is recommended for the treatment of rifampin-resistant tuberculosis (TB), but its role in rifampin-susceptible TB (RS-TB) is less understood. In 45 RS-TB patients treated with linezolid, 8 stopped due to adverse events, most commonly cytopenias. Further research is needed on linezolid efficacy, dosing, and adverse event management in RS-TB.

DOI: 10.1093/ofid/ofaf714
PMCID: PMC12671394
PMID: 41341862

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.

47.Characterization of Drug Resistance Patterns, Mutation Profiles and Prevalence of Mycobacterium tuberculosis in Shaoxing.

Infect Drug Resist. 2025 Dec 9;18:6481-6489. doi: 10.2147/IDR.S570295.
eCollection 2025.

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OBJECTIVE: This study aimed to analyze drug resistance patterns, mutation profiles in Mycobacterium tuberculosis isolates and clinical characteristics of tuberculosis patients in Shaoxing, Zhejiang, China.
METHODS: Clinical specimens and data from tuberculosis patients admitted in 2024 were collected. Cultures were established using the MGIT liquid culture system, and drug susceptibility to twelve anti-tuberculosis agents (four first-line and eight second-line) was assessed by the microbroth dilution method. Mutations in the rpoB gene, katG gene, and inhA promoter were identified using a DNA microarray chip assay.
RESULTS: Among 268 Mycobacterium tuberculosis isolates, 62 (23.1%) exhibited resistance to at least one anti-tuberculosis drug. These comprised 21 (7.8%) mono-resistant, 25 (9.3%) poly-resistant, and 16 (6.0%) multidrug-resistant strains, including 3 (1.1%) classified as pre-extensively drug-resistant and 1 (0.4%) as extensively drug-resistant. Among rifampicin-resistant isolates, mutations at codons 531 (47.4%) and 526 (21.1%) of the rpoB gene were most frequent, while the katG Ser315Thr substitution was detected in 44.8% of isoniazid-resistant strains. Compared with primary cases, re-treated patients were more frequently over 50 years of age, exhibited a higher prevalence of pulmonary cavities, and showed significantly elevated rates of drug resistance ($P < 0.05$).
CONCLUSION: Our findings indicate that although the overall prevalence of drug-resistant tuberculosis in Shaoxing remains low, the resistance patterns are heterogeneous. These results underscore the need for comprehensive drug susceptibility and genetic testing to guide effective treatment strategies.

DOI: 10.2147/IDR.S570295
PMCID: PMC12701658
PMID: 41394331

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

48. In silico analysis of the functional implications of drug resistance associated mutations in Mycobacterium tuberculosis.

Comput Struct Biotechnol J. 2025 Nov 24;27:5425-5440. doi: 10.1016/j.csbj.2025.11.054. eCollection 2025.

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The tuberculosis mutation catalogue published by World Health Organization (WHO) lists a large number of mutations based on the statistical significance of their association with resistance or susceptibility to various drugs. However, the mechanism by which they confer resistance to drugs is often not understood. To address these gaps, we combined known resistance associated mutations from the WHO catalogue and newly discovered mutations by explainable artificial intelligence (XAI). In order to decipher the mechanistic basis of drug resistance, we examined where these mutations occur in three dimensional (3D) structures of key drug targets, measured their proximity to drug binding sites and compared their abundance in drug resistant as well as drug susceptible Mycobacterium tuberculosis (M.tb) strains. In parallel, we analyzed the functions of 112 newly identified drug resistance associated genes and compared them to known resistance genes, finding that most novel genes fall into different functional categories, though six share families with known resistance genes. We mapped coding mutations in all 112 novel genes to their functional domains, predicted 3D structures using Alphafold3 and evaluated their effects on protein stability. Notably, our study highlights that mutations in ribosomal proteins (RpsN1, RpsN2) and the transporter PstB may introduce new resistance mechanisms, such as altered drug interactions or increased drug efflux. Whereas, analysis of non coding mutations revealed that most are located at transcription factor binding sites, potentially affecting gene regulation. The current analysis provides valuable insights for the design of experiments to decode mechanistic basis of drug resistance tuberculosis.

DOI: 10.1016/j.csbj.2025.11.054
PMCID: PMC12703862
PMID: 41404124

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

49. Cerebrospinal fluid penetration of cycloserine/terizidone and clofazimine in patients with pulmonary TB.

Antimicrob Agents Chemother. 2025 Dec 10;69(12):e0093125. doi: 10.1128/aac.00931-25. Epub 2025 Oct 21.

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Tuberculous meningitis (TBM) treatment outcomes are poor, partly due to suboptimal drug penetration into the cerebrospinal fluid (CSF). Little is known about the CSF pharmacokinetics of many TB drugs, both established and new. This study investigated the CSF penetration of cycloserine (administered as terizidone) and clofazimine, two core second-line drugs for drug-resistant tuberculosis (TB). We recruited participants with pulmonary drug-resistant TB, but without TBM, receiving terizidone and/or clofazimine for at least 2 weeks and collected serial plasma samples and a single CSF sample. Drug concentrations were quantified with validated liquid chromatography-tandem mass spectrometry methods. Pharmacokinetic parameters were determined using noncompartmental analysis, and population pharmacokinetic modeling was used to estimate the partition coefficient and equilibration half-life. Data were available from 27 participants, with a median age of 36 (range 20-60) and a weight of 52 kg (30-73 kg), who contributed 216 plasma and 27 CSF samples. The plasma pharmacokinetics of both drugs was in line with previous reports. Terizidone, measured as cycloserine, achieved CSF exposure of 69% relative to plasma, with plasma and CSF concentrations equilibrating with a half-life of 4.7 hours. Clofazimine CSF penetration was 0.13% of plasma exposure, with an equilibration half-life of 55.4 hours. Cycloserine and clofazimine concentrations in CSF approximated their estimated unbound (active) concentration in plasma, thus suggesting good penetration of the unbound drug into the CSF, supporting their potential use in TBM regimens. This study demonstrates a feasible and reproducible method for effective assessment of CSF drug penetration for CNS infections.

DOI: 10.1128/aac.00931-25
PMCID: PMC12691663
PMID: 41118340 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

50. The new thiazolidine-2,4-dione-based hybrids with promising antimycobacterial activity: design, synthesis, biological evaluation, and drug interaction Analysis.

J Enzyme Inhib Med Chem. 2025 Dec;40(1):2442703. doi: 10.1080/14756366.2024.2442703. Epub 2025 Jan 3.

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The ever-increasing drug-resistant tuberculosis (TB) has invigorated the focus on the discovery and development of novel therapeutic agents and treatment options. Thiazolidinone-based compounds have shown good antitubercular properties in vitro. Here, we report the design and synthesis of a number of new derivatives inspired by the structure of thiazolidine-2,4-dione (TZD). The TZD-based hybrids with the thiosemicarbazone or the pyridinecarbohydrazone moiety were synthesised and their antimycobacterial activity was investigated

against the reference H37Rv and two wild Mycobacterium tuberculosis (Mtb) strains. In further studies, a two-drug interaction analysis was also performed for assessing their synergism with the current first-line drugs used for the treatment of TB. It was found that some of the compounds showed high antimycobacterial activity with MICs (0.078-0.283 μM) and a synergistic effect with isoniazid or rifampicin, thereby demonstrating their potential as a promising scaffold for the development of novel coadjuvants for the effective treatment of TB.

DOI: 10.1080/14756366.2024.2442703
PMCID: PMC11703137
PMID: 39749402 [Indexed for MEDLINE]

Conflict of interest statement: The authors report no conflicts of interest.

51. Exploring the role of artificial intelligence toward management of HIV and TB co-infection in Nigeria: a comprehensive narrative review.

Ther Adv Infect Dis. 2025 Nov 24;12:20499361251395916. doi: 10.1177/20499361251395916. eCollection 2025 Jan-Dec.

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Human immunodeficiency virus (HIV) and tuberculosis (TB) co-infection in Nigeria are medical conditions of public health importance because they double the country's and its citizens' burden. Several management measures, including artificial intelligence (AI), are crucial for properly diagnosing and preventing these diseases. This study explores the role of AI in managing HIV and TB co-infection in Nigeria. A comprehensive literature search strategy was developed using the keywords "HIV," "TB," "co-infection," "artificial intelligence," and "Nigeria" across six electronic databases: PubMed, Google Scholar, Cochrane Library, Web of Science, ResearchGate, and African Journals Online. The review focused on articles published between January 2014 and December 2022 to capture recent advancements and trends in AI applications in managing HIV and TB co-infection. Approximately 23%-26% of people with HIV in Nigeria are infected with both TB and HIV. People living with HIV in Nigeria are 26 times more likely to develop TB due to their weakened immune systems. The Early Warning Outbreak Recognition Systems is an AI system used for TB detection that is in practice in Nigeria. However, findings showed that AI models, including deep learning, machine learning, Computer-aided detection, Fuzzy cognitive maps, and Logistic regressions, the Twin model could be helpful in the accurate management of HIV/TB co-infection in Nigeria compared to traditional models, for example, inaccurate classification of radiographs and detection of HIV drug resistance. Despite the importance of AI toward managing these diseases, Nigeria faces challenges, including the unavailability of skilled personnel and AI experts, and the poor quality of the IT infrastructure, which are barriers to integrating AI into healthcare in the country. Strategic collaboration between the Nigerian government, digital health agencies, and healthcare organizations is crucial to implementing AI effectively for the treatment of HIV and TB co-infection in Nigeria. By embracing AI, Nigeria can revolutionize its healthcare system, improve patient outcomes, and address public health challenges such as HIV and TB co-infection.

Plain Language Summary: Artificial intelligence towards management of HIV and TB co-infections in Nigeria • Nigeria has a significant load of HIV/TB co-infection, worsening public health challenges. • Approximately 23% of people with HIV in Nigeria are infected with both TB and HIV. • AI models, including deep learning (DL), machine learning (ML), Computer-aided detection (CAD), Fuzzy cognitive maps (FCMs), and Logistic regressions, are helpful in the accurate management of HIV/TB co-infection. • By embracing AI, Nigeria can revolutionise its healthcare system, improve patient outcomes, and address public health challenges such as HIV and TB co-infection.

DOI: 10.1177/20499361251395916
PMCID: PMC12644435
PMID: 41306468

Conflict of interest statement: The authors declare that there is no conflict of interest.

52. The Phosphate-Specific Transport System Gene pstA1 Contributes to Rifampin Tolerance in Mycobacterium tuberculosis.

bioRxiv [Preprint]. 2025 Nov 25:2025.10.31.685634. doi: 10.1101/2025.10.31.685634.

Danchik C, Anoushka Chinmayi GV, Lee GY, Bader JS, Eoh H, Karakousis PC.

Tuberculosis (TB) caused an estimated 10.8 million new cases and 1.25 million deaths in 2023. Antibiotic tolerance, the ability of bacteria to survive exposure to bactericidal antibiotics without genetic resistance mutations, contributes to the need for prolonged treatment. Targeting antibiotic tolerance mechanisms could promote accelerated clearance of Mycobacterium tuberculosis (Mtb), thereby improving medical adherence. Our previous forward genetic screen for rifampin tolerance genes identified pstA1 , which is involved in phosphate-specific import. The ABC-type transporter permease PstA1 has previously been implicated in Mtb virulence, as mutants lacking this gene exhibit defective survival during phosphate limitation in vitro , in infected macrophages, and in immunocompetent mice. The minimum inhibitory concentration (MIC) of rifampin was not altered in a pstA1 deletion mutant (Δ pstA1), suggesting this difference in susceptibility is not due to antibiotic resistance. Consistent with a role in rifampin tolerance, time-kill assays revealed a shift in the mean duration of killing (2-log reduction) from 1.6 days in wild-type to 1.0 day in Δ pstA1 , and complementation partially restored this phenotype. We found that pstA1 is specifically required for Mtb survival in the absence of exogenous inorganic phosphate and is important for adaptation to growth in culture without detergent, and within macrophages in an interferon-γ-dependent manner. Differential expression analysis revealed that Δ pstA1 exhibited substantial transcriptional reprogramming with 58 differentially expressed genes, including altered expression of metabolic, DNA damage repair, and secretory pathways. PstA1 represents a novel drug target, and inhibitors could serve as adjunctive therapies to shorten treatment times, reducing opportunities for drug resistance emergence.
IMPORTANCE: Tuberculosis remains one of the world's deadliest infectious diseases, causing over a million deaths annually. Current treatment requires months of antibiotic therapy, and poor adherence to these lengthy regimens contributes to the emergence of drug-resistant strains that are increasingly difficult to treat. A major barrier to shorter treatment is antibiotic tolerance, which allows bacteria to survive drug exposure without genetic resistance mutations. This study identifies the phosphate transport component

PstA1 as a critical factor enabling Mycobacterium tuberculosis to tolerate the frontline antibiotic rifampin. Bacteria lacking pstA1 are eliminated more rapidly by rifampin, demonstrating that this transporter actively promotes bacterial survival during treatment. These findings suggest that drugs targeting PstA1 could be combined with standard antibiotics to accelerate bacterial clearance, potentially shortening treatment duration and improving patient adherence. Such adjunctive therapies targeting tolerance mechanisms represent a promising strategy to combat tuberculosis and reduce the global burden of drug-resistant disease.

DOI: 10.1101/2025.10.31.685634
PMCID: PMC12636331
PMID: 41278802

53. Distribution of nontuberculous Mycobacteria among presumptive drug resistance tuberculosis patients from a ministry of health drug resistance surveillance program, in western Kenya.

J Clin Tuberc Other Mycobact Dis. 2025 Aug 19;41:100559. doi: 10.1016/j.jctube.2025.100559. eCollection 2025 Dec.

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INTRODUCTION: Nontuberculous Mycobacteria (NTM) species are emerging pathogens causing Pulmonary diseases with no definitive treatment. Molecular techniques enable characterization and drug resistance profiling, this study sought to determine NTM prevalence, circulating species, and distribution factors among presumptive multidrug-resistant tuberculosis (MDR-TB) patients in western Kenya.
METHOD: Sputum samples were collected between March through October 2022, and transported for testing at Kenya Medical Research Institute (KEMRI) TB laboratory, in Kisumu. The standard NALC-NaOH MGIT culture technique, smear, HAIN AS/CM and NTM drug resistance were carried out.
RESULTS: Of the 155 specimens analyzed, 106 (68.4 %) were males, 41 (26.5 %) HIV

positive, and participants of ages 36-45 years, the majority. An overall NTM prevalence of 99 (63.9 %), of whom 63 (63 %) among males reported. In addition, 11 NTM species identified, with M. intracellulare (44, 44 %).
CONCLUSIONS: High prevalence of NTM species was observed among middle-aged males and HIV negative participants, Kisumu led in distribution (29 %) and among HIV positive. The NTM prevalence among smear negative vs smear positive, was significant a $p < 0.001$, hence adequate TB/HIV integration and management, use of molecular techniques, and accurate identification is critical.

DOI: 10.1016/j.jctube.2025.100559
PMCID: PMC12396555
PMID: 40895129

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

54. Host oxidative stress primes mycobacteria for rapid antibiotic resistance Evolution.

Res Sq [Preprint]. 2025 Dec 4:rs.3.rs-8167376. doi: 10.21203/rs.3.rs-8167376/v1.

Baliga N, Pepper-Tunick E, Srinivas V, Mast F, Li S, Russ S, Hanson W, Zamora A, Wu WJ, Silcocks M, Ha DTM, Dunstan S, Thuong N, Turkarslan S, Aitchison J, Arrieta-Ortiz M.

The rapid emergence of multidrug-resistant Mycobacterium tuberculosis (Mtb) threatens global TB control, yet the mechanisms enabling rapid evolution of drug resistance in Mtb remain poorly understood. Here we reveal that pre-existing mutations in oxidative stress response genes create permissive genomic backgrounds that accelerate high-level isoniazid resistance (INH R) without fitness costs, challenging the paradigm that resistance mutations always precede their fitness compensatory adaptations. Using M. smegmatis mc 2 155 (Msm) as a model, we show that brief exposure to sublethal INH (2× IC 50) enriches for "low-level resistance and tolerance" (LLRT) mutants in a single step. These LLRT mutants, particularly those with ohrR loss-of-function mutations, acquire high-level resistance (> 500× IC 50) at 6-fold higher rates than wildtype, primarily through otherwise-deleterious mycothiol biosynthesis mutations that become tolerable in the oxidative stress-buffered background. Crucially, we demonstrate that sublethal oxidative stress alone, mimicking host immune

pressure, nearly tripled the rate of INH resistance evolution in Msm. Bayesian analysis of 1,578 clinical Mtb isolates from Vietnam confirmed that mutations in oxidative stress response genes were significantly associated with the emergence of INH R strains (p-value = 1.09×10 -7). Independently, reanalysis of genome-wide CRISPRi screens revealed that the OSR network and high Bayes probability genes are functionally associated with treatment escape and survival with multiple antibiotics, including isoniazid, rifampicin, ethambutol, bedaquiline, vancomycin, clarithromycin, linezolid, and streptomycin. Our findings that host-imposed oxidative stress and inadequate drug penetration may synergistically prime Mtb populations for rapid resistance evolution suggest that targeting pre-resistance mechanisms, such as oxidative stress defenses, could help slow the emergence of antibiotic resistance in tuberculosis.

DOI: 10.21203/rs.3.rs-8167376/v1
PMCID: PMC12687858
PMID: 41377970

55. Host oxidative stress primes mycobacteria for rapid antibiotic resistance Evolution.

bioRxiv [Preprint]. 2025 Nov 27:2025.11.19.689367. doi: 10.1101/2025.11.19.689367.

Pepper-Tunick E, Srinivas V, Mast FD, Li S, Russ S, Hanson W, Zamora AD, Wu WJ, Silcocks M, Ha DTM, Dunstan SJ, Thuong TNT, Turkarslan S, Aitchison JD, Arrieta-Ortiz ML, Baliga NS.

The rapid emergence of multidrug-resistant Mycobacterium tuberculosis (Mtb) threatens global TB control, yet the mechanisms enabling rapid evolution of drug resistance in Mtb remain poorly understood. Here we reveal that pre-existing mutations in oxidative stress response genes create permissive genomic backgrounds that accelerate high-level isoniazid resistance (INH R) without fitness costs, challenging the paradigm that resistance mutations always precede their fitness compensatory adaptations. Using M. smegmatis mc 2 155 (Msm) as a model, we show that brief exposure to sublethal INH (2× IC 50) enriches for "low-level resistance and tolerance" (LLRT) mutants in a single step. These LLRT mutants, particularly those with ohrR loss-of-function mutations, acquire high-level resistance (> 500× IC 50) at 6-fold higher rates than wildtype, primarily through otherwise-deleterious mycothiol biosynthesis mutations that become tolerable in the oxidative stress-buffered background. Crucially, we demonstrate that sublethal oxidative stress alone, mimicking host immune pressure, nearly tripled the rate of INH resistance evolution in Msm. Bayesian analysis of 1,578 clinical Mtb isolates from Vietnam confirmed that mutations in oxidative stress response genes were significantly associated with the emergence of INH R strains (p-value = 1.09×10 -7). Independently, reanalysis of genome-wide CRISPRi screens revealed that the OSR network and high Bayes probability genes are functionally associated with treatment escape and survival with multiple antibiotics, including isoniazid, rifampicin, ethambutol, bedaquiline, vancomycin, clarithromycin, linezolid, and streptomycin. Our findings that host-imposed oxidative stress and inadequate drug penetration may synergistically prime Mtb populations for rapid resistance evolution suggest that targeting pre-resistance mechanisms, such as oxidative stress defenses, could help slow the emergence of antibiotic resistance in tuberculosis.

DOI: 10.1101/2025.11.19.689367
PMCID: PMC12699469
PMID: 41394706

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56. Genome graphs reveal the importance of structural variation in Mycobacterium tuberculosis evolution and drug resistance.

Nat Commun. 2025 Nov 28;16(1):10746. doi: 10.1038/s41467-025-65779-9.

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Update of
bioRxiv. 2025 May 07:2025.05.07.652570. doi: 10.1101/2025.05.07.652570.

Structural variants (SVs) are increasingly recognized as key drivers of bacterial evolution, yet their role has not been explored thoroughly. This is due to limitations in traditional short-read sequencing and linear reference-based analyses, which can miss complex structural changes. Tuberculosis (TB), a disease caused by Mycobacterium tuberculosis (Mtb), remains a major global health concern. In this study, we harness long-read sequencing technologies and genome graph tools to construct a Mtb pangenome reference graph (PRG) from 859 high-quality, diverse, long-read assemblies. To enable accurate genotyping of SVs leveraging the PRG, we developed miniwalk, a tool that outperforms a traditional linear genome-based approach in precision for SV detection. We characterize patterns of structural variation genome-wide, revealing a virulence-associated ESX-5 deletion to be recurrent across the phylogeny, and fixed in a sub-lineage of L4. Systematic screens for additional genes that are recurrently affected by SVs implicated those related to metal homeostasis, including a copper exporter fixed in the widely distributed L1.2.1 sub-lineage. Lastly, we genotyped 41,134 isolates and found SVs putatively associated with resistance to various first and second-line drugs. These findings underscore the broader role of SVs in shaping Mtb diversity, highlighting their importance in both understanding evolution and designing strategies to combat drug-resistant TB.

DOI: 10.1038/s41467-025-65779-9
PMCID: PMC12663572
PMID: 41315227 [Indexed for MEDLINE]

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

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57. Adapting global guidelines to local contexts: optimising community-acquired pneumonia (CAP) specific prescribing in Pakistan to counter antimicrobial Resistance.

BMJ Open Respir Res. 2025 Dec 7;12(1):e003699. doi: 10.1136/bmjresp-2025-003699.

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BACKGROUND/OBJECTIVES: Community-acquired pneumonia (CAP) imposes a significant health burden among low- and middle-income countries. The burden is exacerbated by antimicrobial resistance (AMR), often due to inappropriate antibiotic agent use and gaps in antimicrobial stewardship activities. This study aimed to explore physicians' perspectives on the diagnosis, treatment and prevention of CAP in Pakistan, with a focus on how international guidelines are interpreted and adapted to local clinical realities.
METHODS: A qualitative study was conducted using semistructured interviews with 33 purposively selected physicians from various specialties, followed by a focus group discussion with 19 of them. Data were analysed through thematic analysis.
RESULTS: Four cross-cutting themes were identified: (1) selective use of diagnostic agents based on severity and access; (2) pragmatic empiric prescribing influenced by resistance trends and antibiotic availability; (3) stewardship intentions constrained by delayed diagnostics and limited infrastructure and (4) underutilisation of preventive strategies including adult vaccinations due to cost and policy gaps. Physicians were aware of Infectious Diseases Society of America/American Thoracic Society guidelines but adapted them to local challenges and AMR concerns.
CONCLUSIONS: Most physicians were unaware of the exact prevalence of causative pathogens and their resistance patterns in Pakistan due to the unavailability of robust local data. Consequently, international guidelines were adapted to local challenges including resistance patterns, limited diagnostics and resource constraints. Physicians prioritised beta-lactam antibiotics use and restricted moxifloxacin and azithromycin to mitigate resistance propagation linked to multidrug-resistant tuberculosis and extensively drug-resistant typhoid. Efforts to improve antimicrobial utilisation for CAP in Pakistan need to address implementation barriers and focus on enhancing diagnostic access, vaccine coverage and funding for treatment optimisation.

DOI: 10.1136/bmjresp-2025-003699
PMCID: PMC12684091
PMID: 41360615 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

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58. Fifteen years of tuberculosis and HIV diagnostic services in Brazil: disruption, regional disparities, and recovery before, during, and after the COVID-19 Pandemic.

IJID Reg. 2025 Oct 31;17:100796. doi: 10.1016/j.ijregi.2025.100796. eCollection 2025 Dec.

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OBJECTIVES: This study analyzes fifteen years of nationwide trends and regional disparities in tuberculosis (TB) and HIV diagnostics in Brazil, examining the impacts of the COVID-19 pandemic and the uneven recovery of diagnostic services across different regions.
METHODS: This nationwide ecological study analyzed monthly data on TB and HIV diagnostic tests performed in Brazil from 2010 to 2024, utilizing real-world data. Temporal trends and interrupted time-series analyses evaluated the immediate and progressive effects of the COVID-19 pandemic. Spatial patterns and autocorrelation were explored using bivariate Moran's I and Kernel density estimation.
RESULTS: Results showed significant abrupt declines during the COVID-19 pandemic for smear microscopy (-16.4%), culture (-21.4%), and HIV (-16.2%).
Post-pandemic, Xpert MTB/RIF showed the highest monthly increase (+3.8%; 95% confidence interval: 2.9-4.7), while smear microscopy declined (-1.2%; 95% confidence interval: -2.0 to -0.5). Spatial analysis revealed pronounced regional heterogeneity, with Northern and Northeastern municipalities facing the greatest disruptions. The Xpert MTB/RIF test demonstrated greater resilience, with evident growth in its distribution and implementation over time. However,

this increase resulted in a decrease in the conduction of smear microscopy tests and highlighted territorial disparities, since only 167 municipalities (3%) have Xpert MTB/RIF assays, mainly in the Southeast.
CONCLUSIONS: COVID-19 significantly disrupted traditional TB and HIV diagnostics in Brazil, while there was an evident increase and resilience of Xpert MTB/RIF, reducing the use of smear microscopy tests. Policy efforts should prioritize the equitable expansion of molecular diagnostic technologies across all regions. This approach will improve early TB detection and drug resistance testing, thereby reducing diagnostic disparities and strengthening health system resilience toward achieving the End TB Strategy.

DOI: 10.1016/j.ijregi.2025.100796
PMCID: PMC12666353
PMID: 41334286

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

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59. Panduratin A Induces Autophagy Through AMPK Activation Independent of mTOR Inhibition and Restricts Mycobacterium tuberculosis in Host Macrophages.

Mol Microbiol. 2025 Dec;124(6):491-506. doi: 10.1111/mmi.70025. Epub 2025 Sep 26.

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Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains a major global health burden, especially with the increasing prevalence of drug-resistant strains. There is an urgent need for new therapeutics that act via alternative mechanisms. Autophagy, a vital cell-autonomous defense process, allows macrophages to degrade intracellular pathogens such as Mtb and has gained attention as a potential target for host-directed therapy. In this study, we conducted a high-content imaging screen of herb-derived compounds to identify autophagy inducers in RAW264.7 macrophages. Panduratin A (NPA), a natural compound from Boesenbergia rotunda, was found to potently induce autophagy. NPA promoted autophagic vacuole formation in a dose-dependent fashion at low micromolar levels. Its autophagy-inducing effect was validated using RFP-GFP-LC3 dual fluorescence assays and immunoblotting in the presence of bafilomycin A1. Further mechanistic analysis revealed that NPA activates autophagy through AMPK activation, independent of mTOR inhibition. Importantly, NPA significantly promoted intracellular Mtb clearance and increased colocalization of Mtb with autophagosomes and lysosomes, in a manner dependent on Beclin-1. These findings highlight NPA as a potent enhancer of macrophage antimicrobial responses via autophagy, supporting its potential as a candidate for host-directed adjunctive therapy against TB.

DOI: 10.1111/mmi.70025
PMCID: PMC12675973
PMID: 41001742 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflicts of interest.

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60. Differences found in patient profiles and incidence trends between migrants and native-born tuberculosis patients in Ireland: A cross-sectional analysis of national surveillance data, 2011-2021.

IJID Reg. 2025 Sep 15;17:100763. doi: 10.1016/j.ijregi.2025.100763. eCollection 2025 Dec.

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OBJECTIVES: Tuberculosis (TB) remains a global public health threat that was responsible for 1.3 million deaths in 2022 alone. Although Ireland is a low TB incidence country, with crude incidence rates (CIRs) in the Irish-born below six per 100,000 population since 2011, CIRs in the foreign-born population are up to 13 times higher. This study aims to inform TB prevention and care by analyzing the differences in the epidemiology of TB in native-born and foreign-born populations in Ireland.
METHODS: A cross-sectional analysis of all TB notifications reported to the Irish TB Surveillance System from 2011-2021 was performed. Temporal trends in CIRs were analyzed using negative-binomial regression. Independent variables selected with a P-value of <0.25 in univariable analysis were investigated in a multivariable logistic regression model comparing TB patient characteristics between migrants and Irish-born.
RESULTS: Of the 3364 TB patients, 48% were among migrants. Compared with Irish-born, migrants with TB were younger, had higher odds of living with HIV (odds ratio [OR] 3.8, confidence interval [CI] 1.99-7.73), extrapulmonary disease (OR 3.14, CI 2.09-4.79), infection with drug-resistant strains (OR 2.30, CI 1.37-4.01), and residence in congregate residential settings (OR 2.00, CI 1.34-3.05) with lower odds linkage to outbreaks (OR 0.16, CI 0.09-0.28). Recently arrived migrants with TB had higher proportions of international protection applicants and refugees, pulmonary disease, and people living with HIV. Between 2011 and 2021, a significantly declining temporal trend was present for migrants (incidence rate ratio [IRR] 0.96, CI 0.95-0.98), Irish-born (IRR 0.89; CI 0.86-0.92), and total TB patients (IRR 0.95, CI 0.94-0.96). Between 2017 and 2021, a significantly declining temporal trend was still present in Irish-born (IRR 0.76, CI 0.69-0.83) and total patients (IRR 0.91, CI 0.88-0.95), but the trend was no longer significant among migrants with TB (IRR 0.96, CI 0.91-1.01).
CONCLUSIONS: A heightened awareness of extrapulmonary TB within health systems is needed, given the high levels observed among migrants with TB. The pace of TB decline among migrants is no longer significantly declining in the final years of this study period, making TB elimination targets more difficult to achieve. Differences in the epidemiology of TB reported by this study can be used to inform and enhance future TB service provision and promote migrant health.

for Infectious Diseases.

DOI: 10.1016/j.ijregi.2025.100763
PMCID: PMC12547294
PMID: 41143075

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

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61. Eschweilenol C and subfractions from Terminalia plants disrupt haemoglobin metabolism, inhibiting Plasmodium falciparum growth at rings and trophozoite Stages.

Malar J. 2025 Nov 24;24(1):422. doi: 10.1186/s12936-025-05445-z.

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BACKGROUND: The rising prevalence of artemisinin-resistant malaria parasites in Africa underscores the urgent demand for new and effective therapeutic options. Historically, natural products have demonstrated significant anti-Plasmodium efficacy, indicating their potential as a source for malaria drug discovery. Extracts and fractions from Terminalia ivorensis and Terminalia brownii previously exhibited promising anti-Plasmodium potency; however, a thorough assessment of their pharmacodynamics across all asexual blood stages of Plasmodium falciparum and elucidation of their mode of action remains to be conducted. Products from the active fractions of T. ivorensis (TiWEa) and T. brownii (TbMMeOH:Ea) were investigated throughout the asexual-blood and sexual stages of P. falciparum, focusing on their mechanism of inhibition and interaction with some key targets of haemoglobin metabolism.

METHODS: Both active fractions (TiWEa and TbMMeOH:Ea) were fractionated by column chromatography, and the chemical structures of the isolated compound were elucidated through physical and spectroscopic techniques. The resulting compound and subfractions were screened in vitro against P. falciparum strains (Dd2, 3D7, and Dd2-GNF156), stage V gametocytes, and mammalian cells. The pharmacodynamics (stage-specific analysis and killing kinetics) of potent inhibitors were assessed and complemented by the effect on haemozoin formation. The molecular interaction between the potent compound and the two target enzymes was investigated through molecular docking.

RESULTS: The fractionation of TiWEa yielded five subfractions (Ti01, Ti02, Ti03, Ti04, Ti05), while TbMMeOH:Ea yielded three subfractions (Tb01, Tb02, Tb03) along with one compound (01) characterized as eschweilenol C. All Subfractions demonstrated good activity on susceptible and multidrug-resistant strains of P. falciparum (3D7 and Dd2) with an IC50 ranging from 0.15 to 5.73 μg/ml. eschweilenol C equally displayed an IC50 of 490.74 and 379.20 nM, respectively, on PfDd2 and Pf3D7. Two top hits subfractions (Ti03; Ti04) from TiWEa and eschweilenol C from TbMMeOH:Ea exhibited a perfect antiplasmodial profile (IC50 < 1 μg/ml); good selectivity (SI > 10) and demonstrated no spontaneous loss of efficacy when tested against mutant resistant strain (PfDd2-GNF156) of P. falciparum. Ti03, Ti04, and eschweilenol C reduced haemozoin production, exhibited killing activity on ring and trophozoite stages and showed significant binding affinity to PfM1AAP and PfM17LAP.

CONCLUSION: This study identifies eschweilenol C as a promising candidate for malaria drug discovery efforts and its significance for further exploration in the context of the emergence of artemisinin-resistant parasites in Africa.

DOI: 10.1186/s12936-025-05445-z
PMCID: PMC12645700
PMID: 41286749 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The human blood used in this study was collected from a group of volunteers who provided informed consent. The Joint Institutional Review Board for Animal & Human Bioethics (JIRB) approved the protocol at the University of Yaoundé 1, Cameroon under note BTC-JIRB2023-091. All methods were performed in accordance with relevant guidelines and regulations. Competing interests: The authors declare no competing interests.

62. Neoadjuvant personalized viral vaccine prevents tumor relapse in checkpoint-resistant murine melanoma model.

J Immunother Cancer. 2025 Nov 29;13(11):e013035. doi: 10.1136/jitc-2025-013035.

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BACKGROUND: Personalized cancer vaccines targeting tumor-specific neoantigens (nAgs) are an emerging therapeutic strategy, particularly effective in early-stage disease before immune suppression is established. Immune checkpoint inhibitors have demonstrated benefit in the adjuvant setting (postsurgery), and recent evidence suggests neoadjuvant administration (before surgery) may further enhance antitumor immunity. This study evaluated the efficacy of a multiepitope nAg vaccine in a preclinical melanoma model resistant to checkpoint inhibition, comparing neoadjuvant and adjuvant treatment, alone or in combination with anti-programmed cell death protein 1 (PD1) therapy.
METHODS: A viral vector nAg vaccine was developed and administered in the B16F10 murine melanoma model. Mice received the vaccine either before (neoadjuvant) or after (adjuvant) tumor resection alone or in combination with anti-PD1. Tumor recurrence and survival were assessed. Immune profiling was performed to evaluate T cell phenotypes, and CD8+ T cell depletion experiments were conducted to assess the role of this population. Protection against tumor rechallenge was considered to evaluate long-term immunity.
RESULTS: Neoadjuvant vaccination alone provided approximately 70% protection against tumor recurrence. When combined with anti-PD1, protection increased to 90%. Notably, anti-PD1 alone conferred 60% protection when used in a neoadjuvant setting. In contrast, adjuvant vaccination was ineffective as monotherapy and required combination with anti-PD1 to prevent relapse. The efficacy of

neoadjuvant vaccination was dependent on CD8+ T cells and associated with robust effector memory T cell responses. Long-term protection against tumor rechallenge was superior in the neoadjuvant vaccine group compared with anti-PD1 alone.
CONCLUSIONS: Neoadjuvant nAg vaccination elicits potent CD8+ T cell-mediated immunity and offers superior protection against tumor recurrence and rechallenge compared with adjuvant approaches or checkpoint blockade alone. These findings support the clinical evaluation of neoadjuvant cancer vaccines, particularly in settings where tumors are resistant to conventional immunotherapy.

DOI: 10.1136/jitc-2025-013035
PMCID: PMC12666103
PMID: 41320227 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: ES is the founder of Nouscom. AMD, LS, LN, GC, FT, GR, TB, EM, IG, LA are employees of Nouscom.

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63. Characterizing the performance of an antibiotic resistance prediction tool, gnomonicus, using a diverse test set of 2,663 Mycobacterium tuberculosis Samples.

Microb Genom. 2025 Dec;11(12):001592. doi: 10.1099/mgen.0.001592.

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Tuberculosis remains a global health problem. Making it easier and quicker to identify which antibiotics an infection is likely to be susceptible to will be a key part of the solution. Whilst whole-genome sequencing offers many advantages, the processing of the genetic reads to produce the relevant public health and clinical information is, surprisingly, often the responsibility of the end user, which inhibits uptake. Here, we characterize how well a freely available tool we have developed, gnomonicus, predicts the antibiotic resistance profile of a sample (given its variant call file) using our implementation of the second edition of the World Health Organization (WHO) catalogue of resistance-associated variants (WHOv2). To facilitate this, we have constructed a diverse test set of 2,663 publicly available Mycobacterium tuberculosis samples, which have both genetic and drug susceptibility testing (DST) data. We have chosen to apply the catalogue such that our tool will return a result of (i) Fail if there are insufficient reads at a genetic locus associated with resistance, (ii) Unknown if a genetic variant in a resistance gene not listed in the catalogue is encountered and (iii) Resistant if three or more short-reads support the presence of a resistance-associated variant. The last step increases the sensitivity for all 15 antibiotics but only reaches significance in a few in our test set. Comparing our results with those of TB-Profiler, an existing tool, highlights the different design choices and demonstrates that the performance of both tools on our diverse test set is comparable. By only considering high-confidence DST results, we show that gnomonicus, in combination with our translation of WHOv2, achieves sensitivities and specificities in excess of 95% for both isoniazid and rifampicin.

DOI: 10.1099/mgen.0.001592
PMCID: PMC12705075
PMID: 41396803 [Indexed for MEDLINE]

Conflict of interest statement: S.S. and K.G. were employed by the Ellison Institute of Technology, Oxford Ltd. D.W.C. and P.W.F. received consultancy fees from the Ellison Institute of Technology, Oxford Ltd.

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64. In vitro and in vivo characterization of Bisphosphocin Nu-3-a novel broad-spectrum antimicrobial compound with high potency against resistant Pathogens.

Antimicrob Agents Chemother. 2025 Dec 10;69(12):e0094825. doi: 10.1128/aac.00948-25. Epub 2025 Oct 21.

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Lakewood-Amedex Biotherapeutics Inc. has developed a new class of antimicrobials called the Bisphosphocin class, with Nu-3 as a leading candidate, which is currently in clinical development for treating mildly infected diabetic foot ulcers (iDFUs). Nu-3 acts through a novel mechanism of action that destabilizes bacterial membranes within minutes, which significantly reduces the potential for resistance development. It demonstrates broad-spectrum activity against Gram-positive, Gram-negative, and multidrug-resistant bacteria, including recent clinical isolates from infected wounds. Nu-3 is especially effective in acidic environments and can be formulated for topical application at high concentrations and low pH, that has been shown to be beneficial for wound healing, making it well-suited for treating infections in diabetic foot ulcers. Its rapid, bactericidal action has been confirmed against pathogens, such as Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Propionibacterium acnes, Proteus mirabilis, Acinetobacter baumannii, and Staphylococcus saprophyticus, with complete bacterial eradication occurring within minutes. Resistance testing over 21 days showed a very low probability of resistance development. In vivo testing in murine dermal methicillin-resistant Staphylococcus aureus (MRSA) infection models demonstrated robust efficacy for Nu-3 given as a solution- or gel-formulation in both single and multidose protocols. Given its efficacy, broad-spectrum activity, and topical formulation, Nu-3 has the potential to be an important therapeutic intervention for the treatment of mild infections in diabetic foot ulcers-a serious complication of diabetes associated with high amputation risk.

DOI: 10.1128/aac.00948-25
PMCID: PMC12691638
PMID: 41118336 [Indexed for MEDLINE]

Conflict of interest statement: K.C., K.M., T.B., S.P., R.S., and P.D. are current or former employees of Lakewood-Amedex Biotherapeutics Inc. K.C., K.M., T.B., S.P., and P.D. have company shares or stock options.

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65. Correlation Between CD38(+) Cell Levels and Pulmonary Tuberculosis Complicated with Diabetes Mellitus: A Retrospective Analysis Based on Lymphocyte Subsets and Clinical Features.

Diabetes Metab Syndr Obes. 2025 Dec 6;18:4483-4491. doi: 10.2147/DMSO.S556747. eCollection 2025.

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PURPOSE: This study aimed to investigate the association between CD38+ cells and the risk of pulmonary tuberculosis (PTB) complicated with diabetes mellitus (DM), providing insights into the immune mechanisms underlying PTB-DM.
PATIENTS AND METHODS: Clinical data and lymphocyte subset profiles of 596 TB patients admitted to Affiliated Hospital of Shaoxing University from November 2022 to November 2024 were analyzed, including 115 DM-complicated and 481 non-DM cases. Logistic regression was used to evaluate the correlations between clinical indicators, lymphocyte subsets and PTB-DM. Generalized linear models were employed to assess the association of CD38+ cells with PTB-DM risk, while restricted cubic spline curves were used to explore potential linear relationships.
RESULTS: The PTB-DM group exhibited a significantly higher prevalence of advanced age, male gender, and hypertension compared to the non-DM group ($p < 0.05$). Lymphocyte subset analysis revealed marginally elevated NKT cells but reduced B lymphocytes, B1 cells, and CD38+ cells in the DM group, with the most pronounced difference in CD38+ cells ($p < 0.001$). Multivariate logistic regression identified multidrug-resistant TB and hypertension as independent risk factors, whereas higher CD38+ cell counts served as an independent protective factor for TB-DM comorbidity (OR 0.50, 95% CI 0.32-0.77). Generalized linear models demonstrated a persistent negative correlation between CD38+ cell levels (analyzed as continuous or quartile-categorized variables) and PTB-DM risk after adjusting for confounders. Restricted cubic spline analysis confirmed a significant linear inverse association ($p = 0.003$) without evidence of nonlinearity ($p = 0.450$).
CONCLUSION: CD38+ cells play a critical role in the immune regulation of PTB patients, with elevated expression conferring protective effects against PTB-DM comorbidity.

DOI: 10.2147/DMSO.S556747
PMCID: PMC12695711
PMID: 41394294

Conflict of interest statement: The author(s) report no conflicts of interest in this work.

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66. Evaluating selection at intermediate scales within genes provides robust identification of genes under positive selection in M. tuberculosis clinical Isolates.

Tuberculosis (Edinb). 2025 Dec;155:102690. doi: 10.1016/j.tube.2025.102690. Epub
2025 Sep 11.

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Update of
bioRxiv. 2025 Aug 25:2025.05.07.652684. doi: 10.1101/2025.05.07.652684.

Multiple studies have reported genes in the M. tuberculosis (Mtb) genome that are under diversifying selection, based on genetic variants among Mtb clinical isolates. These might reflect adaptions to selection pressures associated with modern clinical treatment of TB. Many, but not all, of these genes under selection are related to drug resistance. Most of these studies have evaluated selection at the gene-level. However, positive selection can be evaluated on different scales, including individual sites (codons) and local regions within an ORF. In this paper, we use GenomegaMap, a Bayesian method for calculating selection, to evaluate selection of genes in the Mtb genome at all three levels. We present evidence that the intermediate analysis (windows of codons) yields the most credible list of candidate genes under selection (excluding PPE and PE_PGRS genes, which are predicted less reliably due to frequent sequencing errors). A further advantage of this approach is that it identifies specific regions within proteins that are under selective pressure, which is useful for structural and functional interpretation. In an analysis of two separate collections of Mtb clinical isolates (from Moldova; and a globally-representative set), we observed 53 and 173 significant genes under selection, with 36 % overlap. The lists of genes under selection include many drug-resistance genes, as well as other genes that have previously been reported to be under selection (resR, phoR). The specific regions under selection identified within drug-resistance genes are shown to correspond to protein structural features known to be involved in resistance, supporting accuracy of the method. Positive selection in several ESX-1-related genes was also observed, suggesting adaptation to immune pressure.

DOI: 10.1016/j.tube.2025.102690
PMCID: PMC12684734
PMID: 41033137 [Indexed for MEDLINE]

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

67. Emergence of Acquired HIV Drug Resistance Among Individuals Receiving Dolutegravir-Based Antiretroviral Therapy in Uganda: A National Laboratory-Based Survey 2023.

Open Forum Infect Dis. 2025 Nov 6;12(12):ofaf679. doi: 10.1093/ofid/ofaf679. eCollection 2025 Dec.

Asio JN(1), Watera C(1), Namayanja G(2), da Silva JF(3), Pals S(3), Ssemwanga D(1)(4), Sanyu G(1), Nannyonjo M(4), Kaganda UK(1), Busobozi R(1), Nansumba H(5), Nabukenya M(5), Ayitewala A(5), Ssali M(6), Katureebe C(6), Magongo EN(6), Balidawa H(6), Nazziwa E(2), Ntale J(2), Raizes E(3), Zheng DP(3), Zeh C(3), Hackett S(3), Naluguza M(2), Mbidde EK(1), Kaleebu P(1)(4).

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BACKGROUND: As dolutegravir (DTG)-based regimens (DBRs) become more widely used and patients remain on treatment longer, cases of virological failure remain rare. This study presents findings from the second annual round of acquired HIV drug resistance (HIVDR) surveillance in Uganda, among individuals with viral nonsuppression (≥1000 copies/mL) receiving DBRs for ≥9 months. The first round was conducted from February to April 2022.
METHODS: This nationally representative cross-sectional survey analyzed randomly selected remnant plasma and dried blood spot specimens collected between April and July 2023 from the Central Public Health Laboratories. Genotyping targeted the integrase, protease, and reverse transcriptase regions of the HIV-1 pol gene, resistance was analyzed using the Stanford HIVDR Database. Weighted HIVDR prevalence and 95% confidence intervals (CIs) were calculated for children (0-14 years) and adults (≥15 years).
RESULTS: Out of 857 specimens tested, 400 (46.7%) were from children and 457 (53.3%) from adults. Median ages were 11 years for children and 36 years for

adults. Median time on DBRs was 1.9 years for children and 2.4 years for adults. Five hundred and fifty-nine (65.2%) specimens were successfully genotyped. The prevalence of DTG resistance was 10.1% (95% CI: 6.4%-13.9%) in children and 8.6% (95% CI: 3.9%-13.3%) in adult, higher than the first round with a prevalence of 6.6% (95% CI: 3.5%-9.6%) and 4.4% (95% CI: 0.7%-7.1%), respectively.
CONCLUSIONS: The increase in DTG resistance among both children and adults highlights the need to strengthen adherence and enhance early identification of individuals at risk of HIVDR through novel and existing programmatic interventions.

DOI: 10.1093/ofid/ofaf679
PMCID: PMC12651561
PMID: 41311912

Conflict of interest statement: Potential conflicts of interest. The authors do not have any conflict of interest relevant to this work. Financial support. This work was supported by the US President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention under the terms of the cooperative agreement, award number 5NU2GGH002132-03. Data availability. The sequence data supporting the findings of this study have been deposited in GenBank, and the accession numbers are PV988491–PV989523. Author contributions. Conceived and designed the study: P. K., J. N. A., C. W., J. d. F. d. S., G. N., D. S., G. S., M. Nan., H. N., M. Nab., U. K. K., R. B., M. S., C. K., E. N. M., H. B., E. N., S. P., E. R.. D. P. Z., C. Z., S. H., M. Nal., and E. K. M. Performed the study: P. K., J. N. A., C. W., G. N., D. S., G. S., M. Nan., U. K. K., R. B., and H. N. Analyzed the data: S. P., J. N. A., C. W., D. S., G. S., M. Nan., and P. K. Wrote the paper: J. N. A., C. W., J. d. F. d. S., G. N., D. S., G. S., M. Nan, H. N., M. Nab., M. S., C. K., E. N. M., H. B., E. N., S. P., E. R., D. P. Z., C. Z., S. H., M. Nal., and P. K.

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68. Antifungal Susceptibility Profile of Aspergillus Strains Isolated From the Lower Respiratory Tract in Eastern Indian Patients: A Hospital-Based Study.

Microbiologyopen. 2025 Dec;14(6):e70136. doi: 10.1002/mbo3.70136.

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Respiratory aspergillosis refers to a range of infections, from allergic to chronic and invasive, which can be life-threatening and are primarily caused by Aspergillus fumigatus and Aspergillus flavus. Other species, including Aspergillus terreus, Aspergillus nidulans, and Aspergillus versicolor, have also been implicated in respiratory infections. Treatment for chronic to invasive pulmonary aspergillosis typically involves azole antifungal drugs, although studies have shown varying minimum inhibitory concentrations (MIC) for these medications, with a growing concern over voriconazole resistance. During the period from August 2022 to May 2024, characteristic hyphae were detected in 7.2% of lower respiratory samples, with culture positivity in 12.8%, including early morning sputum and bronchoalveolar lavage fluid samples. A. flavus (n = 282) was the most frequently isolated species, followed by A. fumigatus (n = 86). Additionally, a seasonal trend was observed for Aspergillus infections, with peaks in April and September. The MIC of itraconazole, voriconazole, posaconazole, amphotericin B, ravuconazole, and caspofungin were assessed for the isolated Aspergillus species. A higher MIC of amphotericin B was observed against A. flavus and A. terreus, whereas azoles exhibited a relatively lower MIC. Caspofungin and posaconazole exhibited the lowest MIC against the isolated Aspergillus species. Therefore, it is crucial to identify the causative fungi and determine the antifungal MIC for Aspergillus species responsible for lower respiratory tract infections. This study emphasizes the significance of respiratory aspergillosis in TB-endemic regions of Eastern India.

DOI: 10.1002/mbo3.70136
PMCID: PMC12624224
PMID: 41250899 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflicts of interest.

Recent TB News

Pennsylvania delivers $1 million to protect residents from TB as cases rise nationwide
https://www.idse.net/Respiratory/Article/12-25/Pennsylvania-tuberculosis-prevention-treatment-funding/79257

The Pennsylvania Department of Public Health is now investing around $1 million towards increasing the state's protection against tuberculosis (TB) as cases of TB continue to rise within the United States. This funding will support programs that aim to improve outpatient and diagnostic services, education, contact tracing, and medications for TB across the state.

This new, one-two punch could knock out drug-resistant TB
https://www.rockefeller.edu/news/38777-this-new-one-two-punch-could-knock-out-drug-resistant-tb/
A recent study has demonstrated that rifampicin (a frontline antibiotic for TB) when paired with a second compound called AAP-SO_2, becomes a more powerful treatment in both suppressing TB resistance and targeting the dormant TB bacteria that other medications struggle to attack. This potential new treatment could help shift TB drug development towards a more precision medicine approach, especially as drug resistant-TB continues to be a worldwide issue.