

Clinical Profile of Pediatric Extrapulmonary Tuberculosis in a Tertiary Hospital: A 10-year Retrospective Study

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Abbreviations

EPTB Extrapulmonary tuberculosis
SPMC Southern Philippines Medical Center
TB Tuberculosis
CNS Central Nervous System
NTP National Tuberculosis Program
MTB. Mycobacterium Tubercle Bacilli

Abstract

Background: Young children are at increased risk of developing severe forms of tuberculosis (TB) disease. Extrapulmonary tuberculosis (EPTB) contributes significantly to TB-related morbidities. This study aimed to determine patients' epidemiologic and clinical profile with EPTB among children aged 0-18 years old admitted and diagnosed from January 2010 to December 2019 at Southern Philippines Medical Center (SPMC). **Methodology:** This is a retrospective cross-sectional study. The child's medical records for EPTB admission in SPMC were retrieved. Data including demographic, clinical presentation, treatment outcomes and survival rate were recorded and subsequently analyzed. **Results:** There were 136 EPTB cases from January 2010 to December 2019. Prevalence of EPTB is 17% among all pediatric TB admissions. A total of 75 EPTB patients were evaluated. The average age of patients is 9 years old. Majority of patients belong to the 11-18yo. No significant difference among male and female patients. Most of the patients were malnourished, received BCG vaccine and had TB exposure to an infected family member. The most common symptoms were fever, seizure, vomiting, and headache. Majority of cases involved the central nervous system (CNS), followed by gastrointestinal involvement and the pleura. Half of the cases completed treatment and only two cases were cured. The average survival time based on Kaplan Meier Curve survival analysis is 34 days. Survival is below 80% on the 25th hospital day and onwards. **Conclusion:** Extrapulmonary tuberculosis in children results in higher morbidity, mortality, and healthcare cost due to prolonged hospitalization and longer duration of treatment. Early diagnosis, intervention and treatment are the cornerstone in decreasing the burden of disease.

Keywords: Extrapulmonary, tuberculosis, extrapulmonary tuberculosis, central nervous system

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1. Introduction

In 2009 the World Health Organization (WHO) reported that the global tuberculosis (TB) burden had reached 9.4 million cases, equivalent to 200 cases per 100,000 population. The majority of cases were in South-East Asia, Africa, and Western Pacific regions with 35%, 30%, and 20%, respectively¹. In 2019, an estimated 10.0 million people fell ill with TB, equivalent to 132 cases per 100,000 population. Most of the estimated number of cases still occurred in the South-East Asia Region. Tuberculosis is still one of the top causes of morbidity and mortality in both developing and industrialized countries. Worldwide, it is the 10th leading cause of death¹. The Philippines is still among the top 10 countries with a high TB burden. It ranked 4th among the 22 high TB burden countries in 2019. Among Filipinos, TB is the 6th leading cause of mortality and morbidity³.

High burden countries have 20-40% more childhood TB cases⁴. The Philippines accounted for 12% of the total cases among 0-14 age group in the 2018 report⁵. Seventy (70%) to eighty percent (80%) of children with TB have pulmonary involvement, while 20-30% have extrapulmonary sites⁶.

Young children are at increased risk of developing severe forms of TB disease such as disseminated TB and TB meningitis. They have increased risk of death especially children less than 2 years old⁸. Extrapulmonary Tuberculosis (EPTB) contributes significantly to TB-related morbidity and can cause complications, lifelong sequelae, and disabilities¹⁰. Due to delay in recognition and lack of consideration of TB especially if presenting symptoms are not respiratory in nature, the incidence of new cases of EPTB has remained constant despite the decline in new cases of active pulmonary TB¹². There are gaps in the actual number of cases due to underdiagnosis and under reporting⁸. Furthermore, there are also limited researches and development related to pediatric TB^{2,8} hence this study is undertaken.

2. Methodology

The study used a retrospective cross-sectional research design. It was done in a tertiary government hospital at Southern Philippines Medical Center in Davao City, Philippines. It is a 1,500 bed-capacity hospital catering the health needs of the City and Southern Mindanao. Included in the study are children aged 0-18 years old admitted with extrapulmonary tuberculosis from January 2010 to December 2019 in the said institution. All records of these patients included in the study. Purposive sampling was done in the selection of the study population. There was no randomization. Collected data were organized and subsequently analyzed (Figure 1). Descriptive statistics such as mean and standard deviation were utilized for demographic and clinical profiling. A proportion was used and estimated using a 95% confidence interval to determine the prevalence. A Kaplan Meier or survival analysis was also utilized for the number of days of survival among patients with EPTB. All statistical testing were compared at a 5% level of significance.

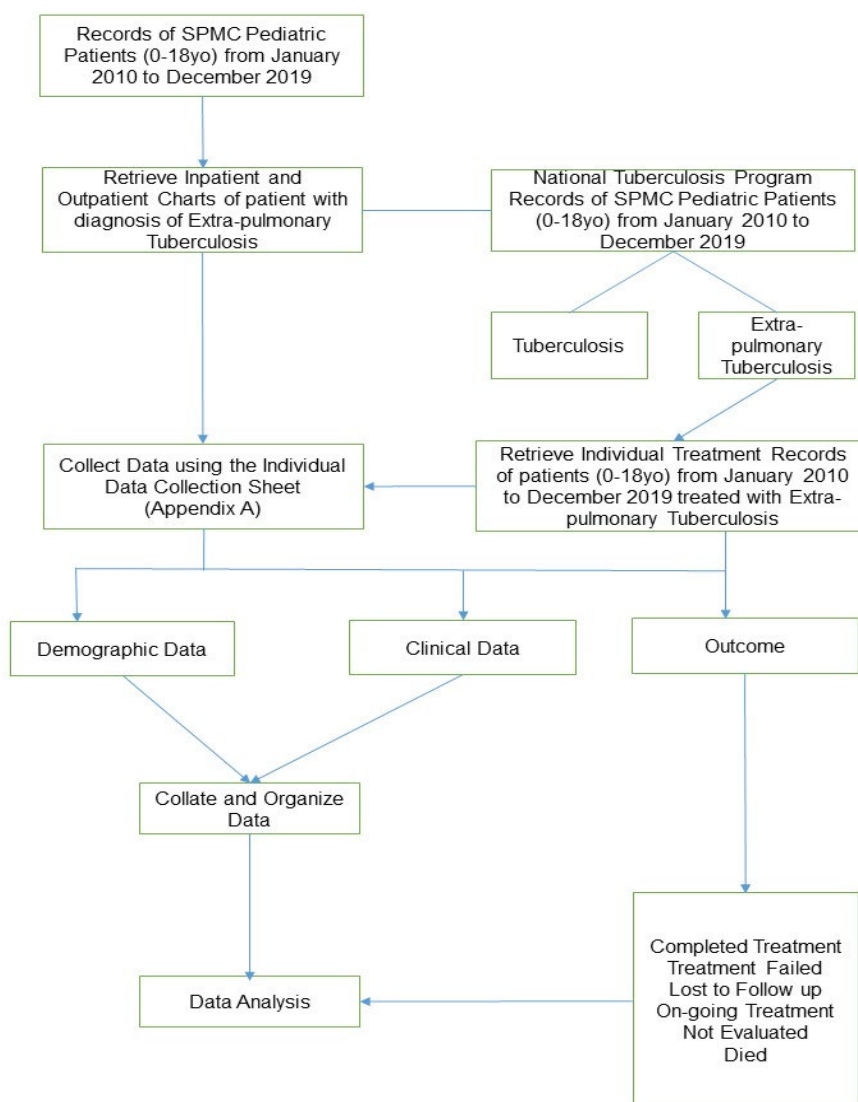


Figure 1. Diagram of Data Collection and Analysis

3. Results

A total of 136 EPTB cases were reviewed from January 2010 to December 2019. From these cases, 98 were successfully retrieved but only 75 qualified. The proportion of admitted cases due to EPTB range from 7-20%. The highest number of which were noted in 2011, 2013, and 2015 with 21.4%, 21.9%, and 21.5% respectively (Table 1).

Table 1. Yearly cases of pediatric tuberculosis and extrapulmonary tuberculosis

Year	Number of TB Cases	Number of Extrapulmonary TB	%
2010	48	9	18.8
2011	56	12	21.4
2012	76	16	21
2013	41	9	21.9
2014	63	16	25
2015	93	20	21.5
2016	92	12	13
2017	106	16	15
2018	105	17	16.1
2019	117	9	7.69
TOTAL	797	136	17

Prevalence of EPTB is 17% among all pediatric TB admissions for 2010-2019. This is in contrast with the Philippine community survey³ done in 2003-2011, which showed a prevalence of only 1.1%. WHO surveillance report in the Philippines (2015) classified only 1.9% of all reported TB as exclusively extrapulmonary²². In a study in 2013, it was noted that the total number of PTB cases was decreasing while the number of EPTB was gradually increasing during the same period. In this study, it showed an increasing trend of TB cases (Figure 2) but EPTB conditions were observed consistently during the 10-year study period.

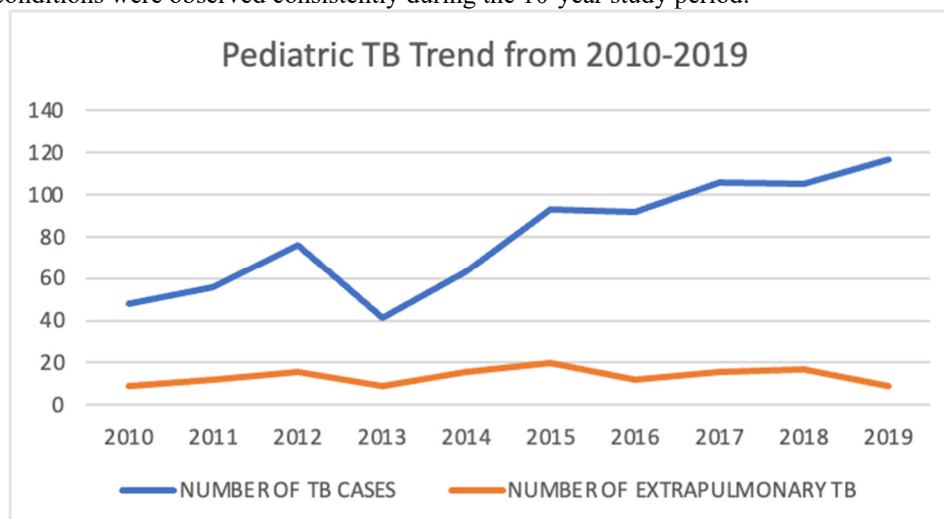


Figure 1. Pediatric TB trend of admitted patients in aged 0-18 from 2010 to 2019.

Of the 75 patients, the mean age with EPTB is nine (9) years old. No patient less than 1-year-old was recorded. Majority are 11-18yo and 1-5yo with 38.7% and 37.3%, respectively. The highest proportion of admitted cases of EPTB was 10-17 years old (Table 2). This is supported by a study of Losa²³, most cases of affected children are 1-5 years old. The host immunity of these patients is the primary determinant of risk for disease development following infection³⁵. Infants with immature immune systems were at the highest risk for extrapulmonary TB such as meningitis or disseminated miliary disease. Adolescence is also recognized as a critical period of tuberculosis infection, disease, and adverse outcomes. They contribute to the ongoing transmission²².

There were 41 (54.7%) males and 34 (46.7%) females. No significant difference was noted between males and females with a 1.2:1 ratio. Most admitted cases were residents of Davao City. More than half (53.3%) came from Davao, and the rest of the patients, 35 (46.7%), are from nearby provinces.

Most of our patients are malnourished (65.3%). Because of inadequate immune response to infection, there is a higher risk of a progressive or generalized infection among these children, making them susceptible to tuberculosis infections.

Eighty-four percent (84%) of patients were given Bacille Calmette Guerin (BCG) vaccine. BCG has been shown to be protective against disseminated forms of TB in young children, with 73% protection against TB meningitis and 77% against miliary disease³⁵. WHO has continued to recommend BCG vaccination in infants to reduce the severity of the disease¹¹.

The presence of TB exposure was noted among 72% of EPTB patients. They were usually exposed to a family member who is the index case in the household. This is high if we compare it to studies done in other countries with only 22 to 28.6%. In a Philippine study³³, 36% was noted to have TB exposure. Social stigma and undiagnosed

cases are the causes of low reports of TB exposure. Diagnosis of childhood EPTB is immediately followed by intensive contact tracing to prevent delays in diagnosis and treatment. Delays may lead to high mortality and potential spread of the disease. This is one of the most vital factors associated with infection in pediatric patients²¹.

Only 28% of the patients were exposed to cigarette smoking. In a study in Iran¹⁹, household exposure to cigarette smoke along with low body weight and household contact with TB treatment failure were the leading risk factors for inadequate response to anti-TB therapy. Among the EPTB patients, 9% patients had comorbidities such as Rheumatic Heart Disease (RHD), Leukemia, Thalassemia, and Henoch-Schonlein purpura Purpura (HSP). These conditions added to their susceptibility to TB infection.

Table 2. Demographic profile of patients admitted with extrapulmonary TB

Demographic Profile	Number of Patients (Percentage)
Age	
0-12 months	0
1yr – 5 years old	28 (37.3)
6-10 years old	18 (24)
11-18 years old	29 (38.7)
Sex	
Male	41 (54.7)
Female	34 (46.7)
Address	
Within Davao	40 (53.3)
Outside Davao	35 (46.7)
Nutritional Status	
Malnourished	49 (65.3)
Well-nourished	26 (34.7)
BCG vaccination	
Given BCG	63 (84)
No BCG	12 (16)
TB Exposure	
With TB Exposure	54 (72)
Without TB Exposure	21 (28)
Cigarette Smoking	
Exposure to cigarette smoking	21 (28)
No exposure to cigarette smoking	54 (72)
Comorbidities	
Diabetes	0
Cardiovascular Diseases	1 (1.3)
Hypertension	0
HIV	0
Others	6 (8)

The most common presenting symptoms noted in our study population were fever (76%), followed by seizure, vomiting, and headache (29%). Most cases of EPTB involved the CNS with 53.3% (40), followed by gastrointestinal involvement (13.3%) and pleura (10.7%). This is similar to other Philippine studies^{12,23,33} where the most common EPTB involvement is the CNS. Other country like India¹¹ also involved the CNS. This is in contrast with other countries like Madrid, Turkey, Colombia, and Tunis where lymphadenopathy^{27,20,21,25} involvement is the most common.

Table 3. Symptoms and primary organ involvement of patients with extrapulmonary tuberculosis

Presentation	Values (Percentage)
Fever	57 (76)
Anorexia	7 (9.3)
Weight Loss	12 (16)
Night sweats	3 (4)
Malaise	3 (4)
Seizure	22 (29)
Vomiting	22 (29)
Change in Sensorium	4 (5.3)
Headache	22 (29)
Hemiparesis	6 (8)
Difficulty breathing	7 (9.3)
Skin abscess/cellulitis	3 (4)
Abdominal pain	8 (10.7)
Hemoptysis	1 (1.3)
Back pain	7 (9.3)
Chills	1 (1.3)
Urinary Symptoms	0
Pleuritic pain	1 (1.3)
Joint pain	1 (1.3)
Joint Swelling	1 (1.3)
Murmur	0
Masses	4 (5.3)
Lymphadenopathy	1 (1.3)
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Organ Involvement	
CNS	40 (53.3)
Lymphatics	6 (8)
Skeletal	6 (8)
Genitourinary	0
Gastrointestinal	10 (13.3)
Cardiovascular	2 (2.7)
Skin/Cutaneous	3 (4)
Pleura	8 (10.7)

In another study in a Children’s Medical Center in Manila³³, more than fifty percent of the cases had TB of the central nervous system, followed by TB of the abdomen, TB of the pleura and TB of the lymph nodes.

Of the 75 patients, it is notable that only 2 (2.7%) patients were microbiologically confirmed. The remaining 73 (97.3%) were clinically diagnosed. Among the EPTB patients, a total of 38 (50.7%) were able to complete the treatment, 2 (2.7%) were cured and 9 (12%) were lost to follow up (Table 3).

Table 3. Treatment Outcome of pediatric patients with extrapulmonary tuberculosis

Treatment Outcome	No of Patients	Percentage
Completed Treatment	38	50.7
Cured	2	2.7
Lost to follow up	9	12
Ongoing Treatment	2	2.7
Not evaluated	13	17.3
Treatment failed	0	0
Died	11	14.7

In the study, patients with favorable outcome are those who completed treatment and considered cured at 53.4%. Mortality is at 11.4%-16.7%. Majority are CNS TB cases. Another study in the Philippines²³ noted a 42%

mortality rate among EPTB patients who are all diagnosed as TB meningitis.

National TB Program (NTP) and WHO recommend a standard treatment rate of 87%. In this study, treatment rate is only at 53.4%. Treatment failure and higher deaths were due to late diagnosis and non-compliance to treatment. Other factors that affect treatment include economic, social, cultural, geographic, health care facilities, incidence of TB in the region, microbial resistance, HIV prevalence, and parental TB awareness¹⁹. In 17.3% of the patients in this study, treatment was transferred to other institution hence treatment record was not evaluated. Twelve percent (12%) were lost to follow-up.

Survival analysis using the Kaplan Meier Curve showed an average survival time of 34.769 days (95% CI 26.604 to 42.934 days) with a median day of survival equal to 30 days (95% CI 18.839 to 41.161 days). The curve revealed that at 25th hospital day from admission, survival is below 80%. The mortality rate is at 14.7% (Figure 2). A total of 11 patients died and 90% of these cases were due to complications of TB Meningitis. Ten (10) patients had TB meningitis, five (5) patients died from septic shock, three (3) had brain herniation secondary to increase intracranial pressure (ICP) and one (1) died from multiorgan failure. One (1) patient died due to respiratory failure secondary to aspiration pneumonia and another one (1) with abdominal TB died due to septic shock.

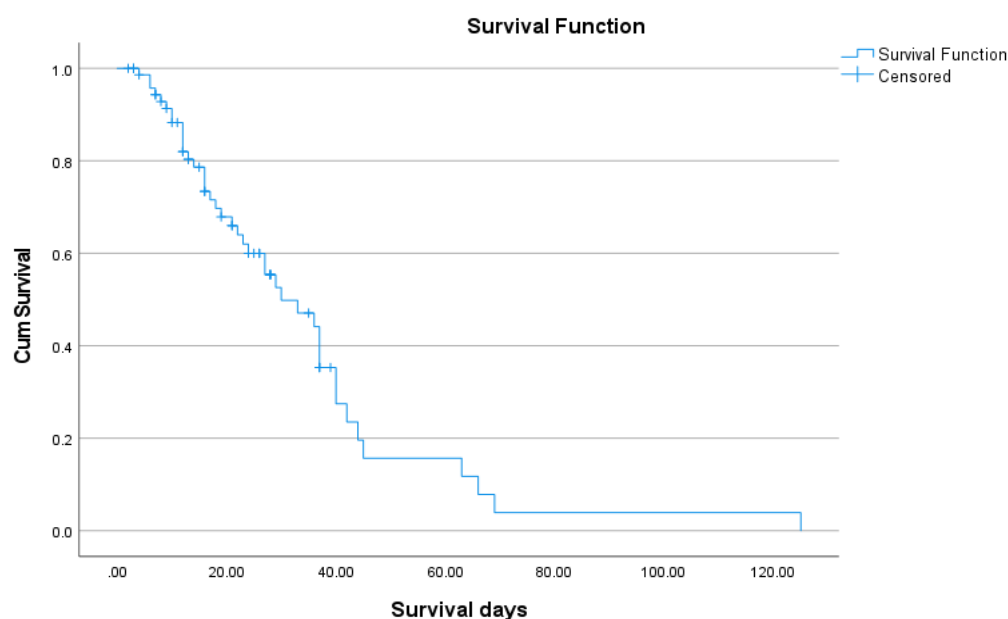


Figure 2. Survival analysis of patients with extrapulmonary tuberculosis

In a Philippine study^{7,12}, mean length of hospitalization is 10 days to 3 weeks. In this study, the mean length of hospital stay is 23 days. Patients with EPTB have prolonged hospitalization resulting in higher morbidity, mortality, and healthcare cost³⁹.

4. Discussion

World Health Organization reported 55% of children with TB (0–14 years) are not reported to national TB programs. Estimated case detection gaps are highest among less than 5 years of age with 69%, which may be due to underdiagnosis and underreporting. Because many nonspecific symptoms overlap with other common childhood diseases, TB is often not considered in children and is frequently missed. TB diagnosis can be challenging due to the lack of a sensitive point-of-care diagnostic test, low access to and use of available tests, difficulties obtaining sputum specimens from children, and frequent negative bacteriological test results in young children with TB².

Young children are at increased risk of developing severe forms of TB disease with an increased risk of death especially in children less than 2 years old⁸. Extrapulmonary TB is addressed infrequently in public health literature due to the perceived clinical peculiarity. It was not one of high priority in the health agenda because it does not contribute significantly to the transmission of the disease. However, extrapulmonary TB in children attributes to TB-related morbidity, and its complications cause lifelong sequelae and disabilities¹⁰. Since EPTB contributes significantly to the total burden of disease and influences the available resources of national health systems, it is crucial to address this group of patients from a public health perspective¹⁰.

4.1 Diagnosis

Extra-pulmonary TB lack specific symptoms hence it is difficult to diagnose. Its manifestations are variable depending on the anatomical involvement of the disease. Presumptive extrapulmonary TB¹⁷ may have any of the following symptoms:

- Gibbus;
- Non-painful enlarged cervical lymphadenopathy with or without fistula formation;
- Neck stiffness (or nuchal rigidity) and or drowsiness;
- Pleural effusion;
- Pericardial effusion;
- Abdominal distention (ascites);
- Non-painful enlarged joint; and
- Signs of tuberculin hypersensitivity (e.g., phlyctenular conjunctivitis, erythema nodosum).

Extra-pulmonary tuberculosis¹⁷ can be bacteriologically and clinically diagnosed. Bacteriologically-confirmed patients are those with a smear/culture/rapid diagnostic test from a biological specimen in an extrapulmonary site (i.e., organs other than the lungs) positive for AFB or Mycobacterium Tubercle Bacilli (MTB) complex. It is clinically diagnosed when a patient has a histological and or clinical or radiologic evidence consistent with active extrapulmonary TB and there is a decision by a physician to treat the patient with anti-TB drugs.

4.2 Treatment and Outcome

The drug therapy of tuberculosis aims to achieve cure of patients by rapid elimination of most metabolically active and rapidly replicating bacilli, prevent death from active TB or its late effect, prevent relapse by eliminating slowly and intermittently multiplying bacilli, prevent drug resistance by using a combination of drugs and decrease TB transmission to others¹⁶.

Drug therapy regimens employed in TB are designed primarily to cure the individual and decrease transmission to the community. A regimen consists of two phases: the initial and continuation phases are used based on the recommended regimens by the National Tuberculosis Control Program of the Philippines' Department of Health (Table 4).

The initial phase is 2HRZE with a duration 2 months (Isoniazid, H; Rifampicin R; Pyrazinamide, Z; and ethambutol, E). The drug treatment is given daily. The continuation phase is a 4-month duration of treatment with isoniazid and rifampicin taken once daily (4HR)¹⁸.

Table 4. Recommended treatment regimens for adults and children.

Category of Treatment	Classification and Registration Group	Treatment Regimen
Category I	Pulmonary TB, new (bacteriologically confirmed or clinically-diagnosed) Extra-pulmonary TB, new (bacteriologically-confirmed or clinically-diagnosed) except CNS/ bones or joints	2HRZE/4HR
Category Ia	Extra-pulmonary TB, new (CNS/bones or joints)	2HRZE/10HR
Category II	Pulmonary or extrapulmonary, previously treated drug-susceptible TB (bacteriologically-confirmed or clinically diagnosed) • Relapse • Treatment After Failure • Treatment After Lost to Follow-up (TALF) • Previous Treatment Outcome Unknown • Other	2HRZES/1HRZE /5HRE
Category IIa	Extra-pulmonary, previously treated drug susceptible TB (bacteriologically confirmed or clinically-diagnosed – CNS/bones or joints)	2HRZES/1HRZE /9HRE
Standard Regimen Drug-resistant (SRDR)	Rifampicin-resistant TB or Multidrug-resistant TB	ZkmLfxPtoCs • Individualized once DST result is available • Treatment duration for at least 18 months
XDR-TB Regimen	Extensively drug-resistant TB	Individualized based on DST result and history of previous treatment

Legend: R – Rifampicin, I – Isoniazid, E – Ethambutol, Z – Pyrazinamide, S Streptomycin, Km -Kanamycin. Lfx – Levofloxacin, Pto – Prothionamide. C – Cycloserine.

Treatment outcome of patients are based on completion of treatment regimen, follow-up diagnostic results, and clinical improvement (Table 5). The recommended treatment rate is 87% determined by the National Tuberculosis Program¹⁸ and WHO².

Table 5. Treatment Outcomes for Drug-susceptible TB Cases

Outcome	Definition
Cured	The patient was confirmed bacteriologically at the start of treatment and had smear or culture-negative in the last month of treatment and at least one occasion in the continuation phase.
Treatment Completed	The patient confirmed bacteriologically or clinically diagnosed completed treatment with no evidence of failure but shows no record that sputum smear or culture results in the last month of treatment and at least one previous occasion were negative because either result was unavailable tests were not done.
Treatment Failed	The patient showed positive sputum smear or culture is at five (5) months or later during treatment. OR A patient clinically diagnosed showed no clinical improvement anytime during treatment.
Died	Patient who dies for any reason during the course of treatment.
Lost to Follow-up	Patient had interrupted treatment for two (2) consecutive months or more.
Not Evaluated	Patient transferred to another facility and those no treatment outcome is assigned.

World Health Organization

Conclusion

Patients' symptomatology of extrapulmonary tuberculosis varies greatly and usually based on the organ involved. Despite changes and advances in diagnostics and confirmation, diagnosis remains challenging. Mortality rate remains high. Early diagnosis, intervention, treatment and follow-up remain the cornerstone in improving survival rate and decreasing its morbidity and mortality.

Declaration of competing of interest

The authors declare no conflicts of interest regarding this manuscript.

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