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Research Article

Prevalence and Treatment Outcomes of Drug-Resistant Tuberculosis in the Kyrgyz Republic

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A B S T R A C T

Introduction: Tuberculosis (TB) remains a significant health concern in the Kyrgyz Republic, with multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) posing significant challenges. This retrospective study examined the prevalence, epidemiological traits, and treatment outcomes of drug-resistant TB (DR-TB), focusing on XDR-TB, in the Kyrgyz Republic from 2019 to 2022.

Methods: This study used national tuberculosis surveillance data covering all administrative regions, health sectors, and prison systems under the National Tuberculosis Program.

Results: Despite the declining number of TB cases during the study period, one in five patients with TB had MDR/XDR-TB, indicating a persistent burden. Coronavirus disease 2019 has affected TB services, leading to a temporary drop in notifications. The proportion of previously treated DR-TB patients increased after 2020, suggesting treatment interruption, relapse, and program failure. Pediatric and female TB cases increased, indicating community transmission and maternal health concerns. XDR-TB isolates showed resistance to bedaquiline and linezolid, threatening the World Health Organization-recommended treatment regimens. Over 20% of XDR-TB cases occurred in untreated patients, suggesting the primary transmission of resistant strains.

Conclusion: Although treatment success rates for rifampicin-resistant TB/M/XDR-TB have improved, they remain suboptimal for XDR-TB. XDR-TB cases clustered in urban areas, highlighting the influence of population dynamics on the transmission.

Keywords: Tuberculosis, drug resistance, molecular epidemiology, treatment Outcomes, Multidrug-Resistant TB, Extensively Drug-Resistant TB

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Introduction

Tuberculosis (TB) remains a significant public health concern, and antitubercular treatment success in patients with different levels of drug resistance (DR) is crucial to the National Anti-Tuberculosis Program in the Kyrgyz Republic.[1,2]

A primary health goal of the United Nations' Sustainable Development Goals is to eradicate tuberculosis by 2030. A World Health Organization (WHO) evaluation indicates that TB remains a major issue globally, affecting 25% of the world's population, approximately 2 billion individuals.3

In 2025, the study of TB epidemiology will remain a dynamic field, especially with the application of molecular techniques to explore transmission patterns and strain variation. Molecular epidemiology has greatly enhanced our understanding of TB, offering fresh perspectives on how the disease spreads and contributing to the formulation of specific control measures.

Molecular epidemiology uses genetic markers and DNA fingerprinting to track Mycobacterium TB (MTB) strains in a population. This method differentiates between newly transmitted TB cases and those resulting from the reactivation of dormant infections. Additionally, it helps identify risk factors associated with recent transmission events.[4,5]

Research has highlighted the changing nature of TB transmission and the need for strong public health measures to prevent exogenous reinfection. These studies emphasize the critical role of genetic diversity among MTB strains, which affects their virulence, spread, and disease outcomes.[4,5]

Wildlife involvement in the spread of TB complicates the management of the disease in both animals and humans. Molecular typing has revealed MTB complex strains in wild ungulates in Spain, highlighting the potential of wildlife as TB reservoirs for livestock and humans.[6]

The WHO Global Report shows that 85-90% of TB cases with drug sensitivity have been successfully treated worldwide. However, for multidrug-resistant TB (MDR-TB), the cure rate is up to 59%, and for extensively drug-resistant TB (XDR TB), it drops to 39%.[7]

The situation regarding TB in the Kyrgyz Republic is critical. WHO data show that the Kyrgyz Republic is among the 18 countries with a high incidence of TB and 30 countries with a significant MDR-TB burden in the WHO European Region.8

Since 2017, the country has used new anti-TB drugs (bedaquiline and delamanide) and repurposed drugs (clofazimine and linezolid) to treat M/XDR TB patients, with pretomanid introduced in 2021.

Despite reduced TB morbidity and mortality, the prevalence of MDR-TB remains high in Kyrgyzstan. While progress has been made in combating TB, MDR-TB, particularly XDR-TB, remains severe and requires further efforts to address. This study aimed to examine the prevalence, epidemiological traits, and treatment results of DR-TB, focusing on XDR-TB, in the Kyrgyz Republic between 2019 and 2022.

Methods

This research involved a retrospective observational and case-control study using national tuberculosis surveillance data from the Kyrgyz Republic from January 2019 to December 2022, covering all administrative regions, the civil health sector, and the prison system under the National Tuberculosis Program.

Data were sourced from standardized national forms №06u–08u, managed by the National Center of Phthisiology, under the Ministry of Health. These forms compile information from primary, secondary, and tertiary TB care facilities, including demographic, clinical, bacteriological, and treatment-related data.

This study included all registered cases of pulmonary TB (PTB) and extrapulmonary TB (EPTB). Drug-resistant TB (DR-TB) patients were categorized as rifampicin-resistant TB (RR-TB), MDR-TB, and XDR-TB based on drug susceptibility testing (DST). Both new and previously treated patients were included, with pediatric cases, female patients, and TB/HIV co-infection analyzed as subgroups.

Until 2020, XDR-TB was defined as resistance to isoniazid, rifampicin, any fluoroquinolone, and a second-line injectable drug. From 2020, the study adopted the WHO definition of XDR-TB as MDR/RR-TB with resistance to any fluoroquinolone and at least one Group A drug.

Patients underwent phenotypic drug susceptibility testing using the MGIT 960 system and Löwenstein–Jensen methods for first- and second-line drugs. Additional testing was performed for new drugs, including bedaquiline, linezolid, clofazimine, and delamanide, according to the WHO protocols.

Treatment information was collected for patients with RR-TB, MDR-TB, and XDR-TB. Patients received short-term, standardized, or individualized regimens based on resistance patterns. Treatment outcomes were defined by the WHO as successful treatment, failure, death, loss to follow-up, or not evaluated.

The variables included demographic data, TB characteristics, treatment history, drug resistance profile, HIV status, and region. The primary outcomes were DR-TB and XDR-TB prevalence and treatment outcomes, with secondary analyses of regional distribution and trends.

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Data entry and cleaning were performed using Microsoft Excel (version 2003), and analysis was conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as numbers and percentages. The χ^2 test was used for comparative analyses when appropriate. To evaluate the relationships between variables and outcomes, binary logistic regression was employed, with results reported as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). A p-value <0.05 was deemed significant.

This study used anonymized surveillance data routinely collected without patient interaction. Approval was obtained through the data governance framework of the National TB Program. Since no personal identifiers were included, individual informed consent was not required, in accordance with national ethical guidelines and WHO recommendations for public health surveillance research. The Ethics Committee of the National Institute of Public Health (formerly Scientific-industrial union "Preventive Medicine" of the Ministry of Health KR) approved this study (Protocol No. 7, dated May 24, 2023).

Results

Between 2019 and 2022, the country recorded 21,106 TB cases, with 4,194 (19.9%) being MDR/XDR TB cases. There is a yearly decline in cases, and analysis of data from 2019 and 2022 showed a significant difference (p<0.001, χ2=-2.5, OR -2.5, 95% CI: -2.1–3.1).

The coronavirus disease 2019 pandemic severely impacted access to TB services in the country. In 2020, newly registered TB cases dropped by 32.8% compared to 2019, resulting in an incidence rate of 64.5 per 100,000 population, down from 95.3%.1,9 While it was expected that high MDR-TB prevalence and coronavirus disease 2019 would worsen poverty, infection risk, and TB development in the coming years, this has not been confirmed.2 The incidence rate in 2022 was 60 cases per 100,000 population.

Despite the coronavirus disease 2019 challenges, treatment coverage for RR/M/XDR TB patients improved, rising from 86.5% (1,270 out of 1,468 patients in 2019) to 92.7% (900 out of 971 in 2020) and 94.8% (870 out of 918 in 2021) (Table.1). However, this rate fell to 90.1% in 2022 (754 out of 837), with the reasons under study.

Data from 2019-2020 shows that among 1,978 patients with RR/M/XDR-TB, new cases were predominant (n=1183 and n=795, respectively, 80.6–81.9%), while previously treated patients formed a smaller portion (n=285 and n=176, respectively, 19.4–18.1%).

During 2021-2022, the trend reversed: new RR/M/XDR-TB cases decreased to 60.7–60.0% (n=557 and n=520), while previously treated patients increased to 39.3–40.0% (n=361 and n=317, respectively).

These changes highlight issues among previously treated patients and underscore the need to investigate and address these trends.

From 2019 to 2022, PTB remained predominant, comprising 89.6-89.5% of cases (n=1305, n=869, n=839, and n=781) compared to EPTB cases (n=163, n=102, n=79, and n=56). Over four years, children and adolescents represented 5.4% of the total TB cases (65, 44, 71, and 71 cases from 2019 to 2022). The percentage of children among total TB cases increased from 4.3% to 7.6% (65 out of 1514 in 2019 and 71 out of 936 in 2022) (p<0.001, χ2=-2, OR -2.0, 95% CI -1.4–2.9). This trend stems from the weaker immune systems and susceptibility to TB in children. Untreated adults can become a source of infection for children, affecting their health. Prompt identification and treatment of TB in adults are crucial to minimize the risk to children and protect family health.[10]

A similar trend was observed among female patients, with an increase from 37.4–42% (567 cases in 2019 and 393 cases in 2022) (p = 0.026, χ2=-2, OR -1.2, 95% CI: 1.0–1.4). Russian researchers found a high percentage of women among patients with TB in 2010, indicating epidemic severity. The incidence in women of reproductive age suggests an endogenous infection reservoir, which poses a risk to children. Of the six children registered in 2010 who were in contact with primary TB patients, half had maternal contact.[9]

Despite the availability of rapid (genotypic) and other (phenotypic) methods for diagnosing DR-TB, bacteriological confirmation is not always possible. The rate of confirmed drug sensitivity of M/XDR-TB decreased from 97.0% in 2019 to 89.4% in 2022 (n=1468 out of n=1514 and n=837 out of n=936, respectively).

Among reported M/XDR-TB cases, 3.3–3.6% had co-infection (n=50 in 2019 and n=34 in 2022). Most patients received antiretroviral therapy (82.0–94.1%).

In neighboring countries, TB (from a lecturing perspective, it is a loner, bedaquiline, and linezolide) has been established over three years at 1.5–2.4–0.5% (n=14, n=20, and n=15, respectively) (Table 1). Nearly all XDR-TB cases were in patients with PTB, except for one EPTB case.

The largest segment of XDR-TB cases (n=49) consisted of TB pathogen strains resistant to both bedaquiline and clofazimine (BDQ + CFZ), accounting for 28.6% (n=14). This was followed by strains resistant to bedaquiline alone (22.4%, n=11) and those resistant to linezolid (LZD) (18.4%, n=9). Individuals exhibited varying responses to bedaquiline

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(n=34, 69.4%), with linezolid resistance being the second most common (n=15, 23.5%), and a smaller group showing resistance to both (n=7, 14.3%). A significant proportion showed resistance to bedaquiline and/or linezolid with clofazimine (n=25, 51.0%).

In the Kyrgyz Republic, XDR-TB most commonly exhibits resistance to bedaquiline, followed by resistance to linezolid. Simultaneous resistance to both drugs is less frequent. When XDR-TB shows resistance to both drugs, particularly clofazimine resistance, it poses significant treatment challenges. XDR-TB was identified in 22.4% (n=11) of patients without a prior treatment history, indicating new cases. This suggests potential spread of infection among previously affected and new individuals (Table 3).

Among previously treated XDR patients, TB was identified in 8.2% (n=4) due to disease recurrence, in 14.3% (n=7) following treatment interruption, and in over half (n=34, 55.1%) after unsuccessful treatment, with 46.9% (n=23) occurring after repeated therapies. Nearly all patients received second-line drugs, except for one who used isoniazid, rifampicin, pyrazinamide, and ethambutol. This indicates that second-line drugs are largely ineffective, highlighting the need for a proper TB treatment strategy and more effective therapies. This emphasizes the importance of completing TB treatment to prevent recurrence and minimize the risk of DR.

Most XDR-TB cases were recorded in populous areas, including Chui (n=18/36.7%), Jalal-Abad (n=13/26.5%), and Osh (n=8/16.2%). The Batken region reported no such cases. Given this, monitoring DR in TB is crucial for effective treatment strategies, and additional efforts are needed to prevent the spread of TB. Special attention to new TB cases is necessary for the timely detection, treatment, and prevention of transmission.

Table 1.Distribution of registered bacteriologically confirmed cases of DR-TB by TB form, cohort 2019-2023

Year	Total TB cases	Confirmed DR-TB cases	RR/M/XDR-TB started on treatment	New cases	Previously treated	PTB
2019	1514	1468 (97.0%)	1270 (86.5%)	1183 (80.6%)	285 (19.4%)	1305 (89.6%)
2020	1017	971 (95.5%)	900 (92.7%)	795 (81.9%)	176 (18.1%)	869 (89.5%)
2021	986	918 (93.1%)	870 (94.8%)	557 (60.7%)	361 (39.3%)	839 (89.6%)
2022	936	837 (89.4%)	754 (90.1%)	520 (60.0%)	317 (40.0%)	781 (89.5%)

Values are expressed as the n (%), n = number of patients, % = percentage of patients. TB – Tuberculosis, DR-TB – Drug-resistant Tuberculosis, RR-TB – Rifampicin-resistant Tuberculosis, MDR-TB – Multidrug-resistant TB, XDR-TB – Extensively drug-resistant Tuberculosis, PTB – Pulmonary Tuberculosis

Table 2.Results of treatment of patients with RU/mu/XDR TB, cohort 2017-2020

TB category	Year	Total patients	Treatment success	Treatment failure	Died of TB	Died (non-TB)	Lost to follow-up
RR/M/XDR-TB (overall)	2017	1323	734 (55.5%)	146 (11.1%)	93 (7.0%)	58 (4.4%)	290 (21.9%)
	2018	1349	830 (61.5%)	108 (7.9%)	79 (5.9%)	62 (4.6%)	270 (20.0%)
	2019	1310	935 (71.1%)	54 (4.1%)	41 (3.1%)	50 (3.8%)	230 (15.6%)
	2020	949	678 (71.4%)	39 (4.1%)	50 (5.3%)	41 (4.3%)	141 (14.9%)
XDR-TB only	2017	157	91 (58.0%)	25 (15.9%)	15 (9.6%)	5 (3.2%)	21 (13.4%)
	2018	105	55 (52.4%)	10 (9.5%)	13 (12.4%)	6 (5.7%)	21 (20.0%)
	2019	102	64 (62.7%)	10 (9.8%)	5 (4.9%)	3 (2.9%)	20 (19.6%)
	2020	68	41 (61.8%)	5 (7.4%)	5 (7.4%)	6 (8.9%)	10 (14.7%)

Values are expressed as the n (%), n = number of patients, % = percentage of patients. TB – Tuberculosis, RR-TB – Rifampicin-resistant Tuberculosis, MDR-TB – Multidrug-resistant TB, XDR-TB – Extensively drug-resistant Tuberculosis

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Table 3.Regional distribution of XDR-TB cases registered and initiated on treatment in the Kyrgyz Republic (2019-2022)

Region	Year	Total DR-TB cases	Bacteriologically confirmed	XDR-TB cases	XDR-TB among confirmed
Chui	2019	303	227	20	6.6%
	2020	245	185	16	6.5%
	2021	242	185	27	11.2%
	2022	233	175	28	12.0%
Osh city	2019	40	22	6	15.0%
	2020	37	29	4	10.8%
	2021	32	27	4	12.5%
	2022	34	26	6	17.6%
Jalal-Abad	2019	256	179	27	10.5%
	2020	196	145	23	11.7%
	2021	201	181	32	15.9%
	2022	153	147	23	15.0%
Kyrgyz Republic (total)	2019	1313	925	109	8.3%
	2020	948	708	82	8.6%
	2021	940	710	116	12.3%
	2022	850	647	113	13.3%

Values are expressed as the n and %, n = number of patients, % = percentage of patients. TB – Tuberculosis, DR-TB – Drug-resistant Tuberculosis, XDR-TB – Extensively drug-resistant Tuberculosis.

Discussion

This nationwide retrospective study examined the epidemiology, resistance trends, and treatment results of DR-TB, focusing on XDR-TB, in the Kyrgyz Republic from 2019 to 2022. The results show progress in TB control while highlighting the structural and biological challenges in maintaining a high MDR/XDR-TB prevalence.

Although the number of TB cases decreased during the study period, approximately one in five patients with TB had MDR/XDR-TB, indicating that Kyrgyzstan remains a high-burden country in the WHO European Region. This proportion matches that of other post-Soviet regions, where historical treatment practices and health system disruptions have led to persistent drug resistance.[10-12] The drop in TB notifications in 2020 coincided with the COVID-19 pandemic, suggesting reduced access to services rather than epidemiological improvement.[13-15]

The shift after 2020 towards more previously treated DR-TB patients indicates issues with treatment interruption, relapse, and programmatic failure. These trends mirror those of Central Asia and Eastern Europe, where socioeconomic instability and migration increase the risk of resistance.[16,17]

The rising number of pediatric TB cases is concerning, serving as an indicator of recent community transmission and undiagnosed adult cases.[18,19] The increasing pediatric burden in Kyrgyzstan indicates ongoing household transmission, necessitating enhanced contact tracing and preventive therapy. The rise in TB among women of childbearing age aligns with Eurasian trends and is attributed to reactivation, delayed diagnosis, and barriers to healthcare access.[20] Maternal TB threatens women's health and pediatric transmission, perpetuating the disease across generations.

Despite Kyrgyzstan's adoption of rapid molecular diagnostics, the decrease in bacteriological confirmation rates by 2022 is worrisome. This decline affects the effectiveness of individualized treatment. Similar diagnostic challenges emerged in resource-limited settings during the COVID-19 pandemic, which disrupted laboratory capabilities and specimen transport.[21]

A key finding was the high prevalence of resistance to bedaquiline and linezolid among XDR-TB isolates. These drugs are central to the WHO-recommended Group A regimens, and the rising resistance threatens all existing oral treatment approaches.[22-24] The overlap in resistance between bedaquiline and clofazimine is associated with mutations in the Rv0678 regulatory pathway.[25,26] Over 20% of XDR-TB cases occurred in previously untreated patients, indicating the primary transmission of resistant strains and

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highlighting the need for enhanced molecular surveillance and infection control.[4]

Success rates for treating RR/M/XDR-TB have improved toward WHO global averages, reflecting optimized treatment regimens and improved access to medications in recent years. However, XDR-TB outcomes remain suboptimal, with many patients experiencing treatment failure, death, or loss to follow-up. These findings align with global data showing poor XDR-TB prognosis despite therapeutic advances.[27] XDR-TB cases emerging after failed treatments highlight the need for early and effective regimens and adherence support. Enhanced patient-centered care and resistance-guided treatment are crucial to prevent resistance escalation.[28]

The clustering of XDR-TB cases in Chui, Jalal-Abad, and Osh shows that urban growth, population movement, and health system burdens influence transmission patterns. This regional variation, observed in countries with high TB prevalence, underscores the need for geographically targeted interventions rather than uniform national strategies.[29]

The strengths of this study lie in its national scope, consistent surveillance data, and resistance profiling over the years. However, it is limited by its retrospective nature, underdiagnosis during COVID-19, and lack of molecular genotyping data, which would enable precise differentiation between transmitted and acquired resistance.

Conclusion

Although Kyrgyzstan has made notable progress in managing DR-TB, XDR-TB remains a significant public health threat. Rising resistance to bedaquiline and linezolid, signs of primary transmission, and treatment failure highlight the need for enhanced molecular surveillance, tailored treatment, and patient support systems. Continued investment in TB control, aligned with the WHO End TB targets, is crucial for preventing the escalation of drug resistance and protecting future generations.

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