Article One

Case Investigation of a Suspected Drug-Resistant Tuberculosis Patient in Chongwe District, Zambia: Importance of Accurate Molecular Diagnostics for Resistance Profiling

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Abstract

Background: Recurrent tuberculosis in patients with prior treatment default raises significant concern for acquired drug resistance, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. This report details the investigation of a 44-year-old male retreatment case in Zambia, initially suspected of XDR-TB. The case underscores the critical role of advanced molecular diagnostics in accurately defining resistance profiles and informing appropriate clinical and public health responses.

Methods: A descriptive case investigation was conducted in Chongwe District, Zambia, in June 2025. Quantitative data were extracted from clinical and laboratory records of the index patient and close contacts, including demographic characteristics, tuberculosis treatment history, and molecular diagnostic results. Qualitative data were collected through structured interviews with the patient, a primary caregiver, and a healthcare worker to explore treatment adherence barriers and care experiences. Laboratory confirmation and drug resistance profiling were performed using GeneXpert MTB/RIF Ultra and GeneXpert MTB/XDR assays. Quantitative data were summarized using descriptive statistics, while qualitative information was thematically synthesized and integrated narratively to contextualize clinical and public health findings.

Results: The index case was confirmed to have Tuberculosis but was found to have mono-resistance to Isoniazid only. No resistance to Rifampicin, Fluoroquinolones, or Group A second-line drugs was detected, thus not meeting the XDR-TB or MDR-TB case definitions. All three close contacts were screened and tested negative for Tuberculosis. Qualitative interviews revealed that prior treatment default was driven by livelihood demands, travel distance, and early symptom resolution. Structured adherence support during retreatment facilitated successful treatment completion.

Conclusion: The investigation confirmed isoniazid mono-resistant TB, not XDR-TB, in a retreatment case with a history of default. Rapid molecular diagnostics were essential for accurate resistance classification and clinical guidance. The findings reinforce the necessity of enhanced adherence support and robust laboratory capacity to effectively manage drug-resistant tuberculosis in high-burden settings.

Keywords: Extensively Drug-Resistant Tuberculosis, XDR-TB, Case Investigation, GeneXpert, Contact Tracing, Zambia, Chongwe District

Introduction

The global tuberculosis (TB) epidemic continues to be shaped by the persistent threat of drug-resistant strains, complicating treatment and control efforts worldwide. In 2022, an estimated 410,000 individuals developed

multidrug- or rifampicin-resistant TB (MDR/RR-TB), with only approximately 40% accessing appropriate treatment (1). Among these, an estimated 25,000 cases met the definition for extensively drug-resistant TB (XDR-TB), a severe form of the disease characterized by resistance to rifampicin, a fluoroquinolone, and at least one Group A second-line drug (1,2). The high mortality and extended, complex treatment regimens associated with drug-resistant TB, particularly XDR-TB, underscore the critical importance of timely and precise diagnosis to optimize patient outcomes and prevent further transmission (3, 4).

The World Health Organization (WHO) African Region carries a significant and disproportionate burden of both drug-susceptible and drug-resistant TB (1). Zambia, within this region, reported an estimated incidence of 12,000 MDR/RR-TB cases among notified pulmonary TB patients in 2022, though the precise contribution of XDR-TB remains under-ascertained due to limited diagnostic capacity (1,5). In high-burden settings, risk factors for acquired drug resistance, including previous treatment default, inadequate therapy, and poor adherence, are common, heightening the suspicion for MDR/RR-TB in retreatment cases and necessitating robust diagnostic protocols (6,7).

Rapid molecular diagnostics have transformed the landscape of TB management. The widely used GeneXpert MTB/RIF Ultra assay enables prompt detection of Mycobacterium tuberculosis and rifampicin resistance, a key proxy for MDR-TB (8). However, GeneXpert MTB/RIF Ultra does not detect resistance to isoniazid or second-line agents. The introduction of the GeneXpert MTB/XDR cartridge represents a significant advancement, allowing for the simultaneous identification of resistance to isoniazid, fluoroquinolones, and second-line injectables in a single test, thereby facilitating the rapid differentiation of pre-XDR and XDR-TB from less resistant forms (8, 9).

At the local level, Chongwe District reflects the national challenge. For the reporting period 2023–2024, Chongwe District recorded an average annual TB notification rate of 156 per 100,000 populations, with treatment success rates for drug-susceptible TB averaging 87% (10). However, outcomes for retreatment cases and those with any drug resistance have been less favorable, with success rates approximately 15–20% lower, highlighting the amplified risk and complexity of managing such cases in this high-burden setting.

In June 2025, Chongwe District Health Office in Zambia was alerted to a 44-year-old male patient with a history of TB treatment default presenting with symptoms suggestive of recurrent TB. The patient had initially been diagnosed with drug-susceptible pulmonary TB in 2022 but defaulted after three months of treatment. He was subsequently retreated successfully in 2024, with culture-based drug susceptibility testing (DST) at that time confirming susceptibility to both isoniazid and rifampicin. Given the strong epidemiological link between treatment interruption and the development of drug resistance, particularly the risk of progression to MDR/RR-TB this recurrence triggered a systematic diagnostic workup to rule out evolving resistance, including the possibility of XDR-TB. This report details the subsequent public health investigation, which utilized a stepwise molecular diagnostic approach to definitively characterize the drug resistance profile, guide appropriate clinical management, and implement necessary infection control measures.

Methods

Study Design Setting

A descriptive case investigation was conducted in June 2025 at Chongwe Referral Health Centre and within the patient's community in Libuko Village, Chongwe District, Zambia. Quantitative data were systematically extracted from the patient's medical and laboratory records, including treatment history and diagnostic results. This was complemented by structured interviews with the patient and relevant healthcare providers to contextualize treatment adherence challenges and care-seeking experiences.

Case Definitions

A Multidrug or Rifampicin-Resistant Tuberculosis (MDR/RR-TB) case was defined as a patient with TB caused by Mycobacterium tuberculosis that is resistant to at least rifampicin (2). An Extensively Drug-Resistant Tuberculosis (XDR-TB) case is defined as a patient with MDR/RR-TB that shows additional resistance to any fluoroquinolone and at least one other Group A second-line drug (e.g., bedaquiline, linezolid). For this investigation, a suspected drug-resistant TB case was defined as a patient with a history of previous TB treatment and poor outcomes (e.g., default or recurrence) presenting with symptoms suggestive of active TB, warranting advanced testing to rule out or confirm drug resistance patterns, including MDR-TB and XDR-T.

Laboratory Methods

Laboratory testing followed a stepwise molecular diagnostic protocol aligned with the rationale of ruling

out evolving drug resistance in a retreatment case with prior default. An initial sputum sample from the index case was tested using the GeneXpert MTB/RIF Ultra assay, which confirmed the presence of M. tuberculosis with no rifampicin resistance detected. Given the patient's history of recurrent TB and prior treatment default key risk factors for acquired resistance and despite a 2024 phenotypic DST result indicating full susceptibility, further testing was warranted to exclude resistance beyond rifampicin. A fresh sample was therefore tested using the GeneXpert MTB/XDR assay at the Chongwe District Hospital laboratory. This test simultaneously investigates resistance to isoniazid, fluoroquinolones (levofloxacin, moxifloxacin), and second-line injectables (amikacin, kanamycin), providing a broader resistance profile essential for classifying pre-XDR or XDR-TB. Sputum samples from identified close contacts were screened using the GeneXpert MTB/RIF Ultra assay.

Data Collection

In this investigation, data collection involved both quantitative and qualitative methods. Quantitative data were systematically extracted from medical records and laboratory registers using a structured form. Captured variables included demographic details (age, sex, occupation, HIV status), TB treatment history (dates, regimens, outcomes), molecular diagnostic results (GeneXpert MTB/RIF Ultra and MTB/XDR), and contact tracing outcomes. Qualitative data were collected through structured interviews with the index patient, one primary caregiver (spouse), and one attending healthcare worker to explore treatment adherence barriers, care experiences, and clinical management practices, thereby contextualizing the quantitative findings.

Data Analysis

The analysis was primarily descriptive. Qualitative information from interviews and record reviews was synthesized and presented narratively to contextualize the case history and adherence factors. Quantitative data from laboratory results and contact tracing were summarized in tables. Data organization and descriptive analysis were performed using Microsoft Excel.

Ethical Considerations

Verbal informed consent was obtained from the patient and all contacts prior to interviews and sample collection. Patient confidentiality was maintained throughout the investigation.

Results

Case Characteristics

The index case was a 44-year-old HIV-negative male resident of Libuko village in Chongwe District, whose medical history was significant for two previous episodes of tuberculosis, as shown in table 1. His initial diagnosis in 2022 was marked by incomplete treatment and documented non-adherence, followed by a subsequent diagnosis in 2024 from which he completed a full course of treatment in March 2025. In June 2025, he re-presented with clinical symptoms indicative of a TB recurrence. An initial GeneXpert MTB/RIF Ultra test confirmed the presence of high levels of Mycobacterium tuberculosis but detected no resistance to Rifampicin. Given the patient's history of recurrent disease and prior treatment default, which are established risk factors for evolving drug resistance, laboratory personnel escalated the diagnostic workup. Consequently, further testing was initiated using the GeneXpert MTB/XDR cartridge to comprehensively investigate the potential for more extensive drug resistance, including Isoniazid, fluoroquinolones, and second-line injectables.

Table 1: Characteristics of the Index Case and Household Contacts, Chongwe District, Zambia, 2025

Category	Details
Index Case	
Age	44 years
Sex	Male
HIV Status	Negative
Occupation	Farmer
TB History	
First Episode (2022)	Diagnosed with drug-susceptible pulmonary TB. Defaulted from treatment after 3 months. DST* (2022) result unavailable.
Second Episode (2024)	Diagnosed with drug-susceptible pulmonary TB based on culture DST from UTH† (susceptible to INH§ and RIF¶). Successfully completed treatment in March 2025.
Current Episode (June 2025)	Presented with cough, fever, and night sweats. GeneXpert MTB/RIF Ultra: MTB** Detected (High), Rifampicin resistance NOT Detected.
Household Contacts (n=3)	
Contact 1	Spouse, 38 years, Female, HIV†† Negative, No history of TB.
Contact 2	Child, 12 years, Male, HIV Negative, No history of TB.
Contact 3	Child, 8 years, Female, HIV Negative, No history of TB.

*DST- Drug Susceptibility Test; †UTH – University Teaching Hospital; §INH – Isoniazid; ¶RIF – Rifampicin; **MTB, Mycobacterium Tuberculosis; ††HIV- Human Immunodeficiency Virus

Qualitative results

Interviews with the patient, his spouse (the primary caregiver), and a healthcare worker provided critical context for his treatment history. The patient attributed his 2022 default to practical and perceptual barriers:

"When the rains came, I had to travel far to my field. I also started feeling better, so I thought I was cured and stopped going to the clinic." - Patient

The spouse described the familial struggle, stating: *"I struggled to convince him to return. He said the journey was too long when he had farm work to do."* – Spouse

The successful 2024 treatment episode was facilitated by structured support. The interviewed healthcare worker noted,

"Its only after we assigned a community volunteer for Directly Observed Therapy that his attendance became consistent. This intervention proved pivotal" – Healthcare Provide

Laboratory Findings

The drug susceptibility profile for the index case, as determined by GeneXpert MTB/XDR testing, is summarized in Table 2. The results confirmed the presence of Mycobacterium tuberculosis with mono-resistance to Isoniazid. No resistance was detected to Rifampicin, fluoroquinolones, or Group A second-line drugs. Consequently, the case was classified as Isoniazid mono-resistant tuberculosis and did not meet the definitions for either MDR-TB or XDR-TB.

Table 2: Results of GeneXpert MTB/XDR drug susceptibility testing for a suspected XDR-TB case, Chongwe District, Zambia, 2025.

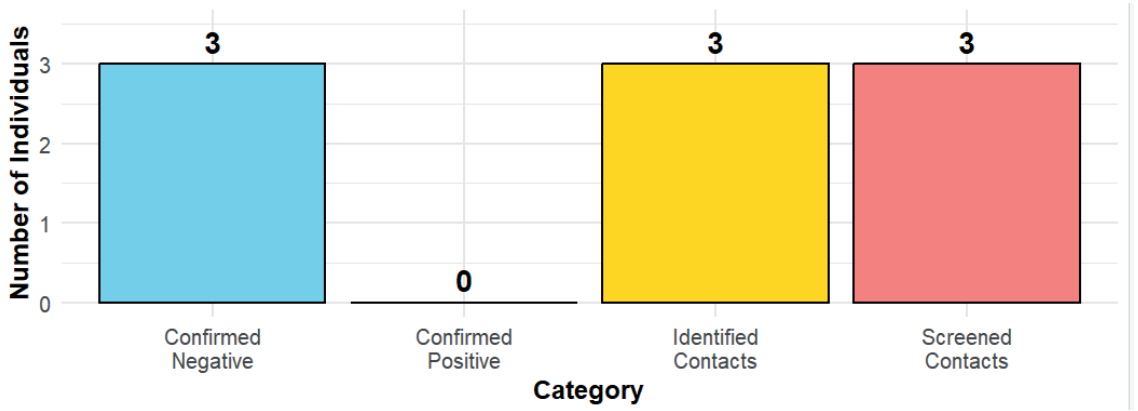
Drug Category	Specific Drug	Resistance Detected
First-Line Drugs	Isoniazid (INH*)	Yes
	Rifampicin (RIF†)	No
Fluoroquinolones	e.g., Levofloxacin	No
Group A Second-Line	e.g., Linezolid	No

*INH – Isoniazid; †RIF – Rifampicin

Contact Tracing Outcomes

A total of three (3) close contacts were identified from the patient's household. All three (100%) were successfully screened and tested using the GeneXpert MTB/RIF Ultra assay. All contacts tested negative for Tuberculosis. The outcomes of the contact tracing are presented in Figure 1.

Figure 1: Contact tracing and screening outcomes for a suspected XDR-TB case investigation, Chongwe District, Zambia, June 2025



Public Health Actions Taken

The patient was promptly referred to the MDR-TB centre at Chongwe District Hospital to initiate a standardized treatment regimen for Isoniazid mono-resistant tuberculosis. Comprehensive health education was provided to both the patient and his caregivers, covering essential topics including TB transmission mechanisms, the critical importance of strict treatment adherence, and practical infection prevention measures to minimize transmission risk within the household. Additionally, despite all contacts initially testing negative, a follow-up plan was established whereby they were advised to seek immediate medical attention if they develop any symptoms suggestive of TB and were thoroughly educated on the specific signs and symptoms to monitor.

By the time of the closure of this investigation, the patient showed significant improvement. Clinical symptoms like cough and fever had subsided, indicating a good response to treatment.

Discussion

This investigation of a suspected XDR-TB case in Chongwe District ultimately confirmed a case of Isoniazid mono-resistant TB. While this outcome is less severe than initially feared, it presents several critical lessons for the TB control program in Zambia. The initial suspicion for XDR-TB, while not aligning with the strict definition which requires confirmed MDR-TB as a prerequisite, was clinically justified given the patient's history of treatment default, a significant risk factor for acquired drug resistance (3). The stepwise diagnostic approach was effective. The absence of rifampicin resistance on the initial GeneXpert MTB/RIF Ultra test effectively ruled out MDR-TB, and consequently, XDR-TB was no longer a possibility. The subsequent MTB/XDR test was therefore not to "rule out XDR-TB" but to identify the specific pattern of resistance (in this case, INH mono-resistance) and to rule out resistance to key second-line drugs, which would classify the strain as "pre-XDR" if MDR were present. This nuanced use of diagnostics ensured accurate classification.

The patient's history underscores the imperative for robust TB program management, with a strong emphasis on adherence counselling and patient support mechanisms, such as Directly Observed Therapy (DOT), especially for retreatment cases (8). The qualitative findings suggest that practical barriers like livelihood needs are key drivers of default, indicating that support packages need to address these socioeconomic factors.
A key strength of this case investigation was the rapid and complete contact tracing and screening. The fact that no secondary cases were detected is reassuring and suggests that the period of infectiousness may have been limited or that infection control measures post-diagnosis were effective.

Conclusion

This investigation successfully ruled out MDR/XDR-TB in a suspected case, instead confirming Isoniazid mono-resistant TB. No secondary transmission was identified among close contacts. The case highlights the critical role of advanced molecular diagnostics in the accurate classification of drug-resistant TB and un-

derscores treatment default as a major risk factor for drug resistance.

Recommendations

Based on the investigation, key recommendations are proposed. For the National TB Program, it is crucial to scale up the use of GeneXpert MTB/XDR cartridges for rapid, extensive resistance detection and to strengthen adherence support by addressing socioeconomic barriers. The Chongwe District Health Office should maintain high suspicion for drug resistance in retreatment cases, institutionalize effective contact tracing, and train staff on MDR/XDR-TB diagnostics. For Laboratory Systems, genotypic results in complex cases should be confirmed with phenotypic culture and drug susceptibility testing to identify resistance beyond molecular assay coverage.

Limitations

This investigation has several limitations. Firstly, the small number of identified contacts limits the generalizability of the transmission findings. Secondly, the focus was solely on active tuberculosis disease; without testing for latent TB infection (LTBI), it remains possible that some contacts were infected. Thirdly, and most critically, drug resistance profiling relied solely on genotypic (GeneXpert) methods. While highly accurate for the specific genetic mutations they target, these tests do not constitute a full phenotypic drug susceptibility profile. No confirmatory phenotypic culture and DST was performed following the MTB/XDR result. Specifically, the absence of rifampicin resistance was determined solely by the GeneXpert rpoB probe result, without a follow-up culture-based DST to definitively rule out rifampicin resistance through phenotypic methods, which remains the gold standard (7). Finally, the findings are based on a single case investigation.

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