WJPMR, 2026, 12(9), 242-247

Review Article

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Impact Factor: 7.533

ISSN (O): 2455-3301

ISSN (P): 3051-2557

Coden USA: WJPMBB

TUBERCULOSIS: PATHOGENESIS, DIAGNOSIS, TREATMENT, DRUG RESISTANCE AND EMERGING THERAPEUTIC TARGETS

Dr. Rahul Kshirsagar Sir, Prof. Ashwini Shikare Mam, *Janvi Sachin Dapke, Nandini Sunil Nagare, Kalyani Ashok Wayde, Sakshi Baburao Salunke, Gauri Sandip Kale, Jayashri Balkrishn Chande, Komal Laxman Pawar

2655 Shri Chhatrapati Shivaji College of Pharmacy, Kannad, Dist. Chhatrapati Sambhajinagar, Maharashtra, India.

***Corresponding Author: Janvi Sachin Dapke**
2655 Shri Chhatrapati Shivaji College of Pharmacy, Kannad, Dist. Chhatrapati Sambhajinagar, Maharashtra, India.

DOI: https://doi.org/10.5281/zenodo.22252782

How to cite this Article: Dr. Rahul Kshirsagar Sir, Prof. Ashwini Shikare Mam, *Janvi Sachin Dapke, Nandini Sunil Nagare, Kalyani Ashok Wayde, Sakshi Baburao Salunke, Gauri Sandip Kale, Jayashri Balkrishn Chande, Komal Laxman Pawar (2026). Tuberculosis: Pathogenesis, Diagnosis, Treatment, Drug Resistance And Emerging Therapeutic Targets. World Journal of Pharmaceutical and Medical Research, 12(9), 242–247.

Article Received on 10/08/2026 **Article Revised on 31/08/2026** **Article Published on 01/09/2026**

ABSTRACT

Tuberculosis (TB) is a communicable disease caused by Mycobacterium tuberculosis (M. tuberculosis) and remains a major global health challenge. The organism primarily affects the lungs but may disseminate to other organs. Following inhalation, bacilli reach the alveoli, interact with alveolar macrophages and dendritic cells, and may survive intracellularly. Recruitment of immune cells and formation of granulomas can contain the infection as latent TB, whereas failure of immune containment may lead to caseation, cavitation, active pulmonary disease and transmission. According to the WHO Global Tuberculosis Report 2025, an estimated 10.7 million people developed TB and 1.23 million died from TB in 2024. Drug-resistant TB, especially multidrug/rifampicin-resistant TB, complicates treatment and requires rapid susceptibility testing and appropriate combination regimens. Diagnosis increasingly relies on rapid molecular tests in addition to microscopy, culture and clinical/radiological assessment. Treatment of drug-susceptible TB uses combination therapy, while newer medicines such as bedaquiline, delamanid and pretomanid have expanded options for drug-resistant disease. This review summarizes the pathogenesis, clinical manifestations, diagnosis, current treatment principles, drug resistance, tuberculous meningitis, challenges in TB control and emerging drug targets. Continued research is needed to shorten therapy, improve safety and adherence, expand access to rapid diagnostics, and develop novel agents capable of overcoming resistance and bacterial persistence.

KEYWORDS: Tuberculosis; Mycobacterium tuberculosis; Pathogenesis; Latent TB; Active TB; Diagnosis; Anti-tuberculosis drugs; MDR/RR-TB; Drug resistance; Tuberculous meningitis; Novel drug targets.

1. INTRODUCTION

TB is an infectious disease caused by M. tuberculosis. It is primarily transmitted through the air and most commonly affects the lungs, although dissemination can produce extrapulmonary disease. After inhalation, bacilli may be eliminated, contained in granulomas as latent infection, or progress to active disease depending on the balance between bacterial survival and host immunity.

The clinical course of TB reflects a dynamic host–pathogen interaction. M. tuberculosis can survive within macrophages and manipulate intracellular pathways, allowing persistence for prolonged periods. Reactivation becomes more likely when cellular immunity is impaired, including in people living with HIV and other immunocompromising conditions.

Effective treatment is available, but TB control remains difficult because therapy requires combination treatment, adherence over an extended period and reliable diagnostic and monitoring systems. Drug-resistant TB further complicates management, while severe extrapulmonary forms such as TBM can cause substantial mortality and neurological disability. Accordingly, an integrated understanding of pathogenesis, diagnosis, pharmacology, resistance and new drug development is essential.

2. GLOBAL BURDEN AND PUBLIC-HEALTH IMPORTANCE

TB remains one of the most important infectious diseases worldwide. The WHO Global Tuberculosis Report 2025 estimates that 10.7 million people developed TB in 2024, including approximately 5.8 million men, 3.7 million

women and 1.2 million children and young adolescents. An estimated 1.23 million deaths occurred, including about 150,000 among people living with HIV. The global decline in TB incidence remains slower than the milestones established by the WHO End TB Strategy, emphasizing the continuing need for prevention, early diagnosis, effective treatment and research.

Drug-resistant TB is an important component of the global antimicrobial-resistance problem. Gaps in detection and treatment, delayed diagnosis, inadequate access to care, treatment interruptions and transmission of resistant strains can compromise TB control. High-risk environments such as prisons may amplify transmission; recent evidence from Ethiopia highlights the need for systematic screening, infection-control measures and appropriate management of drug-resistant pulmonary TB in vulnerable populations.

3. ETIOLOGY, TRANSMISSION AND RISK FACTORS

M. tuberculosis is an aerobic, slow-growing, acid-fast bacillus belonging to the M. tuberculosis complex. Pulmonary TB is the major clinical form and is transmitted primarily through inhalation of airborne particles generated by individuals with infectious pulmonary or laryngeal TB. The probability of transmission is influenced by infectiousness, duration and intensity of exposure, ventilation and host susceptibility.

After inhalation, bacilli that reach the distal airways and alveoli encounter resident alveolar macrophages. Host factors that increase the risk of progression from infection to disease include immunosuppression, HIV infection, extremes of age and other conditions that impair cellular immunity. Social determinants such as overcrowding, poverty and limited access to healthcare can also increase exposure and delay diagnosis.

4. PATHOGENESIS OF TUBERCULOSIS

M. tuberculosis pathogenesis is characterized by a prolonged interaction between the bacillus and host immune system. The outcome can range from early clearance or containment to persistent latent infection and, in susceptible individuals, progressive active disease.

4.1 Inhalation and initial infection. Inhaled bacilli reach the alveoli and are phagocytosed by alveolar macrophages. Some bacilli are destroyed by innate antimicrobial mechanisms, whereas surviving organisms can replicate within macrophages. M. tuberculosis can interfere with phagosome maturation and other host antimicrobial pathways, facilitating intracellular persistence.

4.2 Innate and adaptive immune responses. Infected macrophages and dendritic cells produce inflammatory mediators and present mycobacterial antigens to lymphocytes. Monocytes, neutrophils, T cells and B cells are recruited to the site of infection. T-cell-mediated immunity, particularly CD4+ T-cell responses and macrophage activation, contributes substantially to control of bacterial replication.

4.3 Granuloma formation and latent infection. Organized granulomas develop as a host strategy to contain M. tuberculosis. Mature granulomas may contain infected macrophages, epithelioid cells, multinucleated giant cells, foamy macrophages, lymphocytes and a fibrous component. In many individuals, bacterial replication is restrained and the infection remains clinically silent as latent TB infection.

4.4 Progression to active disease. If immune containment fails, granulomas can undergo necrosis and caseation. Liquefaction of caseous material and communication with an airway can produce cavitary disease, allowing large numbers of bacilli to enter the airways and increasing infectiousness. Reactivation can occur years after the initial infection when immune surveillance becomes inadequate.

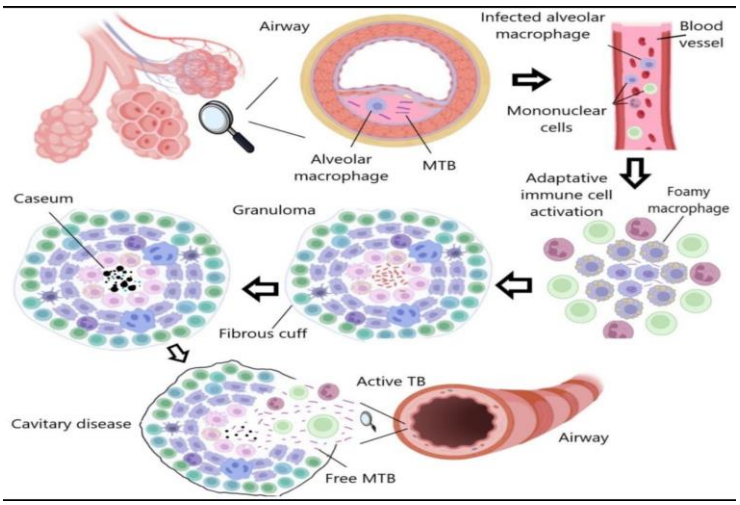

Figure 1: Pathogenesis and progression of pulmonary tuberculosis. Inhaled M. tuberculosis is taken up by

alveolar macrophages; immune-cell recruitment and granuloma formation can contain infection, whereas caseation, cavitation and release of bacilli into the airway can lead to active transmissible disease.
Source: user-provided figure; concept cross-checked against Russell et al.[4]

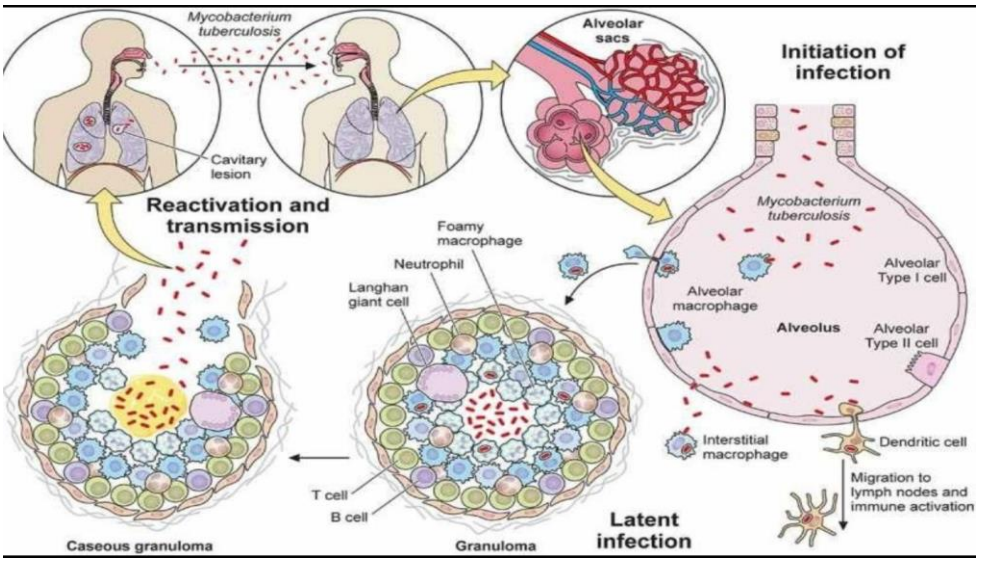

Figure 2: Cellular events associated with initiation of M. tuberculosis infection, granuloma formation and transition toward latent or active disease.
Source: user-provided figure; related mechanisms discussed by Yan et al.[5] *and Alsayed & Gunosewoyo.*[1]

5. CLINICAL MANIFESTATIONS

Pulmonary TB commonly presents with persistent cough, sputum production, fever, night sweats, weight loss, fatigue and, in some patients, haemoptysis. Extrapulmonary TB can involve lymph nodes, pleura, bones and joints, genitourinary organs, the abdomen and the central nervous system. Clinical manifestations vary according to the affected organ and host immune status.

TB meningitis (TBM) is among the most severe forms of extrapulmonary TB. It can cause headache, fever, altered consciousness, cranial nerve abnormalities, seizures and neurological deficits. A 2025 systematic review and meta-analysis of 10 studies involving 2005 patients reported a pooled all-cause mortality of 27.7%, with higher mortality among HIV-positive patients. These findings emphasize the need for early diagnosis, appropriate treatment and long-term neurological follow-up.

6. DIAGNOSIS

Diagnosis should integrate clinical assessment, imaging and microbiological or molecular evidence. Sputum smear microscopy remains useful because it is inexpensive and widely available, but its sensitivity is limited. Mycobacterial culture remains an important reference method and allows susceptibility testing, although the slow growth of M. tuberculosis delays results.

Rapid molecular tests can detect M. tuberculosis and, in appropriate assays, provide information about resistance to key drugs much earlier than conventional culture. Chest radiography and other imaging methods support assessment of pulmonary and extrapulmonary disease but are not, by themselves, definitive microbiological confirmation. Drug-susceptibility testing is particularly important when drug resistance is suspected or detected.

7. TREATMENT OF DRUG-SUSCEPTIBLE TB

Anti-TB therapy uses multiple drugs with complementary mechanisms to rapidly reduce bacterial burden, prevent relapse and suppress selection of resistant mutants. The traditional first-line agents are isoniazid, rifampicin, pyrazinamide and ethambutol. WHO recommendations have evolved, and treatment should follow the current national/WHO regimen appropriate to the patient's age, disease site, drug susceptibility and clinical circumstances.

The standard first-line drugs act at different bacterial targets. Isoniazid, after activation, inhibits mycolic-acid biosynthesis. Rifampicin inhibits the DNA-dependent RNA polymerase and blocks transcription. Ethambutol inhibits arabinosyl transferases involved in cell-wall arabinogalactan synthesis. Pyrazinamide is converted to pyrazinoic acid and is particularly active under acidic conditions and in specific bacterial metabolic states. The complementary activity of these drugs is central to successful combination therapy.

Adherence support, monitoring for adverse effects, assessment of drug interactions and follow-up of microbiological response are essential. Treatment interruption can increase the risk of relapse and selection of resistant organisms.

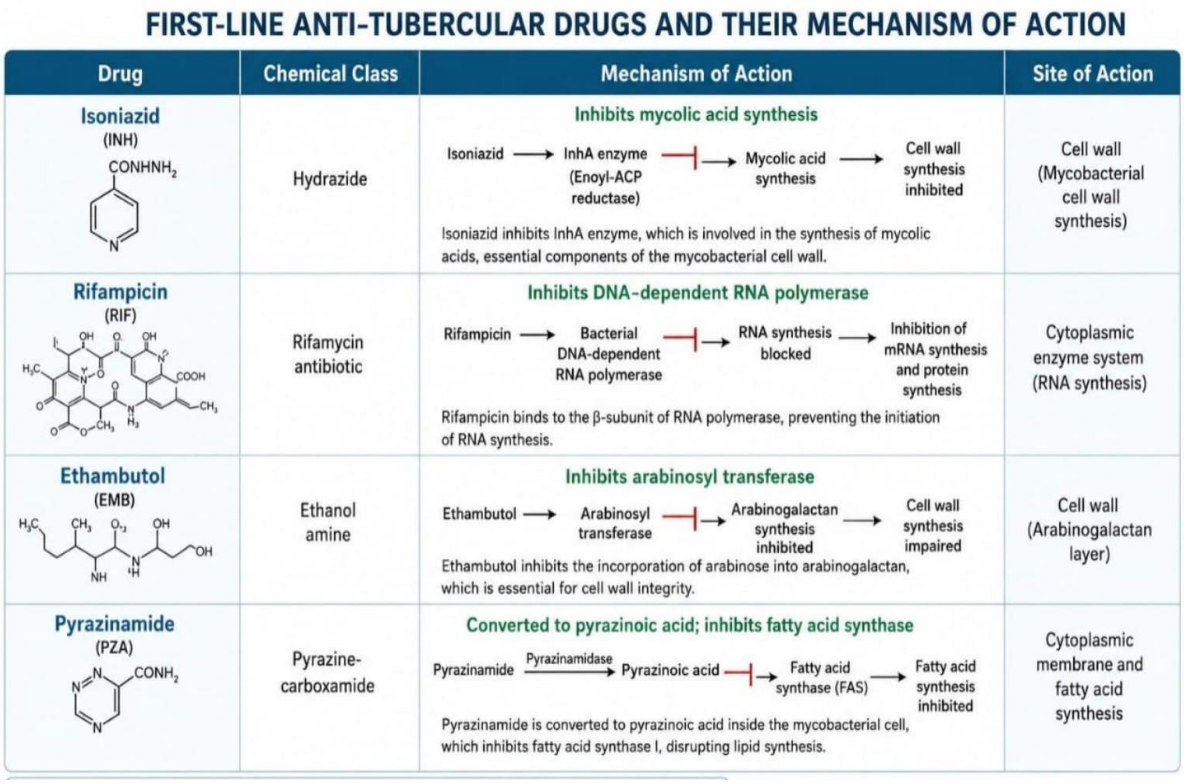

Figure 3. First-line anti-tuberculosis drugs and their principal mechanisms of action.
Source: user-provided educational figure; mechanisms cross-checked with Tripathi[8] and WHO treatment guidance.[3,9]

8. DRUG-RESISTANT TUBERCULOSIS

Multidrug-resistant TB (MDR-TB) is classically defined by resistance to at least isoniazid and rifampicin. Rifampicin-resistant TB (RR-TB) requires similarly careful management even when isoniazid resistance has not been demonstrated. Resistance can arise through genetic mutations selected during inadequate or incomplete therapy and can also be transmitted directly from an individual with resistant disease.

Management of MDR/RR-TB has changed substantially. The WHO 2025 consolidated guidelines recommend several shorter all-oral options for eligible patients, including a 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen in appropriate MDR/RR-TB populations, with modification according to fluoroquinolone susceptibility and other clinical factors. Regimens must be individualized according to drug-susceptibility testing, previous drug exposure, contraindications and national guidance.

Drug-resistant TB remains challenging because of toxicity, drug interactions, treatment complexity, adherence barriers and limited access to rapid susceptibility testing. Strong laboratory capacity and patient-centred support are therefore integral to successful management.

9. TUBERCULOUS MENINGITIS

TBM results from dissemination of M. tuberculosis to the central nervous system and subsequent meningeal inflammation. The disease may cause vasculitis, infarction, hydrocephalus and other neurological complications. Treatment is complex because drug penetration into cerebrospinal fluid varies among agents and because inflammatory complications may persist despite microbiological control.

Evidence from the 2025 systematic review cited above demonstrates substantial mortality and neurological disability despite treatment. Early recognition, rapid diagnostic evaluation, appropriate anti-TB therapy, management of complications and careful monitoring are essential.

10. EMERGING ANTI-TUBERCULOSIS DRUGS AND NOVEL TARGETS

Genome sequencing and advances in molecular biology have expanded the search for new mycobacterial targets. Important targets investigated in contemporary drug discovery include DNA gyrase (GyrA/GyrB), ATP synthase, QcrB, DprE1, FadD32, Pks13 and MmpL3. These targets represent diverse biological processes including DNA replication, energy metabolism, respiratory-chain function and cell-envelope lipid biosynthesis.

Bedaquiline targets the mycobacterial ATP synthase and introduced a novel mechanism into TB therapy. Delamanid and pretomanid are nitroimidazole derivatives with activity against mycobacterial respiratory and nitrosative pathways after intracellular

activation. These agents have expanded treatment options, particularly for drug-resistant TB, but safety, resistance, pharmacokinetic interactions and access remain important considerations.

Future drug discovery should prioritize compounds that penetrate diverse lesion microenvironments, retain activity against persistent bacilli, avoid rapid resistance and have favourable pharmacokinetic and safety profiles. Target-based discovery, phenotypic screening, structure-based design and host-directed approaches may be complementary strategies.

11. CHALLENGES IN TB CONTROL

Major challenges include delayed diagnosis, incomplete treatment, treatment toxicity, drug resistance, inadequate access to healthcare, stigma, socioeconomic barriers and transmission in high-risk settings. TB control is also complicated by the biological heterogeneity of lesions and the ability of M. tuberculosis to persist in host tissues.

Improving TB outcomes requires rapid molecular diagnosis, reliable drug-susceptibility testing, uninterrupted access to quality medicines, adherence support, infection-control measures, preventive therapy for eligible individuals, vaccination strategies and sustained research funding. Vulnerable populations require targeted screening and patient-centred services.

12. FUTURE PERSPECTIVES

Future TB research should focus on shorter and safer regimens, novel targets, combination strategies active against persistent organisms, improved drug delivery to granulomas and caseous lesions, host-directed therapies and rapid point-of-care diagnostics. Translational research should evaluate not only bactericidal activity but also lesion penetration, pharmacokinetics, toxicity, resistance prevention and clinical outcomes.

Continued integration of genomics, structural biology, medicinal chemistry, systems biology and clinical research is likely to accelerate discovery of next-generation anti-TB medicines. Equitable implementation is equally important: scientific advances will have limited population impact unless diagnostics and effective treatments are affordable and accessible.

13. CONCLUSION

TB remains a major global health challenge despite the availability of effective anti-TB therapy. Latent infection, treatment interruption, drug resistance, delayed diagnosis, HIV co-infection and inequitable access to care continue to sustain transmission and mortality. Drug-resistant TB is particularly difficult to manage and reinforces the need for rapid susceptibility testing and effective, shorter combination regimens.

Advances in M. tuberculosis genomics have identified promising drug targets including GyrA/GyrB, ATP synthase, QcrB, DprE1, FadD32, Pks13 and MmpL3. However, toxicity, inadequate in-vivo activity, pharmacokinetic limitations and resistance can hinder translation of candidates into clinical use. Overall, novel drug candidates, optimized regimens, improved diagnostics, adherence support and targeted interventions for vulnerable populations are essential to improve treatment outcomes and support global TB elimination.

Table 1: Principal first-line anti-tuberculosis drugs and mechanisms.

Drug	Class	Principal target/mechanism	Major role
Isoniazid (INH)	Hydrazide	Activated by KatG; inhibits mycolic-acid synthesis	Potent early bactericidal activity
Rifampicin (RIF)	Rifamycin	Binds bacterial DNA-dependent RNA polymerase β-subunits	Inhibits transcription; sterilizing activity
Ethambutol (EMB)	Ethanolamine	Inhibits arabinosyl transferases	Impairs cell-wall arabinogalactan synthesis
Pyrazinamide (PZA)	Pyrazine carboxamide	Converted to pyrazinoic acid; activity linked to acidic	anImd poerstaisnttesntebrialcizililnagrycostmatpeosnent of combination therapy

4. SUMMARY OF REVIEW THEMES

- Pathogenesis: inhalation → alveolar macrophage uptake → intracellular survival → adaptive immune activation → granuloma formation → latent containment or progression.
- Diagnosis: clinical/radiological assessment plus rapid molecular testing, microscopy, culture and drug-susceptibility testing as appropriate.
- Treatment: combination therapy is required to achieve cure and reduce resistance; regimens should follow current WHO/national guidance.
- Drug resistance: rapid detection and individualized, all-oral regimens have improved options for eligible MDR/RR-TB patients.
- Drug discovery: novel targets and drugs should address persistence, lesion penetration, resistance, safety and treatment duration.

REFERENCES

1. Alsayed SSR, Gunosewoyo H. Tuberculosis: Pathogenesis, Current Treatment Regimens and New Drug Targets. Int J Mol Sci., 2023; 24(6): 5202. doi:10.3390/ijms24065202.
2. World Health Organization. Global Tuberculosis Report 2025. Geneva: World Health Organization, 2025.

3. World Health Organization. WHO consolidated guidelines on tuberculosis: Module 4: treatment and care. Geneva: WHO; 2025. ISBN 978-92-4-010724-3.
4. Russell DG, Barry CE 3rd, Flynn JL. Tuberculosis: what we don't know can, and does, hurt us. Science, 2010; 328(5980): 852-856. doi:10.1126/science.1184784.
5. Yan W, Zheng Y, Dou C, et al. The pathogenic mechanism of Mycobacterium tuberculosis: implication for new drug development. Mol Biomed, 2022; 3: 46. doi:10.1186/s43556-022-00106-y.
6. Diriba G, Alemu A, Meaza A, et al. Drug resistance pulmonary tuberculosis among prisoners in Ethiopia: A systematic review and meta-analysis. J Clin Tuberc Other Mycobact Dis, 2026; 43: 100598. doi:10.1016/j.jctube.2026.100598.
7. Afazel S, Nasiri MJ, Venketaraman V. Anti-TB treatment outcomes in TB meningitis: A systematic review and meta-analysis. New Microbes New Infect, 2025; 67: 101623. doi:10.1016/j.nmni.2025.101623.
8. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. New Delhi: Jaypee Brothers Medical Publishers; 2019. p. 897-901.
9. World Health Organization. WHO operational handbook on tuberculosis: Module 4: treatment—drug-susceptible tuberculosis treatment. Geneva: WHO, 2022. ISBN 978-92-4-005076-1.
10. World Health Organization. WHO consolidated guidelines on tuberculosis: Module 4: treatment and care—drug-resistant tuberculosis recommendations. Geneva: WHO, 2025.
11. Rattan A, Kalia A, Ahmad N. Multidrug-resistant Mycobacterium tuberculosis: molecular perspectives. Emerg Infect Dis, 1998; 4(2): 195-209.
12. Russell DG. Foamy macrophages and the progression of the human TB granuloma. Nat Rev Microbiol, 2009; 7: 1-7.
13. World Health Organization. WHO consolidated operational handbook on tuberculosis: Module 4: treatment and care. Geneva: WHO, 2025.