EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 9.2 www.in-academy.uz/index.php/ejmns

STUDY OF THE PROBLEM OF ADVERSE EVENTS FROM CHEMOTHERAPY FOR TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

Tashpulatova Fatima Kudratovna
Doctor of Medical Sciences (DSc), Associate Professor
Department of Infectious Diseases, Pediatric Infectious Diseases, Phthisiology and Pulmonology
Tashkent State Medical University
https://doi.org/10.5281/zenodo.18616823

ARTICLE INFO

Received: 05th February 2026
Accepted: 10th February 2026
Online: 11th February 2026

KEYWORDS

tuberculosis, children, adolescents, chemotherapy, adverse drug reactions, hepatotoxicity, pharmacovigilance, pediatric TB.

ABSTRACT

Tuberculosis (TB) remains a major global health problem, particularly among children and adolescents in high-burden countries. Although anti-tuberculosis chemotherapy is effective, it is frequently associated with adverse drug reactions (ADRs), which may compromise treatment adherence, therapeutic outcomes, and quality of life. This study aims to analyze the spectrum, frequency, risk factors, and clinical consequences of adverse events associated with anti-tuberculosis chemotherapy in children and adolescents.

Introduction

Each year, an estimated 1.8 million adolescents (aged 10–19 years) and young adults (aged 20–24 years) become sick with tuberculosis (TB), representing approximately 18% of the annual global TB incidence. Although it is preventable and treatable, TB is a leading cause of death among adolescents and young adults (AYAs) globally. The World Health Organization (WHO) estimates that in 2019, 71,000 adolescents (11,000 between the ages of 10–14 years and 60,000 between the ages of 15–19 years) and 90,000 young adults died of TB (Figure 1). TB is a leading cause of hospitalization and mortality among people with HIV, including AYAs.

AYAs face unique challenges with respect to TB and TB care. The risks of Mycobacterium tuberculosis infection and progression to TB disease increase during this period. Females are at greater risk for TB than males during early adolescence; risk among males increases during late adolescence.10 Risk for TB progression is exacerbated by HIV infection, which is a substantial concern in this age group. In 2021, approximately 28% of new HIV infections worldwide occurred in individuals between 15–24 years of age; moreover, AYAs experience worse outcomes in the HIV care cascade as compared to other age groups. Among AYAs with TB, those who are living with HIV, living in conditions of extreme poverty and/or violence, and/or were previously treated for TB disease are at risk for poor adherence to TB treatment and loss to follow-up.15–20 Between the ages of 10–24 years, individuals undergo rapid growth and development; acquire the physical, cognitive, emotional, and social resources required for achieving

health and well-being in adulthood; and become more autonomous and independent of caregivers. TB illness and treatment impact these transitions, and these transitions, in turn, shape how AYAs experience TB illness and treatment. The WHO and other institutions have highlighted the need for healthcare services and research to address the specific needs of AYAs. However, policies and practices by most national TB programs (NTPs) do not currently account for AYA-specific needs and considerations. In 2021, to inform the update of the WHO guidelines and operational handbook for the management of TB in children and adolescents, the WHO commissioned an evidence review to answer the following background question: How can adolescents with TB or eligible for TB preventive treatment (TPT) be optimally engaged in care? Given the dearth of evidence on best practices in this area, we convened an international expert panel to generate a consensus statement regarding needed interventions to optimize TB care for this age group.

Chemotherapy for TB involves prolonged multidrug regimens, typically including isoniazid, rifampicin, pyrazinamide, and ethambutol. While these drugs are highly effective, their long-term administration increases the risk of adverse drug reactions (ADRs), particularly in children and adolescents whose metabolic systems are still developing.

Adverse events may lead to treatment interruption, poor adherence, drug resistance, and increased healthcare costs. Adolescents represent a particularly vulnerable group due to hormonal changes, psychosocial factors, and higher rates of non-adherence.

Despite global TB control programs, limited large-scale data are available regarding the incidence and severity of ADRs specifically in pediatric and adolescent populations. Therefore, systematic evaluation of chemotherapy-related complications in this age group is of critical importance.

The aim of this study is to comprehensively analyze adverse events associated with anti-TB chemotherapy in children and adolescents and to identify clinical and demographic predictors.

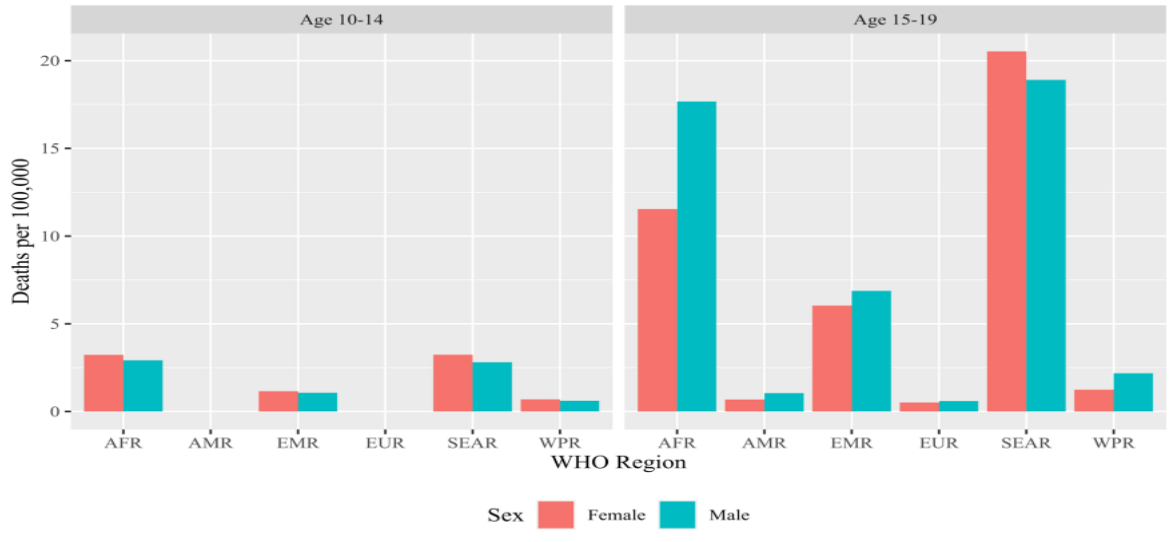


Figure 1: Tuberculosis Mortality among Adolescents by Sex and World Health Organization Regions
Abbreviations: AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asian Region; WHO, World Health Organization; WPR, Western Pacific Region.

Materials and Methods

Study Design

A prospective observational cohort study was conducted in a tertiary pediatric TB center between 2022 and 2024.

Participants

Inclusion criteria:

- Confirmed pulmonary or extrapulmonary tuberculosis
- Age between 1 and 17 years
- Initiation of standard first-line anti-TB therapy

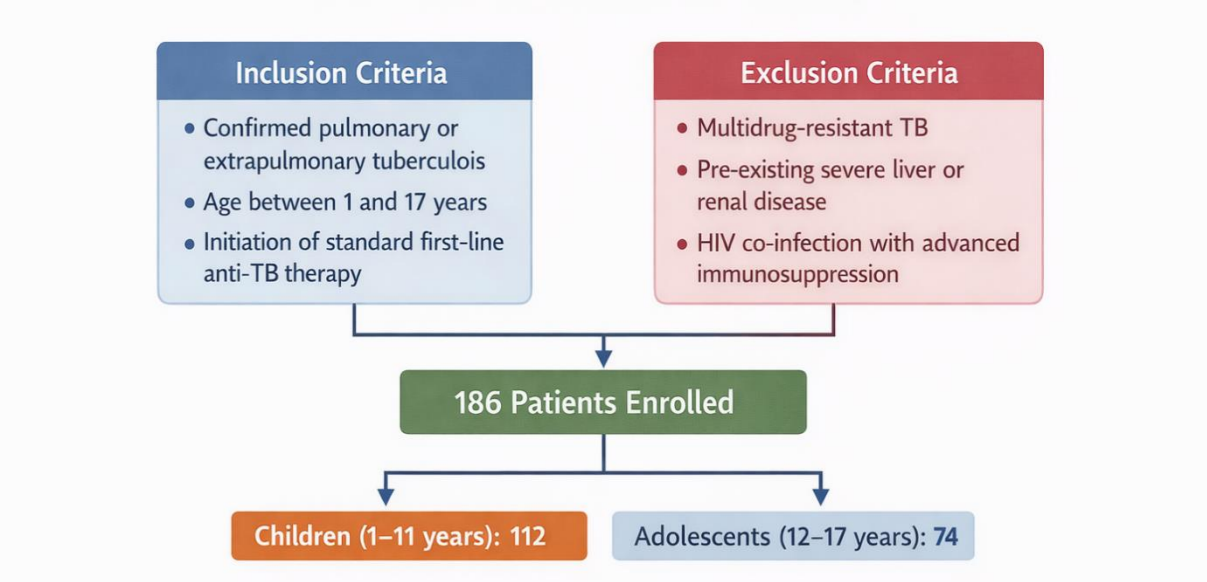
Exclusion criteria:

- Multidrug-resistant TB
- Pre-existing severe liver or renal disease
- HIV co-infection with advanced immunosuppression

A total of 186 patients were enrolled:

- Children (1–11 years): 112

Adolescents (12–17 years): 74



Treatment Regimen

All patients received standard WHO-recommended regimens:

- Intensive phase (2 months): isoniazid, rifampicin, pyrazinamide ± ethambutol
- Continuation phase (4 months): isoniazid + rifampicin

Monitoring and Data Collection

Patients underwent:

- Baseline and monthly liver function tests
- Complete blood count
- Neurological examination
- Clinical assessment of gastrointestinal symptoms
- Documentation of dermatological and allergic manifestations

Adverse events were graded according to:

- WHO causality assessment
- CTCAE version 5.0 severity grading

Statistical Analysis

Data were analyzed using SPSS 26.0. Chi-square tests and logistic regression were used to identify risk factors. A p-value < 0.05 was considered statistically significant.

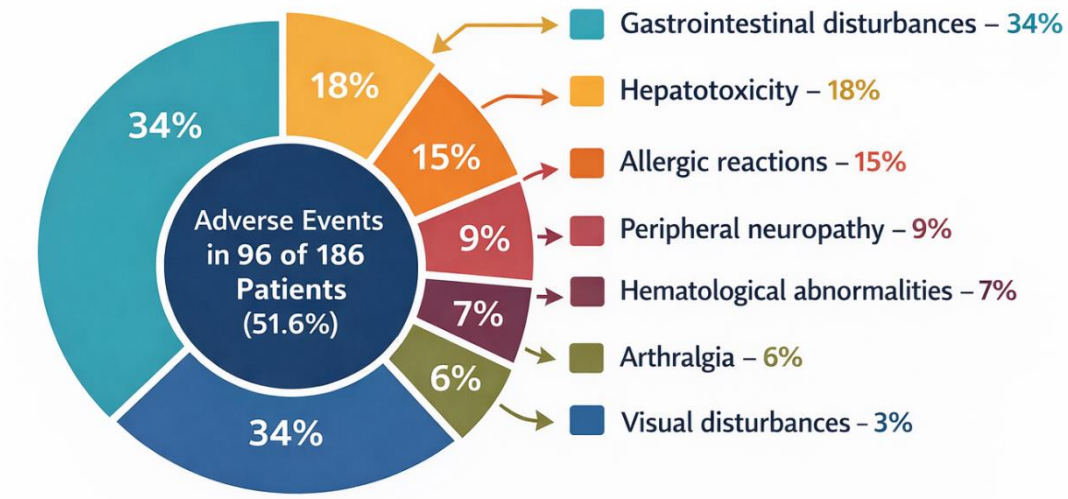
Results

Overall Incidence of Adverse Events

Adverse events were observed in 96 out of 186 patients (51.6%).

Distribution:

Adverse events pie chart analysis



Hepatotoxicity

Hepatotoxicity was defined as ALT/AST > 3× upper limit with symptoms or >5× without symptoms.

Incidence:

- Adolescents: 24%
- Children: 14% (p = 0.03)

Risk factors:

- Malnutrition (OR 2.1)
- Female sex in adolescents
- Concomitant use of hepatotoxic drugs

Gastrointestinal Disorders

Most common symptoms:

- Nausea
- Vomiting
- Abdominal pain
- Loss of appetite

These were generally mild to moderate (Grade 1–2).

Neurological Complications

Peripheral neuropathy occurred primarily in adolescents receiving high-dose isoniazid without adequate pyridoxine supplementation.

Treatment Modification

In 12% of cases, temporary drug interruption was required. Permanent discontinuation occurred in 3% of patients.

The findings confirm that adverse drug reactions are common during pediatric TB chemotherapy, affecting over half of treated patients. Gastrointestinal symptoms were the most prevalent but were generally manageable.

Hepatotoxicity remains the most clinically significant complication. Adolescents demonstrated higher vulnerability, possibly due to hormonal influences and differences in drug metabolism. Previous studies similarly report hepatotoxicity rates ranging from 10% to 25%.

Malnutrition emerged as a significant risk factor. Nutritional deficiencies may impair hepatic detoxification mechanisms, increasing susceptibility to liver injury.

Pharmacovigilance remains underdeveloped in many TB programs. Regular biochemical monitoring, especially during the intensive phase, is crucial for early detection.

Individualized dosing based on weight bands and therapeutic drug monitoring may improve safety profiles.

Clinical Implications

- Mandatory baseline liver function assessment
- Monthly monitoring during intensive phase
- Routine pyridoxine supplementation
- Nutritional support programs
- Adolescent-focused adherence counseling
- Strengthening national pharmacovigilance systems

Limitations

- Single-center study
- Moderate sample size
- Lack of long-term follow-up data
- Exclusion of MDR-TB patients

Future multicenter studies with pharmacogenetic analysis are recommended.

According to the recommendations of the World Health Organization (WHO) and the clinical guidelines of the Russian Foundation for Respiratory Tuberculosis in Children, 2016, chemotherapy for MDR tuberculosis for most patients, including children and adolescents, should last 18-24 months (intensive phase - 6-8 months or more until two consecutive negative culture results are obtained at an interval of one month - at least 12 months). According to the same principle, treatment is prescribed to patients with tuberculosis from confirmed foci of tuberculosis infection with MDR MBT at the source of infection until the results of drug susceptibility testing (DST) are received [6–8]. It should be noted that the WHO position does not exclude the study of new approaches to chemotherapy of tuberculosis with MDR MBT aimed at reducing the duration of treatment, but treatment regimens should be improved only in the context of scientific research and under close monitoring for at least 12 months after the end of treatment. Follow-up monitoring is aimed at the early identification of patients who may be at high risk of disease relapse. Only with this approach can the issue of reducing the duration of chemotherapy in this category of patients be resolved.

The clinical study focused on the development of chemotherapy regimens for respiratory tuberculosis in children who were in contact with a tuberculosis patient excreting MBT with MDR and XDR anti-TB drugs, and chemotherapy in adolescents excreting MBT with MDR anti-TB drugs. The need and possibility of a personalized approach to chemotherapy are determined by the characteristics of respiratory tuberculosis in this category of patients. In children, these are predominantly newly identified processes with primary resistance of MBT to anti-TB drugs (77.8%). This is confirmed by the fact that the sources of infection are close relatives and, according to our data, partial or complete coincidence of DST is 65–72%. Among children with tuberculosis, the proportion of MBT excretors is extremely small (5.2%) [3]. The choice of the starting combination of anti-TB drugs for the treatment of tuberculosis in children who are in contact with a tuberculosis patient is based exclusively on the results of DST at the source of infection [9]. In general, the problem of chemotherapy for active tuberculosis in children living in foci with MDR MBT at the source of infection has remained virtually unstudied to date. At the same time, chemotherapy for primary tuberculosis in children, taking into account the DST of the source of infection and the prevalence of the process, ensures rapid clinical, radiological, and laboratory dynamics of the process and allows for scientific justification for shortening the duration

of chemotherapy and reducing the number of anti-TB drugs in the chemotherapy regimen. In conducting the study, we took into account that the wider the spectrum of MBT drug resistance in an adult patient, the more difficult it is to select an adequate combination of anti-TB drugs for a sick child. With an expansion of the spectrum of MBT drug resistance, the number of anti-TB drugs that can be used for treatment decreases [10–12]. In addition, the presence of age restrictions for the use of a number of anti-TB drugs, such as ethambutol, fluoroquinolones, capreomycin, cycloserine, bedaqueline, perchlozone, also determines the need for personalized approaches to the selection of the starting combination of anti-TB drugs in the treatment of tuberculosis in children from foci with MDR pathogen at the source of infection [13, 14]. The characteristics of the tuberculosis process are important. Treatment regimens differ in the number of anti-TB drugs included in the starting combination: from 3 anti-TB drugs for minimal pathological changes in the lungs or intrathoracic lymph nodes ("minor" forms) to 4 anti-TB drugs for limited and 5-6 anti-TB drugs for widespread and complicated processes. The rationale for isolating the intensive phase of chemotherapy was the presence of widespread or complicated processes in the infiltration phase. Moreover, the overall treatment duration, compared with standard IV and V chemotherapy regimens used to treat this category of patients, was reduced and ranged from 6 to 18 months, depending on the nature of the tuberculosis process in the child. The tactics and regimens of tuberculosis chemotherapy in children from foci with MDR/XDR MBT at the source of infection are presented in Tables 1 and 2. Thus, chemotherapy of respiratory tuberculosis in children from foci of tuberculosis infection with DR MBT at the source of infection to anti-TB drugs should be carried out taking into account the nature of the tuberculosis process in the child and the spectrum of DR MBT at the source of infection. This made it possible to reduce the overall duration of the main chemotherapy course in this category of patients to 6–9 months for “minor” and limited processes using a chemotherapy regimen of 3–4 drugs and up to 12–18 months for widespread and complicated processes using 5–6 drugs, taking into account the DST of the source of infection. A reduction in the duration of treatment and the number of drugs in chemotherapy regimens based on the results of long-term observations did not affect the effectiveness of treatment in all observed patients (186 people).

Conclusion

Adverse events associated with anti-tuberculosis chemotherapy in children and adolescents are frequent and clinically significant. Gastrointestinal disturbances and hepatotoxicity are most common, with adolescents at higher risk.

Early detection, individualized therapy, nutritional support, and structured pharmacovigilance programs are essential to improve treatment safety and outcomes.

Informed by this expert consensus statement, the global TB community can ensure that TB prevention, diagnosis, and treatment are optimized for this age group, with full consideration of AYAs’ development and well-being. These reforms are needed to address the needs of individuals in this vulnerable age group in order to achieve improved TB outcomes—and ultimately, to help end the global TB epidemic.

References:

1. World Health Organization. Global tuberculosis report 2023. Geneva: WHO; 2023.
2. Graham SM, et al. Clinical management of childhood tuberculosis. Int J Tuberc Lung Dis. 2015;19(9):1050–1057.
3. Marais BJ, et al. Tuberculosis in children and adolescents. Lancet. 2022;399(10337):1830–1844.
4. Saukkonen JJ, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935–952.
5. Tostmann A, et al. Antituberculosis drug-induced hepatotoxicity. Drug Saf. 2008;31(8):633–645.
6. Sharma SK, et al. Safety of antituberculosis therapy in children. Pediatr Infect Dis J. 2010;29:1020–1023.
7. Nahid P, et al. Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63:e147–e195.
8. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. Pediatr Drugs. 2011;13:1–9.
9. WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014.
10. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology. 2006;11:699–707.
11. Kohlenberg A, Kodmon C, van den Boom M, van der Werf MJ Tuberculosis surveillance in adolescents: What to learn from European Union/European Economic Area data? Int J Tuberc Lung Dis 2020;24(3):347–352. DOI: 10.5588/ijtld.19.0547.
12. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC The age of adolescence. Lancet Child Adolesc Health 2018;2(3):223–228. DOI: 10.1016/s2352-4642(18)30022-1.
13. Patton GC, Sawyer SM, Santelli JS, et al. Our future: A Lancet commission on adolescent health and wellbeing. Lancet 2016;387(10036):2423–78. DOI: 10.1016/S0140-6736(16)00579-1.
14. World Health Organization. Making health services adolescent friendly: Developing national quality standards for adolescent-friendly health services. Available at: https://apps.who.int/iris/ bitstream/handle/10665/75217/9789241503594_eng.pdf?sequence=1. Accessed Feb. 21, 2022.
15. World Health Organization. Global standards for quality health care services for adolescents. Available at: https://www.who.int/maternal_child_adolescent/documents/globalstandards-adolescent-care/en/. Accessed Feb. 21, 2022.
16. Zeitvogel K Fogarty's adolescent research key to future good health. Available at: https://www.fic.nih.gov/News/GlobalHealthMatters/march-april-2018/Pages/adolescent-healthresearch.aspx. Accessed Feb. 21, 2022
17. Blok N, van den Boom M, Erkens C, et al. Variation in policy and practice of adolescent tuberculosis management in the WHO European Region. Eur Respir J 2016;48(3):943–6. DOI: 10.1183/13993003.00704-2016.

18. Laycock KM, Eby J, Arscott-Mills T, et al. Towards quality adolescent-friendly services in TB care. Int J Tuberc Lung Dis 2021;25(7):579–583. DOI: 10.5588/ijtld.21.0059.
19. Moscibrodzki P, Enane LA, Hoddinott G, et al. The impact of tuberculosis on the well-being of adolescents and young adults. Pathogens 2021;10(12). DOI: 10.3390/pathogens10121591.
20. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. New Engl J Med 2004;350(20):2060–7. DOI: 10.1056/NEJMsa031667.
21. Middelkoop K, Bekker LG, Liang H, et al. Force of tuberculosis infection among adolescents in a high HIV and TB prevalence community: A cross-sectional observation study. BMC Infect Dis 2011;11:156. DOI: 10.1186/1471-2334-11-156.