e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13 (5); 136-144

Original Research Article

Analysis of the Development of Resistance to Anti-Tubercular Drugs among Previously and Newly Treated Patients

Priyanka Das[1*], Naliniprava Das[2], Gopal Krushna Sahu[3], Hemanta Kumar Sethy[4], Sushree Swetapadma[5], Debabrata Barik[6]

[1]Assistant Professor, Department of Pulmonary Medicine, M.K.C.G Medical College and Hospital, Berhampur, India

[2]Professor, Department of Pulmonary Medicine, S.L.N Medical College and Hospital, Koraput, India

[3]Assistant Professor, Department of Pulmonary Medicine, S.L.N Medical College And Hospital, Koraput, India

[4]Professor, Department of Pulmonary Medicine, M.K.C.G Medical College and Hospital Berhampur, India

[5]Junior Resident, Department of Pulmonary Medicine, M.K.C.G Medical College and Hospital, Berhampur, India

[6]Junior Resident, Department of Microbiology, M.K.C.G Medical College and Hospital, Berhampur, India

Received: 21-03-2023 / Revised: 19-04-2023 / Accepted: 15-05-2023

Corresponding author: Dr. Priyanka Das

Conflict of interest: Nil

Abstract:

Introduction: The paper discusses drug-resistant tuberculosis (TB) treatment. In resource-poor countries, TB is a public health threat. TB treatment involves long-term antibacterial and sterilizing medications. MDR-TB, resistant to at least two first-line anti-TB medications, is complicated. Better-targeted, easier-to-administer TB drugs are needed to improve treatment. Drug susceptibility tests and effective MDR and XDR-TB treatment programmess are essential for fighting the disease.

Aims and objective: The study aims to evaluate anti-tuberculosis medication resistance in once-treated and recently treated patients.

Methods: An observational study conducted using a cross-sectional design was carried out on the 693 patients who visited the outpatient department of our hospital. We collected sputum samples from clinically suspicious people diagnosed with lung sickness and tested them in the Diagnostic Microscopic Centre (DMC) under the Department of Pulmonary Medicine and Department of Microbiology for MTB using standard detection methods and Drug Susceptibility Testing (DST). In addition, the CBNAAT and LPA molecular procedures were carried out by our team at the Pulmonary Medicine Department.

Result: 693 individuals, 64 per cent of whom were male, were screened for pulmonary tuberculosis during the trial. Patients' average age ranged from 21 to 40. Of those patients, 84% were newly diagnosed, whereas 16% had been treated before. Twenty-four per cent of the 218 individuals with a positive AFB smear grew Mycobacterium TB. The prevalence of extensively drug-resistant tuberculosis (MDR-TB) was 0% in newly diagnosed patients and 7.1% in previously treated patients.

Conclusion: The study has concluded that previous anti-TB treatment is the most critical risk factor for the development of MDR-TB. However, it is also being reported in newly diagnosed TB patients.

Keywords: Resistance, Anti-Tubercular, *Mycobacterium tuberculosis.*

Introduction

Millions of individuals are still afflicted by the high-priority transmissible disease tuberculosis (TB), the 2nd most significant cause of contagious death globally. The disease disproportionately affects people living in areas with few resources, especially those in Africa and Asia. Over 78.4% of TB and TB-related fatalities occurred in poor nations [1,2].

To ensure antimicrobial efficiency, avoid the choice of Resistance to drug mutants, and attain a permanent cure, successful tuberculosis (TB) treatment depends on a combination of bactericidal and sterilizing medications taken for an acceptable period [3]. The current therapy protocols for drug-resistant multiple tuberculosis {(MDR-TB) referred to as Resistance to both isoniazid and rifampicin)} are nevertheless unsatisfactory because of low efficacy, severe side effects, prolonged length and a heavy demand on health resources; interactions between drugs rifampicin in a combination of protease inhibitors as well as antiretrovirals (ARVs) demonstrated that these are also significant. Some varieties contain medications, such as oxazolidinones, clofazimine, or carbapenems, that are repurposed and utilized despite being authorized for purposes other than treating TB "off-label" to treat instances of extremely resistant TB [4,5].

The first anti-TB treatment, streptomycin, was the catalyst for the discovery of drug resistance in Mycobacterium tuberculosis (TB), which has since been recognized by science as a biological phenomenon. Streptomycin injections saved many lives while temporarily removing M. tuberculosis from their sputum. They soon began excreting germs no longer susceptible to streptomycin in the labarotory while continuing to receive treatment [6,7].

The introduction of novel medicines like thioacetazone, para-aminosalicylic acid, and isoniazid, introduced in 1952, made it clear that combination therapy was effective chemotherapy and essential for limiting the emergence of Resistance [8]. The 18 months of treatment were needed for the first combination regimens. Still, following the identification of the most potent anti-TB medication, rifampicin, in 1957, medicine in terms of sterilization short-course chemotherapy, which contains isoniazid and rifampicin, was made possible [9].

Initially, it was believed that nosocomial transmission, particularly among HIV-positive patients, was the primary source of MDR-TB outbreaks. Throughout the decades of the 1980s & 1990s, New York was the site of one of the most significant and well-documented epidemics [10]. When DST laboratory capacity within resource-constrained locations increased, and global drug-resistant TB monitoring programmes progressed, it became evident that MDR-TB was growing more prevalent globally and a substantial risk to everyone's health. [11].

Mycobacterium tuberculosis strains that are resistant to at least two first-line anti-TB medications, rifampicin and isoniazid, are referred to as having multidrug-resistant tuberculosis (MDR-TB) [12]. MDR-TB develops when an individual contracts a resistant form of the disease or when inadequate or ineffective therapy results in the drug being chosen for the resistant strain when an individual who has never received First-line anti-TB medication causes MDR-TB to develop, so-referred to as initial refusal of all first-line TB medications and

MDR-TB. In contrast, when an individual who has previously received anti tubercular treatment and resistance to one or more of the first-line drugs against TB develops during first-line anti-TB treatment, it is referred to as Secondary Resistance. [13,14].

The current recommended six-month, four-drug regimen consisting of pyrazinamide (Z), isoniazid (H), rifampicin (R), and ethambutol (E) (2HREZ/4HR) is used to treat TB that is drug-sensitive. Both clinical trials and therapy closely monitored by TB control programs have demonstrated remarkable efficacy in reaching cure rates of about 90.5–95.8%. It is challenging for patients to take their prescription every day for six months, even though the regimen is beneficial when followed exactly as directed [15]. Additionally, the regimen may result in severe reactions, including hepatotoxicity and significant adverse events and is not always tolerated well, dosed, or absorbed. Resistance may develop as a result of issues with compliance, inadequate medication levels, and tolerability. More targeted, better-tolerated medication regimens are required to eliminate TB more effectively and rapidly [16].

To improve adherence to treatment of MDR/XDR-TB, decrease failure to follow-up, susceptibility, lack of Resistance, and more tolerated regimens are urgently needed to be emphasized. This will simplify diagnosis and therapy. Compared with the management of drug-susceptible TB, MDR-TB requires an extended duration, costlier medications, and has a higher toxicity profile [17]. It is more difficult to administer, manage, and monitor individuals who often cannot comply with or tolerate therapy because of the need for many antimicrobials and the prolonged treatment time. Additionally, the availability of medication tests for susceptibility and efficient MDR and XDR-TB treatment plans further complicates things [18].

In individuals without suspicion of Resistance, the ideal course of treatment entails a four-month HRE continuation phase after two months of intense HRZE use. If a susceptibility test reveals that the isolate from the patient is vulnerable to HR, ethambutol can be stopped. If the client has cavitation on their chest radiograph, assuming a culture test remains valid at the end of the initial stage, the recommendation was to delay the maintenance phase by a further three months [19,20].

Materials and Methods

Study design

A cross-sectional observational study was conducted on 693 patients who came to the outpatient department of our hospital. Sputum samples were taken from patients with pulmonary disease who are clinically suspected. All conventional MTB detection methods and Drug Susceptibility Testing (DST) were performed at the Department of Microbiology. In contrast, CBNAAT and LPA molecular procedures were performed at the Department of Pulmonary Medicine.

Inclusion and exclusion criteria

Patients with pulmonary tuberculosis who came to the department and provided informed consent were included in the study.

Patients with extrapulmonary tuberculosis who are already on treatment with anti-tuberculous drugs are excluded from the study.

Sample collection

Before consuming food or liquids, the patient's sputum was collected twice (on the spot and in the morning) in sterile wide-capped containers. The individuals were instructed to take two to four deep breaths before repeatedly coughing to expel mucus from their lungs and deposit it into a container.

The collected samples are stained with Zeihl and Neilson (ZN stain), and the

bacteria are interpreted under the binocular microscope.

Digestion and decontamination

To remove the bacilli from any mucus, cells, or tissue that may be embedded in during the culture of tubercle bacilli, specimens must be homogenized. The recovery of the tubercle bacilli is better, the milder the homogenization procedure. The vitality of tubercle bacilli shouldn't be affected by homogenization or cleaning.

Culture media

Three primary kinds of media, namely egg-based media, agar-based media, and liquid media, can be distinguished among the various media developed to cultivate tubercle bacilli. Egg-based media are the primary option for sputum specimen cultivation since they satisfy all these criteria. The most often used media for tuberculosis culture is Lowenstein-Jensen (LJ) medium.

Inoculation and incubation

Each 5 mm loop of the centrifuged material was spread over the surface of two slopes on each specimen. After eight weeks, all cultures that did not grow were rejected as unfavourable. All cultures were incubated between 35 and 37 °C. Slopes that were contaminated were also removed.

Niacin production, nitrate reduction, heat stable catalase test, and semiquantitative catalase test are the procedures used to identify mycobacterium tuberculosis (MTB).Inoculum and line probe assays are used for drug susceptibility tests.

Statistical analysis

The study used SPSS 25 for practical statistical analysis. The continuous data has been written in mean±standard deviation, while the discrete data has been presented as frequency and its respective percentage. The study employed ANOVA as the statistical tool for its analysis. The level of significance was considered to be $p<0.05$.

Ethical approval

Each patient was explained the study process, and consent was obtained from each. The Institutional Ethical Committee of M.K.C.G Medical College and Hospital has approved the study process.

Results

During the study period, 693 sputum samples in total were examined. 442 (64%) of the 693 patients with clinically suspected pulmonary tuberculosis were men, and 251 (36%) were women. It was discovered that males predominated over females. The majority of patients were between the ages of 21 and 40. Of the 693 patients, 582 (84%) were new cases, while 111 (16%) were TB patients who had already received treatment. 16 (14%) of the previously treated cases were defaulters, 7 (6%) had treatment failures, 11 (10%) had relapsed, and 77 (70%) had fully recovered (Table 1).

Table 1: Baseline characteristics of patients in this study

Baseline characteristics	Frequency	Percentage (%)
Gender		
Male	442	64
Female	251	36
Age		
0-20	56	8
21-40	263	38
41-60	190	27
>60	184	27
New case	582	83.9
Previously treated cases		
Completely cured	77	11.1

Defaulter	16	2.3
Treatment failure	7	1.0
Relapse	11	1.5

Out of 693 patients, 74 (11%) were found to have diabetes, whereas 619 others did not. While 676 were found to be non-reactive, 17 (3%) were found to be reactive for anti-HIV antibodies. 23 (3%) of the patients had a history of COPD, 42 (6%) had contact with TB patients in the past, and 56 (8%) had hypertension. 218 (31%) patients had a positive AFB smear, while 475 (69%) did not. 178 (82%) of the 218 AFB Smear-positive patients were new suspicious cases, and 40 (18%) were PTB patients who had already undergone treatment. Mycobacterium tuberculosis was growing in 168 (24%) tubes, pollutants were growing in 67 (10%) tubes, and there was no growth in 458 (66%) tubes (Table 2).

Table 2: risk factors, ZN staining, and growth pattern of TB

	Frequency	**Percentage (%)**	**p-value**
Co-morbid condition			0.00001
Diabetes mellitus	74	10.7	
HIV positivity	17	2.4	
Chronic obstructive pulmonary disease (COPD)	23	3.3	
Known history of contact with TB patients	42	6.0	
Hypertension (HTN)	56	8.0	
ZN smear grade			
Scanty	40	18	
1+	58	27	
2+	58	27	
3+	62	28	
Growth pattern in LJ medium			
No growth	458	66	
Contaminants	67	10	
Mycobacterium tuberculosis	168	24	

The results of sputum AFB microscopy were compared to those of culture on LJ, which showed that 168 samples out of 218 that had positive smear results (% of positivity =77%) had positive growth on LJ (Table 3).

Table 3: ZM smear status and culture status of sputum (new cases, previous cases, and new+previous cases)

Smear grade	**New samples**	**No:of culture positive on LJ**	**No:of culture negative on LJ**	**% of positivity**	**P value**
New cases					0.00001
Negative	404	5	399	1	
scanty	34	20	14	59	
1+	49	37	12	76	
2+	45	34	11	76	
3+	50	44	6	88	
Total	582	140	442	24	
Previously treated cases					0.00001
Negative	71	1	70	1.4	

Scanty	6	2	4	33.3	
1+	9	5	4	55.5	
2+	13	10	3	76.9	
3+	12	10	2	83.3	
Total	111	28	83	25	
New + previously treated					0.00001
Negative	475	6	469	1.3	
Scanty	40	22	18	55	
1+	58	42	16	72.4	
2+	58	44	14	75.9	
3+	62	54	8	87.1	
Total	693	168	525	24.2	

Resistance to any first-line anti-tubercular medication was 2 (1.4%) in newly treated patients and 8 (28.6%) in those who had already received treatment. MDR-TB prevalence was 0% in newly diagnosed patients and 2 (7.1%) in patients who had already received treatment (Table 4).

Table 4: Drug susceptibility patterns of *M. tuberculosis* isolates (new, previous cases, and new+previous cases)

Resistance status	Frequency	Percentage (%)
New cases (total isolates = 140)		
Total susceptible	138	98.6
Resistance to H only	0	0
Resistance to R only	2	1.4
Resistance to Z only	0	0
Resistance to E only	0	0
Resistance to S only	0	0
Resistance to H + R (MDR)	0	0
Previously treated (total isolates = 28)		
Total susceptible	20	71.5
Resistance to H only	0	0
Resistance to R only	6	21.4
Resistance to Z only	0	0
Resistance to E only	0	0
Resistance to S only	0	0
Resistance to H + R (MDR)	2	7.1
New + previously treated cases (total isolates = 168)		
Total susceptible	158	94
Resistance to H only	0	0
Resistance to R only	8	4.8
Resistance to Z only	0	0
Resistance to E only	0	0
Resistance to S only	0	0
Resistance to H + R (MDR)	2	1.2

Discussion

Global efforts to prevent tuberculosis face severe threats from extensive and multidrug-resistant TB. It is unknown how common is anti-TB medicine resistance in Uganda. We performed a national survey

on drug resistance to examine the prevalence and trends in developing anti-TB medications, both primary and secondary medications, among untreated and managed TB with positive sputum smear cases. Compared to WHO estimations, the frequency of anti-TB drug resistance amongst newly diagnosed Patients is few in Uganda. Concerns concerning the effectiveness, the increasing frequencies of MDR-TB and Resistance to treatment increase the importance of directly observed therapy (DOT) and dedication to the programme drugs among patients who have already received treatment. To prevent and track drug-resistant TB's emergence and growth, this calls for enhancing current TB control methods, including DOT, routine drug sensitivity tests (DST) among TB patients who have already received treatment, or annual drug resistance surveys [21].

Among the most common types of significant ongoing dangers for global public health is the number of patients with resistance to anti-tubercular drugs. In India, there are more cases of extra pulmonary tuberculosis (EPTB), and drug-resistant tuberculosis (MDR-TB) is increasing the spread of resistant strains. In Northern India's referral hospitals, a study aimed to examine patterns of Resistance to anti-tuberculosis medication in newly diagnosed and EPTB patients that have already been treated. The study concludes that MDR-TB gradually becomes more prevalent in EPTB cases and is resistant to treatment in EPTB cases that have already been treated. For individuals with MDR-TB, molecular drug sensitivity testing (DST) can assist in making an early decision on chemotherapy. The RNTCP and professional medical organizations must use the International Standards of treatment to improve TB treatment in the nation [22].

Despite the lack of information, India's efforts to combat multidrug-resistant tuberculosis (MDR-TB) is enormous, as they comprise a substantial burden amongst drug-resistant tuberculosis (DR-TB). MDR-TB has existed in India for some time. However, there aren't many diagnostic laboratories to screen for drug sensitivity. The study aimed to assess the occurrence of MDR-TB, first-line medication resistance trends, and any evolving tendencies during four years in northern India. The study discovered a high frequency of freshly diagnosed patients and cases of MDR-TB that had already been treated. The research provides a strong justification for developing systems for evaluating, monitoring, surveillance, and managing patients involving medication resistance [23].

MDR-TB (multidrug-resistant tubercul osis), tuberculosis), has evolved into a significant global concern for TB control, especially resistance to the two main first-line anti-TB medications, isoniazid and rifampicin. However, its impact on local communities has yet to be widely known. To determine the primary & secondary Resistance to every anti-TB medicine in the first-line predominance medications as well as Central Ethiopia's Oromia Regional State's Hitossa District, MDR TB was the study's principal objective. The research area has emphasized significant primary and secondary Resistance to every first-line TB medication, prevalent medications, and MDR-TB. The DOTS program's subpar effectiveness in identifying and counting instances of contagious TB and determining cure rates in the research area may have contributed to the Resistance. Previous TB therapy is associated to drug resistance to anti-TB treatments. To diagnose MDR-TB cases promptly and administer the proper care to halt the spread of MDR-TB in Ethiopia, it is necessary to improve DOTS and DOTS-Plus programmes and expand MDR-TB diagnostic resources [24].

Everywhere it occurs, including Zambia, where drug-resistant tuberculosis poses a severe danger because of its complexity and importance, increasing morbidity and mortality rates. The primary motivation for performing the study, however, was the absence of knowledge on the Susceptibility

patterns for first- and second-line anti-tuberculosis (anti-TB) drugs and innovative and repurposed drugs used in Zambia to treat drug-resistant tuberculosis. The study discovered a substantial frequency of tuberculosis resistance to multiple drugs. And further found that pre- and XDR-TB, MDR- and XDR-TB surveillance must be increased to help guide suggestions for effective treatment and monitoring in the future [25].

Conclusion

The study has concluded that previous anti-TB treatment is the most critical risk factor for the development of MDR-TB. However, it is also being reported in newly diagnosed TB patients. The study recommends using LPA testing for rapid detection of MDR-TB, as it is susceptible and specific with significantly lesser turnaround time than conventional DST methods. However, the test requires appropriate infrastructure and trained laboratory personnel, and it may not be helpful in specimens with a lower bacillary load or paucibacillary extrapulmonary TB specimens. The study also highlights the need for a standardized approach to diagnosing drug resistance and a multi-pronged approach to address the problem of the high burden of DR-TB in India. Universal MDR testing of TB patients needs to be rapidly scaled up to combat this growing epidemic, and control of DR-TB is imperative for TB elimination as a whole.

References

1. Tiberi, S., Muñoz-Torrico, M., Duarte, R., Dalcolmo, M., D'Ambrosio, L., & Migliori, G. New drugs and perspectives for new anti-tuberculosis regimens. Pulmonology, 2018; 24(2): 86-98.
2. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona J, Becerra M, Benedetti A, Burgos M, Centis R, et al. Multidrug-resistant pulmonary tuberculosis treatment regimens and patient outcomes: An individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012; 9:153: e1001300.
3. Becerra M, Franke MF, Appleton SC, Joseph JK, Bayona J, Atwood SS, Mitnick CD. Tuberculosis in children exposed at home to multidrug-resistant tuberculosis. Pediatr Infect Dis J. 2013; 32: 115–119.
4. Cegielski JP. Extensively drug-resistant tuberculosis: "There must be some kind of way out of here". Clin Infect Dis. 2010; 50: S195–S200.
5. Centres for Disease Control and Prevention (CDC). Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep. 2013; 62: 1–12.
6. Chavez Pachas AM, Blank R, Fawzi Smith MC, Bayona J, Becerra M, Mitnick CD. Identifying early treatment failure on category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. Int J Tuberc Lung Dis. 2004; 8: 52–58.
7. Lienhardt, C., Raviglione, M., Spigelman, M., Hafner, R., Jaramillo, E., Hoelscher, M., & Gheuens, J. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. Journal of infectious diseases, 2012; 205(suppl_2), S241-S249.
8. Singh MM. Tuberculosis: Triumphs and tragedy. Indian J Tuberculosis. 2000;47:129–32.
9. Chiang CY, Hsu CJ, Huang RM, Lin TP, Luh KT. Anti-tuberculosis drug resistance among re-treatment tuberculosis patients in a referral centre in Taipei. J Formos Med Assoc. 2004;103:411–5.
10. Gupta S, Bandyopadhyay D, Gupta S, Sadhukhan S, Banerjee S. A sociodemographic study of multidrug-resistant tuberculosis cases from DOTS clinics of Kolkata. J Indian Med Assoc. 2012;110:723–5.
11. Almeida D, Rodigues C, Udwadia ZF, Lalvani A, Gothi GD, Mehta P, et al.

Incidence of multidrug-resistant tuberculosis in urban and rural India and implications for prevention. Clin Infect Dis. 2003;36:152–4
12. Tiberi, S., Payen, M. C., Sotgiu, G., D'Ambrosio, L., Guizado, V. A., Alffenaar, J. W., & Migliori, G. B. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR-and XDR-TB. European Respiratory Journal, 2016; 47(4), 1235-1243.
13. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona J, Becerra M, Benedetti A, Burgos M, Centis R, et al. Multidrug-resistant pulmonary tuberculosis treatment regimens and patient outcomes: An individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012; 9: e1001300.
14. Chavez Pachas AM, Blank R, Fawzi Smith MC, Bayona J, Becerra M, Mitnick CD. Identifying early treatment failure on category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. Int J Tuberc Lung Dis. 2004; 8: 52–58.
15. Curry International Tuberculosis Center, California Department of Public Health. Tuberculosis Drug Information Guide, 2nd ed. Curry International Tuberculosis Center, San Francisco, California. 2012.
16. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: Strategies to beat multidrug-resistant tuberculosis. Science. 2002; 295: 2042–2046.
17. Frieden TR, Sterling T, Pablos-Mendez A, Kilburn JO, Cauthen GM, Dooley SW. The emergence of drug-resistant tuberculosis in New York City. New Engl J Med. 1993; 328: 521–526.
18. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—Turning the tide. New Engl J Med. 1995; 333: 229–233
19. Becerra M, Franke MF, Appleton SC, Joseph JK, Bayona J, Atwood SS, Mitnick CD. Tuberculosis in children exposed at home to multidrug-resistant tuberculosis. Pediatr Infect Dis J. 2013; 32: 115–119.
20. Cegielski JP. Extensively drug-resistant tuberculosis: "There must be some kind of way out of here". Clin Infect Dis. 2010; 50: S195–S200.
21. Centres for Disease Control and Prevention (CDC). Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep. 2013; 62: 1–12.
22. Lukoye D, Adatu F, Musisi K, Kasule GW, Were W, Odeke R, Kalamya JN, Awor A, Date A, Joloba ML. Anti-tuberculosis drug resistance among new and previously treated sputum smear-positive tuberculosis patients in Uganda: results of the first national survey. PLoS One. 2013 Aug 1;8(8): e70763.
23. Maurya AK, Singh AK, Kumar M, Umrao J, Kant S, Nag VL, Kushwaha RA, Dhole TN. Changing patterns and trends of multidrug-resistant tuberculosis at referral centre in Northern India: a 4-year experience. Indian J Med Microbiol. 2013 Jan-Mar;31(1):40-6.
24. Hamusse, S. D., Teshome, D., Hussen, M. S., Demissie, M., & Lindtjørn, B. Primary and secondary anti-tuberculosis drug resistance in Hitossa District of Arsi Zone, Oromia Regional State, Central Ethiopia. BMC Public Health, 2016; 16:593.
25. Monde, N., Munyeme, M., Chongwe, G., Wensman, J. J., Zulu, M., Siziya, S., Tembo, R., Siame, K. K., Shambaba, O., & Malama, S. First and Second-Line Anti-Tuberculosis Drug-Resistance Patterns in Pulmonary Tuberculosis Patients in Zambia. Antibiotics, 2023; 12(1): 166.