

Linezolid phenotypic resistance in *Mycobacterium tuberculosis* due to presence of non-tuberculous mycobacteria: a case report

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Case Report

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Abstract

Background

Linezolid is one of the three core drugs endorsed by the World Health Organization for treatment of rifampicin-resistant tuberculosis (RR-TB). Discordance between phenotypic and genotypic drug-susceptibility testing (DST) can complicate clinical decision-making. DST discordance is usually attributed to poor sensitivity of sequencing assays due to incomplete knowledge of resistance mechanisms, failure to detect resistant subpopulations, technical challenges with phenotypic DST, and the presence of an area of technical uncertainty in phenotypic DST. We hypothesize that DST discordances for linezolid could also be due to contamination or mixed infection with *Mycobacterium tuberculosis* (*Mtb*) and non-tuberculous mycobacteria (NTM) as linezolid resistance is caused by changes in ribosomal DNA, a highly conserved mechanism across bacterial species.

Case presentation:

A 48-year-old man in South Africa with a history of two episodes of multidrug-resistant TB (in 2006 and 2024) was diagnosed with another episode of RR-TB in 2025. Phenotypic DST of the baseline *Mtb* liquid culture isolate reported resistance to linezolid whereas Illumina-based whole genome sequencing (WGS) did not detect any variants in the *rrl* or *rp1C* genes. WGS on a subculture of the baseline isolate detected the presence of both *Mtb* and *Mycobacterium sinense*. Minimum inhibitory concentration (MIC) assays confirmed baseline linezolid resistance. WGS of the linezolid-containing MIC tube confirmed that the linezolid resistance was due to the presence of *Mycobacterium sinense*. A Deeplex MycMTB assay on the linezolid-containing phenotypic DST tube detected the presence of *Mycobacterium kumamotonense*. The culture collected at month two of treatment showed susceptibility to linezolid but emerging resistance to bedaquiline on both phenotypic DST and WGS.

Conclusions

An in-depth investigation of a discordant DST result for linezolid with phenotypic resistance and genotypic susceptibility identified the presence of a slow growing *M. sinense* as the probable cause of the observed discordance, rather than error or poor sensitivity of WGS. The presence of an NTM in the culture isolate should be investigated by macroscopic examination and Ziehl-Neelsen stain before reporting a phenotypic DST result as *Mtb* linezolid resistant, especially when sequencing results do not detect a resistance-conferring mutation.

Background

Bedaquiline, fluoroquinolones and linezolid are listed by the World Health Organization (WHO) as group A drugs for the treatment of rifampicin-resistant tuberculosis (RR-TB)[1]. Since May 2022, the WHO-

endorsed BPaL(M) [bedaquiline, pretomanid, linezolid (moxifloxacin)] regimens, consisting of bedaquiline, pretomanid, linezolid with or without a fluoroquinolone, are increasingly used as the initial empiric regimen for RR-TB. Resistance to fluoroquinolones was already prevalent prior to 2002, and resistance to the other BPaL drugs, particularly bedaquiline, is emerging globally. In the Western Cape Province of South Africa, resistance to bedaquiline is rapidly emerging, with reported prevalences of 5% in 2020 and 12% in 2024 [2, 3]. Rates of linezolid resistance in the general population of patients with RR-TB are lower (ranging from 0% to 3.6% in 2025) [4], but higher rates of linezolid resistance have been reported in at-risk populations. In South Africa, linezolid resistance was detected by phenotypic or genotypic methods in 13 of 39 (33%) patients who had failed a linezolid-containing treatment regimen [5].

Culture-based phenotypic drug susceptibility testing (pDST) remains the reference method for DST for bedaquiline, linezolid and pretomanid as the sensitivity of next generation sequencing (NGS) assays is suboptimal for these drugs at present. The sensitivity of NGS assays is estimated to be 84% for bedaquiline and 46% for linezolid for both targeted NGS (tNGS, Deeplex MycMTB) and whole genome sequencing (WGS) when assessed against a composite reference standard [6, 7]. In South Africa, baseline culture isolates from patients diagnosed with RR-TB are therefore routinely assessed for resistance to bedaquiline and linezolid by both pDST and tNGS (Deeplex MycMTB) [8].

Discordant results between genotypic and phenotypic *Mtb* DST assays create confusion and complicate patient management. False negative genotypic DST (gDST) results mainly occur for drugs for which the genomic mechanism conferring drug resistance is not yet fully characterized (e.g. delamanid) or when there is micro-heteroresistance, with the resistant population present below the detection NGS threshold [9–11]. False resistant pDST results mainly occur when pDST for specific drugs is technically challenging, such as pyrazinamide [12], or when the minimum inhibitory concentration (MIC) is only slightly raised above the critical concentration, which frequently occurs for bedaquiline [11].

In this case report, we discuss an in-depth investigation of discordant gDST-pDST results for linezolid in a participant of the Precision Action for Rifampicin-Resistance Tuberculosis (PARR-TB) study.

Case presentation

A patient in the Western Cape Province of South Africa was first diagnosed with RR-TB 20 years ago, for which he received an injectable-based regimen (Fig. 1). Eighteen years later, he experienced a second episode of RR-TB for which he received treatment with the standard BPaL-L (bedaquiline, pretomanid, linezolid and levofloxacin) regimen. Phenotypic DST on the baseline isolate collected for this second RR-TB episode showed susceptibility to fluoroquinolones, bedaquiline and linezolid. The patient had poor treatment adherence, only achieved culture conversion at month five, and completed after 7 months of BPaL-L treatment. The treatment outcome was listed as cure, as there were two documented consecutive negative cultures without subsequent culture-reversion.

Thirteen months later (in 2025), the patient was again diagnosed with multidrug-resistant TB, with resistance to isoniazid and rifampicin detected by the molecular Cobas® MTB-RIF/INH assay and initiated BPaL-L treatment at the regional laboratory of the National Health Laboratory Services (NHLS). The baseline sputum sample was smear positive (++), the Xpert MTB/XDR assay showed that the infecting *Mtb* strain was susceptible to fluoroquinolones. Based on the results, the patient received BPaL-L treatment.

At month three of treatment, the routine pDST of the baseline isolate became available and showed susceptibility to bedaquiline and resistance to linezolid, both at the WHO-recommended critical concentration of 1 mg/L performed on BACTEC MGIT960 instrument [13]). A line probe assay for common mycobacteria detected the presence of *Mtb* (presence of bands 10 and 16). As per routine processes, the isolate was referred to the National TB reference laboratory of the NHLS National Institute of communicable Diseases (NICD) in Johannesburg for confirmation of linezolid resistance. When evaluated macroscopically, the MGIT was found to be turbid and not suitable for further pDST. Microscopically, Ziehl Neelson staining detected acid-fast bacilli in clumps. Results of WGS (performed as part of the PARR-TB study) were available two days after pDST results and showed a gDST-pDST discordance. The isolate was reported as linezolid susceptible given that the MAGMA bioinformatics pipeline did not detect any variants in the *rrl* and *rplC* genes, the two candidate linezolid resistance-conferring genes listed in the WHO catalogue of mutations [14]. The culture collected one month following treatment initiation was contaminated, the culture collected at month two was positive for *Mtb*.

Based on the clinical information and diagnostic results, the national clinical advisory committee (NCAC) advised the treating clinician at month four of treatment to refer the patient for admission to the regional specialized TB hospital for the administration of an individualized regimen and psychosocial support. The NCAC suggested a 9-drug regimen containing pyrazinamide, terizidone, ethambutol, mereponem/clavulanic acid, levofloxacin, bedaquiline, clofazimine, and delamanid as well as linezolid if the patient does not experience any linezolid toxicity. This recommendation was based on the history of repeated RR-TB treatment, the fact that the culture was positive at month 2 of treatment and reflects the uncertainty regarding the strain's susceptibility to linezolid by including linezolid without counting on it as an effective drug. The patient refused to be hospitalized; hence an 8-drug regimen (without mereponem/clavulanic acid) was administered under directly observed therapy. NCAC further suggested performing additional investigations on the month 2 culture isolate, including an Xpert XDR, NGS and extended pDST.

WGS of the month two culture isolate (performed as part of the PARR-TB study) detected resistance to rifampicin (due to variant *rpoB* Ser450Leu, 100% allele frequency), resistance to isoniazid, ethionamide, and prothionamide (due to variant *inhA* – 777C > T, 100% allele frequency), and resistance to bedaquiline and clofazimine (due to variant *mmpR5*Ala36Val, 19% allele frequency, associated with resistance-interim in the WHO catalogue of mutations 2nd edition). The WGS analysis reported susceptibility to all other drugs, including linezolid. Based on these results, NCAC strongly recommended inpatient care to administer a regimen consisting of delamanid, levofloxacin, linezolid, terizidone, ethambutol,

pyrazinamide, meropenem/clavulanic acid and intravenous amikacin. Following discussion and shared decision-making, the patient accepted the new regimen and inpatient treatment plan.

At month three of treatment, the patient achieved stable culture conversion and showed a favorable clinical response. At month five of treatment, the patient developed terizidone-associated psychosis and was discharged for disciplinary reasons. The patient was later admitted to another hospital for continued care and recently discharged for an additional 12-months of outpatient treatment with delamanid, levofloxacin, linezolid, ethambutol, pyrazinamide, high dose isoniazid. A patient perspective for this case report could not be obtained because the patient was unavailable for interview following transfer of care. The decision to continue treatment with linezolid in presence of possible linezolid resistance was not discussed directly with the patient.

Ethics statement: The patient gave informed consent for participation in the PARR-TB study (Stellenbosch University HREC2-2024-29721). Medical file review was conducted under ethical approval (N09/11/296).

In depth investigations

Several in-depth investigations were performed to prove the hypothesis that the gDST-pDST discordance was due to the presence of an NTM.

Analysis of the baseline WGS data using NTM profiler version 0.8.2 [15] identified the presence of *Mtb* (relative abundance 34.6%) and *M. sinense* (relative abundance 65.4%, average nucleotide identity of 99.3%). Alignment between *Mtb* and *M. sinense* for the genomic positions in the *rrl* and *rplC* genes associated with resistance (as per WHO catalogue 2nd version), was evaluated using the H37Rv reference for *Mtb* and strain JDM601 (GenBank CP002329.1) for *M. sinense* in the National Center for Biotechnology Information database. This showed an overall identity of 84% for *rplC* and 91% for *rrl* and conservation in the seven positions associated with resistance to linezolid in *Mtb* by the WHO catalogue of mutations (Fig. 2).

MIC analysis was performed for the baseline isolate showed phenotypic linezolid resistance at concentrations 0.5, 1, and 2 mg/L. WGS of the growth control MGIT tube confirmed the presence of both *Mtb* (relative abundance 6%) and *M. sinense* (relative abundance 94%). Sequencing the linezolid-containing MGIT tubes (0.5 and 2.0 mg/L) only identified the presence of *M. sinense*. The tNGS Deeplex MycMTB assay performed on the LZD drug pDST tube only detected the presence of *M. kumamotonense*.

Investigations of the month two isolate assay at the NICD TB reference laboratory showed susceptibility to fluoroquinolones on the Xpert MTB/XDR assay. WGS did not detect any linezolid-conferring mutations and phenotypic DST confirmed linezolid susceptibility. Results of extended pDST performed on the sample collected at month two of treatment was available at month six and reported susceptibility to

linezolid, fluoroquinolones, para-amino salicylic acid, pretomanid, ethambutol and amikacin but resistance to bedaquiline and clofazimine, confirming the findings of WGS.

Discussion

Following the endorsement by WHO of tNGS for clinical diagnosis of drug resistance in *Mtb*, clinicians may increasingly encounter discrepancies between the results of pDST and NGS assays. Such gDST-pDST discordances pose a clinical challenge and complicate decision-making. We report the first case of discordant DST results for linezolid with phenotypic resistance and genotypic susceptibility, which challenged the management of a patient with a history of multiple episodes of RR-TB and prior exposure to linezolid. Concern regarding possible linezolid resistance and continued culture positivity at month 2 of BPAL-L treatment contributed to NCAC's recommendation to initiate a 9-drug individualized regimen. The regimen required hospitalization for administration of meropenem, which was rejected by the patient, and included terizidone, which led to psychosis and contributed to a disruption in the patient's care.

In this case report, we investigated whether the gDST-pDST discordance could be attributed to the presence of an NTM. The tNGS Deeplex MycMTB, performed on the linezolid-containing MGIT tube reported the sole presence of *M. kumamotonense* based on a single hsp65 marker, a method which has not been validated for species-level identification. NTM-Profiler analysis of the WGS data (performed from a subculture of the growth control MGIT tube) identified the presence of both *Mtb* and *M. sinense*. NTM-Profiler screens the raw sequences against a database of short fixed-length DNA sequences (k-mers) that are uniquely specific for distinct NTM species, resulting in a much more granular assessment. Sequencing alignment showed that *M. sinense* and *M. kumamotonense* an 87% average nucleotide identity overall. The identity for the *rplC* and *rrl* gene between *Mtb* and *M. sinense* was high (84.1% for *rplC* and 91.6% for *rrl*) while there was no significant genomic similarity between *Mtb* and *M. kumamotonense*. These results strongly suggest that the NTM present in the culture isolate was *M. sinense*.

M. sinense is a slow-growing opportunistic NTM belonging to the *M. terrae* complex. *M. sinense* is an opportunistic pathogen that was originally isolated from a human sputum sample in China exhibiting a tuberculosis-like disease and has since also been isolated from domestic and wild animals [16–18]. *M. sinense* (strain JDM601) has been reported to be resistant to several antimycobacterial drugs, with high-level resistance to streptomycin, levofloxacin, capreomycin, para-amino salicylic acid, isoniazid, and prothionamide, and intermediate resistance to rifampicin and amikacin [16]. While susceptibility for linezolid has not yet been reported for *M. sinense*, linezolid has been shown to be less active against isolates from the *M. terrae* complex [19]. In our case report, the WGS analysis performed on the growth recovered from the MIC tubes confirms phenotypic susceptibility of the *Mtb* strain, as the growth of control tube contained *Mtb* but no *Mtb* was detected in the growth of the linezolid-containing tubes. These WGS results also confirm phenotypic resistance of *M. sinense*, as this NTM was detected in the growth of the control tube as well as the linezolid-containing tubes.

Taken together the routine and in-depth investigations of the sputum samples and culture isolates strongly suggest that the phenotypic resistance for linezolid reported for this patient was a false resistant pDST result caused by the erroneous attribution of linezolid resistance in *M. sinense* to linezolid resistance in *Mtb*. This challenges the common belief that linezolid pDST-gDST discordance for *Mtb* is due to a false negative genotypic result given that resistance-associated mutations only explain about half of phenotypic resistance observed [20, 21]. The proportion of gDTS-pDST discordances in clinical isolates with a false resistant phenotypic result due to the presence of a slow growing NTM, as observed in this case, remains unknown. Better understanding of the frequency of occurrence of this phenomenon will be essential to better appreciate the true sensitivity of NGS to detect linezolid resistance.

In conclusion, the combined pDST, MICs, tNGS and WGS are indicative of the presence of a slow-growing NTM causing a false linezolid resistant phenotypic result for a clinical *Mtb* isolate. This highlights the value of combining phenotypic and genotypic DST methods to prevent misclassification of linezolid resistance, especially in patients with a high pre-test probability of linezolid resistance. Future studies should investigate the frequency of linezolid resistance due to presence of an NTM to better understand to which extent this contributes to the reported low sensitivity of NGS for detection of linezolid resistance.

Declarations

Participant consent for publication: The patient provided written informed consent to participate in the PARR-TB study, including consent for publication of his clinical case.

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Figures

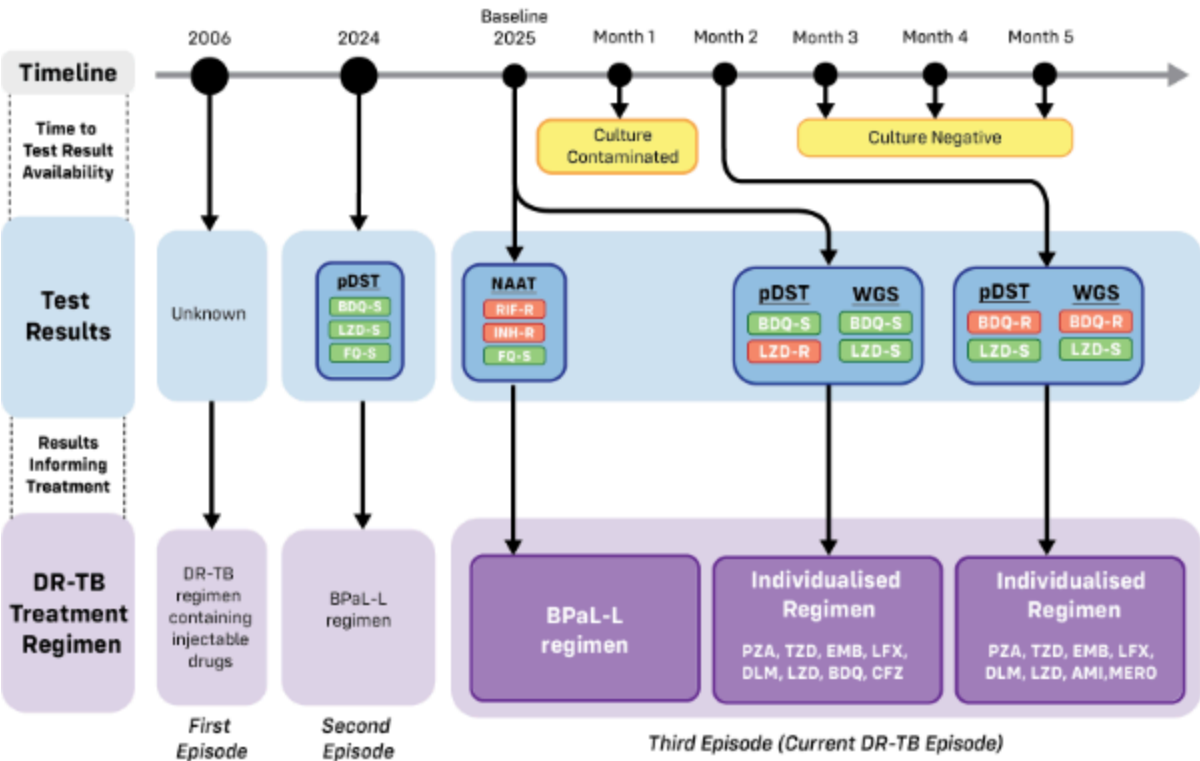


Figure 1

Timeline of routine diagnostic test results, WGS results and treatment decision-making for a patient with genotypic-phenotypic drug resistance discordance observed for linezolid on the baseline culture isolate



Figure 2

Alignment of DNA sequences of the wild-type positions of the *rrl* and *rplC* gene codons where mutations have been associated with linezolid resistance (WHO catalogue of mutations)