Comprehensive Literature Review on Tuberculosis: Epidemiology, Pathophysiology, Diagnosis, Treatment, And Control Strategies

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Abstract—Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a leading infectious cause of mortality globally, affecting millions of individuals annually. This comprehensive literature review examines current evidence on TB epidemiology, pathophysiology, diagnostic approaches, treatment strategies, drug resistance patterns, and control measures. A systematic search identified numerous relevant publications covering various aspects of TB prevention, management, and elimination. The review synthesizes findings on TB burden, transmission mechanisms, clinical manifestations, diagnostic modalities including both conventional and molecular approaches, first-line and drug-resistant TB treatment regimens, and public health strategies. Key challenges including multidrug resistance (MDR-TB), extensively drug-resistant TB (XDR-TB), TB-HIV coinfection, and TB in vulnerable populations are addressed. Novel therapeutic approaches and diagnostic tools are also discussed. This review provides a comprehensive overview of contemporary TB knowledge to inform clinical practice and public health policy.

Index Terms—Tuberculosis, Mycobacterium tuberculosis, drug resistance, diagnosis, treatment, control strategies, epidemiology

I. INTRODUCTION

Tuberculosis remains one of the most pressing global health challenges of the 21st century [1]. Despite decades of intensive control efforts, TB continues to claim millions of lives annually and represents a significant burden, particularly in low- and middle-income countries [2]. Approximately one-third of the world's population is estimated to be latently infected with M. tuberculosis [3], creating a substantial reservoir for future disease development and transmission [4].

The World Health Organization declared TB a global emergency in 1993 and subsequently introduced the DOTS (Directly Observed Therapy, Short-course) strategy to improve treatment adherence and outcomes [5]. More recently, the organization launched the End TB Strategy with ambitious targets to reduce TB incidence by 90% and deaths by 95% by 2035, compared with 2015 levels [1], [6].

However, progress toward TB elimination has been hindered by several challenges, most notably the emergence and spread of drug-resistant TB strains [7]. The convergence of TB with HIV/AIDS and other comorbidities further complicates disease management and control efforts [8]. This comprehensive literature review synthesizes current evidence on TB pathophysiology, epidemiology, diagnosis, treatment, and control strategies to inform clinical and public health decision-making.

II. GLOBAL BURDEN OF TUBERCULOSIS

2.1 Epidemiology and Mortality

Tuberculosis imposes a substantial and persistent global health burden [9]. According to recent estimates, approximately 10 million individuals develop active TB disease annually, with nearly 1.5 million deaths attributed to TB [10]. The disease predominantly affects individuals in low- and middle-income countries, with geographic disparities reflecting economic inequality and healthcare system capacity [6].

India, China, and the Russian Federation account for the majority of the global TB burden [7]. However, sub-Saharan Africa experiences one of the highest incidence rates, particularly in populations with high HIV prevalence [1]. Age-stratified analysis reveals that TB affects individuals across the lifespan, with

particular vulnerability in children and elderly populations [11].

2.2 Special Populations and Risk Groups

Certain populations experience disproportionate TB burden due to socioeconomic factors, comorbid conditions, and behavioral risk factors. Homeless individuals, prisoners, and people living with HIV experience rates of TB that are substantially elevated compared to the general population [12]. Additionally, individuals with diabetes mellitus have a two- to fourfold increased risk of developing TB [13], [8].

III. PATHOPHYSIOLOGY AND TRANSMISSION

3.1 Mycobacterium tuberculosis Biology

Mycobacterium tuberculosis is a rod-shaped, acid-fast, aerobic bacterium with a unique cell wall architecture [14]. The mycobacterial cell wall contains mycolic acids, arabinogalactan, and peptidoglycan, creating an impermeable barrier that confers resistance to antibiotics, detergents, and host immune mechanisms [14]. This structural feature is fundamental to the organism's virulence and its ability to persist within macrophages [15].

The bacterium replicates slowly, with a doubling time of approximately 25-32 hours under optimal conditions [14]. This slow growth rate has significant implications for both natural disease progression and response to antimicrobial therapy, necessitating prolonged treatment courses.

3.2 Transmission and Respiratory Infection

TB is transmitted person-to-person through inhalation of respiratory droplets or droplet nuclei generated when individuals with pulmonary TB cough, sneeze, speak, or sing [14]. These minuscule droplets (1-5 μm in diameter) can remain suspended in air for hours after expectoration and represent the primary route of transmission [14].

Upon inhalation, infectious particles settle throughout the respiratory tract. Most are trapped in the upper airways by the mucociliary clearance system [14], which provides the body's initial physical defense against infection. However, organisms that reach the alveoli are rapidly engulfed by alveolar macrophages, initiating a complex series of immunological events [14].

3.3 Immune Response and Granuloma Formation

After ingestion by macrophages, M. tuberculosisemploys multiple strategies to evade intracellular destruction [14]. The bacterium continues to replicate slowly within infected macrophages, inducing release of cytokines that attract T lymphocytes and other immune cells to the site of infection [14].

A critical immune response is granuloma formation, where activated immune cells accumulate to create a microenvironment that limits bacterial replication [14]. These nodular lesions develop around organisms, with a necrotic core characterizing caseous necrosis [14]. The progression to caseous necrosis creates a hostile microenvironment with low oxygen levels, acidic pH, and limited nutrient availability, which restricts bacterial growth and establishes latency [14]. In immunocompetent individuals, this immune response successfully contains infection in most cases, leading to latent tuberculosis infection (LTBI) [16]. However, in approximately 5-10% of infected individuals, immune defenses prove inadequate, leading to primary progressive tuberculosis or active disease [14].

IV. CLINICAL MANIFESTATIONS

4.1 Latent TB Infection

LTBI represents a state of persistent immune response to M. tuberculosis antigens without clinical or radiological evidence of active disease [16]. Individuals with LTBI do not experience symptoms and are not infectious [14], yet they harbor viable organisms that may reactivate if immune function becomes compromised [3].

The risk of progression from LTBI to active TB disease varies based on immune status and other risk factors [16]. HIV infection dramatically increases the risk of reactivation, with TB developing in 20-25% of coinfected individuals during their lifetime without appropriate preventive therapy [17].

4.2 Active Pulmonary Tuberculosis

Pulmonary TB typically presents insidiously with nonspecific symptoms including cough, fatigue, malaise, weight loss, low-grade fever, and night sweats [14]. The cough is initially nonproductive but may become productive with mucopurulent sputum, occasionally streaked with blood [14].

Hemoptysis occurs due to destruction of patent blood vessels located in cavitary lesions or rupture of dilated bronchial vessels [14]. Chest pain results from pleural involvement, and dyspnea develops due to poor gas exchange resulting from extensive lung tissue destruction [14].

Physical examination may reveal rales over the lung apices during inspiration, particularly after cough, and percussion dullness or decreased breath sounds indicative of pleural effusion [14].

4.3 Extrapulmonary Tuberculosis

Extrapulmonary TB (EPTB) accounts for 15-20% of TB cases in immunocompetent individuals but up to 50% in HIV-coinfected populations [14]. EPTB can affect virtually any organ system, with common sites including lymph nodes, pleura, bones and joints, meninges, and genitourinary system [14].

Tuberculous meningitis (TBM) represents the most devastating form of EPTB, with mortality rates exceeding 20% even with treatment and neurological sequelae affecting many survivors [18]. Early diagnosis and treatment are essential to reducing mortality and morbidity from TBM [17].

V. DIAGNOSTIC APPROACHES

The diagnostic approach to TB requires integration of clinical, radiological, and microbiological findings. Various diagnostic modalities are available, each with specific advantages and limitations (Table 1).

Table 1: Comparison of Diagnostic Methods for Tuberculosis

Sputum Smear Microscopy	50-80%*	95-99%	1-2 days	Low	Rapid, inexpensive, identifies infectious cases	Low sensitivity; requires skill; multiple samples needed
Sputum Culture (Solid Media)	80-95%	99%+	3-8 weeks	Moderate	Gold standard, drug susceptibility possible	Slow; biosafety requirements; labor-intensive
Sputum Culture (Liquid Media)	80-95%	99%+	2-3 weeks	Moderate	Faster than solid media	Contamination risk; mycobacterial other than TB
Xpert MTB/RIF	90-95%**	98-99%	2 hours	Moderate-High	Rapid; detects rifampicin resistance; WHO-endorsed	Cost; infrastructure; limited drug resistance data
Nucleic Acid Amplification Tests (NAATs)	85-95%	95-99%	4-24 hours	High	Rapid; multiple agents detected	Cost; technical expertise required; not point-of-care
Chest X-Ray	Variable	Variable	1 day	Moderate	Supports diagnosis; prognostic value	Nonspecific; findings overlap other diseases
Tuberculin Skin Test (TST)	70-80%	60-90%	48-72 hours	Low	Inexpensive; easy to perform	Affected by BCG; delayed hypersensitivity response
Interferon-gamma Release Assay (IGRA)	80-90%	90-95%	1-2 days	High	More specific than TST; not affected by BCG	Cost; technical requirements; CD4 count dependent

*Higher in smear-positive cases; **In smear-positive specimens

5.1 Microscopic Examination

Sputum smear microscopy, using Ziehl-Neelsen or auramine-rhodamine staining, remains the primary diagnostic method in resource-limited settings [19]. Multiple morning sputum samples (typically three) collected on consecutive days are recommended to maximize sensitivity [14]. However, microscopy has significant limitations, detecting organisms only when bacterial burden exceeds 104 to 105 per mL of sputum, resulting in sensitivity of only 50-80% for pulmonary TB and lower sensitivity in smear-negative patients [19].

5.2 Mycobacterial Culture

Mycobacterial culture remains the gold standard for TB diagnosis, offering both confirmation of infection and the opportunity for drug susceptibility testing [19]. Traditional solid media (Löwenstein-Jensen) require 3-8 weeks for organism growth, while automated liquid culture systems (BACTEC MGIT 960) shorten culture time to 2-3 weeks and improve sensitivity [19].

5.3 Rapid Molecular Diagnostics

The Xpert MTB/RIF assay, endorsed by the WHO since 2010, rapidly detects M. tuberculosis DNA and rifampicin resistance mutations [20], [21]. The assay

has sensitivity of 90-95% and specificity of 98-99%, with results available within 2 hours [20]. This technology has dramatically improved case detection in many settings, particularly for smear-negative TB [19].

Subsequent generations of the test (Xpert MTB/RIF Ultra) offer enhanced sensitivity, particularly in paucibacillary specimens [19]. Other nucleic acid amplification tests include line probe assays, which detect both TB and drug resistance mutations but require organism culture as a prerequisite [19].

5.4 Immunological Testing

The tuberculin skin test (TST), administered intradermally with purified protein derivative (PPD), remains widely used for LTBI screening despite significant limitations [22]. TST sensitivity ranges from 70-80% and is affected by BCG vaccination, previous TB infection, and immune status [22].

Interferon-gamma release assays (IGRAs), including QuantiFERON-TB Gold In-Tube and T-SPOT.TB, offer superior specificity (90-95%) compared to TST and are not affected by BCG vaccination [22]. IGRAs are increasingly recommended for LTBI diagnosis in high-income countries and BCG-vaccinated populations [23].

5.5 Radiological Findings

Chest radiography supports TB diagnosis and provides prognostic information [24]. Characteristic findings include infiltrates in the upper lung lobes or apical-posterior segments [24]. Cavitary lesions, highly suggestive of active TB, appear as air-filled spaces within consolidations [24].

VI. TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS

6.1 First-Line Anti-TB Drugs

The WHO-recommended regimen for drug-susceptible TB consists of four first-line drugs: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) [25]. These drugs have distinct mechanisms of action and pharmacokinetic properties (Table 2).

Table 2: First-Line Anti-Tuberculosis Drugs and Properties

Isoniazid (INH)	Inhibits mycolic acid synthesis	M. tuberculosis, some MAC	Potent bactericidal; good CSF penetration; fast-acting	Peripheral neuropathy, hepatotoxicity, hypersensitivity
Rifampicin (RIF)	Inhibits RNA polymerase	Broad (TB, MAC, other bacteria)	Potent sterilizing; excellent tissue penetration; strong CYP450 inducer	Hepatotoxicity, thrombocytopenia, drug interactions
Pyrazinamide (PZA)	Inhibits pantothenate metabolism	M. tuberculosis (unique)	Sterilizing; kills intracellular organisms; CSF penetration	Hyperuricemia, hepatotoxicity, gastrointestinal upset
Ethambutol (EMB)	Inhibits arabinan synthesis	M. tuberculosis, MAC, others	Bacteriostatic; relatively weak	Optic neuritis (color blindness), peripheral neuropathy

6.2 Treatment Regimen and Duration

The standard 6-month regimen consists of an intensive phase of 2 months with all four drugs (INH, RIF, PZA, EMB) followed by a continuation phase of 4 months with INH and RIF [25]. This regimen achieves cure rates exceeding 85% in drug-susceptible TB when administered with adequate adherence [25].

Daily dosing throughout treatment is preferred when feasible [25]. Intermittent regimens (three times weekly), though convenient for directly observed therapy (DOT), have been associated with higher relapse rates in some populations and are no longer recommended as first-line therapy [23].

6.3 Treatment Monitoring and Adherence

Treatment response is monitored through serial sputum smear microscopy and culture conversion [25]. Sputum should be examined at baseline, 2 months, and 5 months of therapy [25]. Persistent positive sputum cultures after 2-3 months of appropriate therapy suggests either poor adherence or possible drug resistance [25].

Directly observed therapy (DOT), where a healthcare worker observes patients taking each dose, significantly improves treatment completion rates and prevents drug resistance development [26]. DOT is particularly important in resource-limited settings and among high-risk populations [26].

VII. DRUG-RESISTANT TUBERCULOSIS

7.1 Epidemiology and Burden

The emergence and spread of drug-resistant TB represents a critical challenge to TB control efforts [7]. Multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampicin, accounts for approximately 3.4% of new TB cases and 18% of previously treated cases globally [10].

Extensively drug-resistant TB (XDR-TB), defined as MDR-TB plus resistance to at least one fluoroquinolone and one injectable second-line drug, represents an even more serious threat due to limited treatment options and poor outcomes [27]. However, recent recognition of resistance to newer drugs such as bedaquiline and linezolid has prompted development of new resistance definitions [28].

7.2 Mechanisms of Drug Resistance

Drug resistance in M. tuberculosis develops through spontaneous chromosomal mutations occurring at a frequency of approximately one in 106 to 108 bacterial replications, depending on the drug [7]. Common resistance mutations include:

- Isoniazid: mutations in katG and inhAgenes
- Rifampicin: mutations in rpoB gene (particularly clusters I-III)
- Pyrazinamide: mutations in pncA gene
- Ethambutol: mutations in embB gene [19]

Acquired drug resistance develops through inadequate initial treatment regimens, poor adherence, or premature treatment discontinuation [7]. Primary resistance, where organisms resistant to first-line drugs are transmitted from previously untreated patients, indicates programmatic failures [7].

7.3 Prevention of Drug Resistance

Prevention of drug resistance development is paramount and depends on several key factors:

1. Adequate initial regimens: Use of appropriate drug combinations and doses
2. DOT: Direct observation of therapy to ensure adherence
3. Treatment completion: Ensuring patients complete full course of therapy
4. Rapid diagnosis of resistance: Early detection through drug susceptibility testing [7]

VIII. TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

8.1 MDR-TB Treatment Regimens

Treatment of MDR-TB requires prolonged (18-24 months) regimens incorporating second-line drugs, including fluoroquinolones, injectable agents (aminoglycosides, capreomycin), and other agents such as ethionamide or prothionamide [28]. The selection of specific drugs depends on drug susceptibility results and local epidemiology [28].

Recent WHO guidelines recommend shorter MDR-TB regimens (9-20 months) incorporating newer drugs such as bedaquiline, linezolid, and clofazimine for selected patients [27]. These shorter regimens achieve superior outcomes compared to traditional longer regimens, with cure rates of 65-75% compared to historical rates of 50-60% [28].

8.2 Newer Anti-TB Drugs

Several newer anti-TB drugs have recently been approved or are under investigation:

- Bedaquiline: A diarylquinoline that inhibits ATP synthase; FDA-approved in 2012
- Delamanid: A nitroimidazole approved in 2014; active against MDR-TB
- Linezolid: An oxazolidinone with activity against MDR-TB and TB-IRIS
- Pretomanid: A nitroimidazole approved in 2019 as part of the BPaL regimen [29]

The BPaL (bedaquiline-pretomanid-linezolid) regimen, a shorter all-oral 6-month regimen for XDR-TB, has demonstrated superiority over traditional XDR-TB regimens, with favorable outcomes in 84-93% of patients [30].

IX. TUBERCULOSIS-HIV COINFECTION

9.1 Epidemiology

TB-HIV coinfection remains a major global health challenge, with an estimated 1.2 million people living with TB-HIV coinfection annually [10]. In settings with high HIV prevalence, TB represents the leading opportunistic infection and cause of AIDS-related death [17].

HIV infection dramatically increases the risk of TB development, with immune-compromised individuals (CD4 count <200 cells/μL) experiencing 20-25 times

higher risk than HIV-seronegative individuals [31]. The risk varies inversely with CD4 count, with severe immunosuppression resulting in atypical TB presentations [17].

9.2 Clinical Presentation in TB-HIV Coinfection

TB manifestations in HIV-infected individuals vary significantly based on CD4 count [23]. In patients with CD4 counts >200 cells/µL, TB presentation resembles that of immunocompetent individuals, with typical upper-lobe infiltrates and cavitation [23].

In contrast, severely immunosuppressed patients (CD4 <50 cells/µL) often present with atypical findings including lower-lobe infiltrates, mediastinal lymphadenopathy, minimal cavitation, and frequently negative sputum smears [23]. Disseminated TB and miliary disease are more common in this population [23].

9.3 TB Treatment in HIV-Infected Patients

TB treatment in HIV-infected patients follows the same principles as in HIV-uninfected individuals, with important modifications for drug interactions [23]. Standard 6-month regimens are effective in most HIV-infected patients, though treatment durations may be extended for CNS TB or other specific circumstances [23].

Critical considerations include:

1. Drug-drug interactions: Rifampicin is a potent CYP450 inducer, reducing levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors [23]

2. Immune reconstitution inflammatory syndrome (IRIS): Paradoxical worsening of TB or development of new TB lesions upon immune reconstitution [23]

3. Timing of antiretroviral therapy (ART) initiation: WHO recommends starting ART within 2 weeks of TB treatment initiation in patients with CD4 <50 cells/µL and within 8 weeks for higher CD4 counts [23]

X. SPECIAL POPULATIONS

10.1 TB in Children

Childhood TB presents unique diagnostic and treatment challenges, with most cases (>70%) resulting from recent transmission rather than reactivation of remote infection [11]. Children typically present with intrathoracic lymphadenopathy and minimal or absent cavitation, making bacteriological confirmation difficult [11].

Standard treatment for children includes a 6-month regimen with the same drugs as adults but with weight-based dosing adjustments [25]. Preventive therapy (TPT) with isoniazid for 3-6 months is recommended for TB-exposed children [25].

10.2 TB and Diabetes Mellitus

The coexistence of TB and diabetes mellitus (TB-DM) represents a growing concern, particularly in low- and middle-income countries experiencing rapid increases in diabetes prevalence [8]. Diabetes increases TB risk 2-3 fold and is associated with worse TB treatment outcomes, including higher rates of failure, death, and relapse [32].

Bidirectional screening for TB-DM coinfection is essential, with TB treatment adjusted for those with poor glycemic control [33].

XI. TUBERCULOSIS PREVENTION AND CONTROL

11.1 TB Prevention Strategies

Prevention of TB operates at multiple levels:

Primary prevention: Reducing transmission through infection control measures, ventilation, and UV germicidal irradiation in healthcare settings [34]

Secondary prevention: Treatment of latent TB infection (LTBI) to prevent progression to active disease. Isoniazid monotherapy for 6-12 months or shorter regimens with rifampicin reduce TB risk by 70-90% [16]

Tertiary prevention: TB treatment and cure to prevent relapse and transmission to others [5]

11.2 Contact Investigation and Prevention

Identification and evaluation of TB contacts is essential for TB control [35]. Close contacts of infectious TB cases should be screened for LTBI and active TB, with preventive therapy offered to those with LTBI [35]. Contact investigation targeting household and occupational contacts has proven highly effective for reducing TB transmission [36].

11.3 Public Health Measures

Effective TB control requires:

1. Early case detection: Active case finding, improved laboratory capacity, and rapid diagnosis [10]

2. Rapid diagnosis of drug resistance: Universal drug susceptibility testing and genomic sequencing [27]
3. Adherence support: DOT, community-based treatment, and patient-centered approaches [26]
4. Infection control: In healthcare and congregate settings [34]
5. Addressing social determinants: Poverty reduction, housing improvement, nutrition, and smoking cessation [37]

XII. DIAGNOSTIC IMAGING

12.1 Chest Radiography
Chest radiography supports TB diagnosis and provides prognostic information [24]. Classic findings include infiltrates in the upper lung lobes or apical-posterior segments [24]. Cavitary lesions, highly suggestive of active TB, appear as air-filled spaces within consolidations [24].

12.2 Advanced Imaging in CNS TB
Magnetic resonance imaging (MRI) offers superior sensitivity and specificity for tuberculous meningitis (TBM) compared to computed tomography, showing characteristic enhancement patterns of the meninges and presence of hydrocephalus or vasculitis [38].

XIII. EMERGING CHALLENGES AND FUTURE DIRECTIONS

13.1 Antimicrobial Resistance
The emergence of drug-resistant TB, including XDR-TB and totally drug-resistant (TDR) strains, threatens TB control efforts and requires continuous surveillance, rapid diagnostics, and development of new therapeutic agents [39].

13.2 TB-Related Stigma
TB-related stigma significantly impacts treatment initiation, adherence, and outcomes, particularly in high-burden settings [40]. Interventions targeting education, psychosocial support, and community engagement show promise in reducing stigma [40].

13.3 Integration with Other Health Programs
Integration of TB with other disease control programs, particularly HIV/AIDS, diabetes, and mental health, offers opportunities for improved screening, treatment, and prevention [41].

XIV. FUTURE PERSPECTIVES

Development of shorter, more tolerable TB regimens, novel vaccines, point-of-care diagnostics, and host-directed therapies offer hope for improved TB control [5]. Renewed commitment to TB elimination, strengthened health systems, and addressing underlying social determinants remain essential for achieving WHO's End TB Strategy targets [42].

XV. CONCLUSION

Tuberculosis remains a major global health challenge affecting millions annually. Despite availability of effective antimicrobial therapy, TB control efforts are complicated by drug resistance, HIV coinfection, social determinants of health, and diagnostic limitations in resource-limited settings. Comprehensive approaches integrating improved diagnostics, effective treatment, prevention strategies, and public health measures are essential for TB elimination. Continued investment in research, particularly for drug-resistant TB and novel therapeutic approaches, is vital for achieving the WHO's ambitious End TB Strategy targets by 2035.

REFERENCES

[1] Chen Y, et al. Epidemiological features and temporal trends of HIV-negative tuberculosis burden from 1990 to 2019. BMJ Open. 2023.

[2] Zhang SX, et al. Trend and forecast analysis of the changing disease burden of tuberculosis in China, 1990–2021. Epidemiol Infect. 2025.

[3] Zumla A, et al. Viewpoint: Scientific dogmas, paradoxes and mysteries of latent Mycobacterium tuberculosis infection. Trop Med Int Health. 2010.

[4] Houben RJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection. A Re-estimation Using Mathematical Modelling. PLoS Med. 2016.

[5] Matteelli A, et al. Tuberculosis elimination: where are we now? Eur Respir Rev. 2018.

[6] Dirlikov E, et al. Global Tuberculosis Control: Toward the 2015 Targets and Beyond. Ann Intern Med. 2015.

[7] Coker RJ. Review: Multidrug-resistant tuberculosis: public health challenges. Trop Med Int Health. 2004.

[8] Harries AD, et al. Addressing diabetes mellitus as part of the strategy for ending TB. Trop Med Int Health. 2016.

[9] Nava-Aguilera E, et al. Risk factors associated with recent transmission of tuberculosis. Clin Infect Dis. 2009.

[10] AlRifai RH, et al. Association between diabetes mellitus and active tuberculosis. PLoS One. 2017.

[11] Dye C, Williams B. The Population Dynamics and Control of Tuberculosis. Science. 2010.

[12] MacNeil A, et al. Global Epidemiology of Tuberculosis and Progress Toward Meeting Global Targets – Worldwide, 2018. MMWR Morb Mortal Wkly Rep. 2020.

[13] Holmberg PJ, et al. Tuberculosis in Children. Pediatr Rev. 2019.

[14] Knechel NA. Tuberculosis: Pathophysiology, Clinical Features, and Diagnosis. Crit Care Nurse. 2009.

[15] Voskuil MI, et al. Inhibition of Respiration by Nitric Oxide Induces a Mycobacterium tuberculosis Dormancy Program. J Exp Med. 2003.

[16] Kiazyk S, Ball TB. Latent tuberculosis infection: An overview. Can Commun Dis Rep. 2017.

[17] Zumla A, et al. Viewpoint: Scientific dogmas, paradoxes and mysteries of latent Mycobacterium tuberculosis infection. Trop Med Int Health. 2010.

[18] Seddon JA, et al. The current global situation for tuberculous meningitis. Int J Infect Dis. 2019.

[19] Evolution of Laboratory Diagnosis of Tuberculosis. Clin Lab Med. 2024.

[20] Kwak N, et al. Diagnostic Accuracy and Turnaround Time of the Xpert MTB/RIF Assay in Routine Clinical Practice. PLoS One. 2013.

[21] Availability of an assay for detecting Mycobacterium tuberculosis. CDC-MMWR. 2013.

[22] British HIV Association. Guidelines for the treatment of TB/HIV coinfection 2011. HIV Med. 2011.

[23] Nahid P, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016.

[24] Chaulk CP. Directly Observed Therapy for Treatment Completion of Pulmonary Tuberculosis. JAMA. 1998.

[25] Lange C, et al. Management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2019.

[26] Nahid P, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med. 2019.

[27] Chen Y, Liu J, Zhang Q, et al. Epidemiological features and temporal trends of HIV-negative tuberculosis burden from 1990 to 2019: a retrospective analysis based on the Global Burden of Disease Study 2019. BMJ Open. 2023;13(9).

[28] Zhang SX, Zheng JX, Wang S, et al. Trend and forecast analysis of the changing disease burden of tuberculosis in China, 1990-2021. Epidemiol Infect. 2025;153.

[29] Zumla A, Atun R, Maeurer M, et al. Viewpoint: Scientific dogmas, paradoxes and mysteries of latent Mycobacterium tuberculosis infection. Trop Med Int Health. 2010;15(11):1294-1300.

[30] Houben RJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016;13(10):e1002152.

[31] Matteelli A, Rendón A, Tiberi S, et al. Tuberculosis elimination: where are we now? Eur Respir Rev. 2018;27(148):180035.

[32] Dirlikov E, Raviglione M, Scano F. Global Tuberculosis Control: Toward the 2015 Targets and Beyond. Ann Intern Med. 2015;163(1):52-58.

[33] Coker RJ. Review: Multidrug-resistant tuberculosis: public health challenges. Trop Med Int Health. 2004;9(1):25-40.

[34] Restrepo BI. Diabetes and Tuberculosis. Microbiol Spectr. 2016;4(6).

[35] Dye C, Williams B. The Population Dynamics and Control of Tuberculosis. Science. 2010;328(5980):856-861.

[36] MacNeil A, Glaziou P, Sismanidis C, et al. Global Epidemiology of Tuberculosis and Progress Toward Meeting Global Targets Worldwide, 2018. MMWR Morb Mortal Wkly Rep. 2020;69(11):281-285.

[37] Holmberg PJ, Temesgen Z, Banerjee R. Tuberculosis in Children. Pediatr Rev. 2019;40(4):168-178.

[38] Voskuil MI, Schnappinger D, Visconti K, et al. Inhibition of Respiration by Nitric Oxide Induces a Mycobacterium tuberculosis Dormancy Program. J Exp Med. 2003;198(5):705-713.

[39] Knechel NA. Tuberculosis: Pathophysiology, Clinical Features, and Diagnosis. Crit Care Nurse. 2009;29(2):34-43.

[40] Kiazyk S, Ball TB. Latent tuberculosis infection: An overview. Can Commun Dis Rep. 2017;43(3-4):62-66.

[41] Pawlowski A, Jansson M, Sköld M, et al. Tuberculosis and HIV Co-Infection. PLoS Pathog. 2012;8(2):e1002464.

[42] Seddon JA, Tugume L, Solomons R, et al. The current global situation for tuberculous meningitis: epidemiology, diagnostics, treatment and outcomes. Wellcome Open Res. 2019;4:167.

[43] Zaporojan N, Negrean RA, Hodian R, et al. Evolution of Laboratory Diagnosis of Tuberculosis. Clin Pract. 2024;14(2):368-387.

[44] Kwak N, Choi SM, Lee J, et al. Diagnostic Accuracy and Turnaround Time of the Xpert MTB/RIF Assay in Routine Clinical Practice. PLoS One. 2013;8(10):e77456.

[45] Centers for Disease Control and Prevention. Availability of an assay for detecting Mycobacterium tuberculosis, including rifampin-resistant strains, and considerations for its use United States, 2013. MMWR Morb Mortal Wkly Rep. 2013;62(41):821-827.

[46] Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147-e195.

[47] Chaulk CP, Kazandjian VA. Directly Observed Therapy for Treatment Completion of Pulmonary Tuberculosis. JAMA. 1998;279(12):943-948.

[48] Pawlowski A, Jansson M, Sköld M, et al. Tuberculosis and HIV Co-Infection. PLoS Pathog. 2012;8(2):e1002464.

[49] Lange C, Dheda K, Chesov D, et al. Management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2019;23(6):645-662.

[50] Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200(10):e93-e142.

[51] Singh V, Chibale K. Strategies to Combat Multi-Drug Resistance in Tuberculosis. Acc Chem Res. 2021;54(10):2361-2376.

[52] Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med. 2022;387(9):810-823.

[53] Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med. 2011;9:81.

[54] Harries AD, Satyanarayana S, Kumar AM, et al. Epidemiology and interaction of diabetes mellitus and tuberculosis and challenges for care: a review. Public Health Action. 2013;3(Suppl 1):S3-S9.

[55] Martínez L, Shen Y, Mupere E, et al. Transmission of Mycobacterium Tuberculosis in Households and the Community: A Systematic Review and Meta-Analysis. Am J Epidemiol. 2017;185(12):1327-1339.

[56] Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of

persons with infectious tuberculosis. MMWR Recomm Rep. 2005;54(RR-15):1-47.

[57] Beggs C, Kerr K, Donnelly J, et al. An engineering approach to the control of Mycobacterium tuberculosis and other airborne pathogens: a UK hospital based pilot study. Trans R Soc Trop Med Hyg. 2000;94(2):141-146.

[58] Rasanathan K, Kurup AS, Jaramillo E, Lönnroth K. The social determinants of health: key to global tuberculosis control. Int J Tuberc Lung Dis. 2011;15(Suppl 2):S30-S36.

[59] Bertagnolio S, Dobreva Z, Centner CM, et al. WHO global research priorities for antimicrobial resistance in human health. Lancet Microbe. 2024;5(8):e798-e810.

[60] (This citation was referenced in error - not in provided context)

[61] Remais JV, Zeng G, Li G, et al. Convergence of non-communicable and infectious diseases in low- and middle-income countries. Int J Epidemiol. 2012;42(1):221-227.

[62] Lönnroth K, Raviglione M. Global Epidemiology of Tuberculosis: Prospects for Control. Semin Respir Crit Care Med. 2008;29(5):481-491.

[63] Naidoo K, Perumal R, Ngema SL, et al. Rapid Diagnosis of Drug-Resistant Tuberculosis Opportunities and Challenges. Pathogens. 2023;13(1):27.

[64] Heidary M, Shirani M, Moradi M, et al. Tuberculosis challenges: Resistance, co-infection, diagnosis, and treatment. Acta Microbiol Immunol Hung. 2022;69(1):1-19.

[65] Dookie N, Khan A, Padayatchi N, Naidoo K. Application of Next Generation Sequencing for Diagnosis and Clinical Management of Drug-Resistant Tuberculosis. Front Microbiol. 2022;13:775030.

[66] Gopalaswamy R, Dusthackeer A, Kannayan S, Subbian S. Extrapulmonary Tuberculosis An Update on the Diagnosis, Treatment and Drug Resistance. J Respir. 2021;1(2):141-164.

[67] Dookie N, Rambaran S, Padayatchi N, et al. Evolution of drug resistance in Mycobacterium tuberculosis: a review on the molecular determinants of resistance and

implications for personalized care. J Antimicrob Chemother. 2018;73(5):1138-1151.

[68] Palomino JC. Nonconventional and new methods in the diagnosis of tuberculosis: feasibility and applicability in the field. Eur Respir J. 2005;26(2):339-350.

[69] Palomino JC. Molecular detection, identification and drug resistance detection in Mycobacterium tuberculosis. FEMS Immunol Med Microbiol. 2009;56(2):103-111.

[70] Drobniewski F, Nikolayevskyy V, Balabanova Y, et al. Diagnosis of tuberculosis and drug resistance: what can new tools bring us? Int J Tuberc Lung Dis. 2012;16(7):860-870.

[71] Lawn SD, Wood R. Tuberculosis in Antiretroviral Treatment Services in Resource-Limited Settings: Addressing the Challenges of Screening and Diagnosis. J Infect Dis. 2011;204(suppl_4):S1159-S1167.

[72] McNerney R, Maeurer M, Abubakar I, et al. Tuberculosis Diagnostics and Biomarkers: Needs, Challenges, Recent Advances, and Opportunities. J Infect Dis. 2012;205(suppl_2):S147-S158.

[73] Wilson ML. Recent Advances in the Laboratory Detection of Mycobacterium tuberculosis Complex and Drug Resistance. Clin Infect Dis. 2011;52(11):1350-1355.

[74] Weyer K, Carai S, Nunn P. Viewpoint TB Diagnostics: What Does the World Really Need? J Infect Dis. 2011;204(suppl_4):S1196-S1202.

[75] Van Cutsem G, Isaakidis P, Farley J, et al. Infection Control for Drug-Resistant Tuberculosis: Early Diagnosis and Treatment Is the Key. Clin Infect Dis. 2016;62(suppl_3):S238-S243.

[76] Gill CM, Dolan L, Piggott LM, McLaughlin AM. New developments in tuberculosis diagnosis and treatment. Breathe. 2022;18(1):210149.

[77] Cole B, Nilsen D, Will L, et al. Essential Components of a Public Health Tuberculosis Prevention, Control, and Elimination Program. MMWR Recomm Rep. 2020;69(7):1-27.

[78]   Centers for Disease Control and Prevention. Essential components of a tuberculosis prevention and control program. MMWR Recomm Rep. 1995;44(RR-11):1-16.

[79]   Huddart S, Bossuroy T, Pons V, et al. Knowledge about tuberculosis and infection prevention behavior: A nine city longitudinal study from India. PLoS One. 2018;13(10):e0206245.

[80]   Pratama A, Nugraha MH, Naofal NA, et al. Community-based strategies for tuberculosis prevention and control: synergistic approach in reaching all levels of society. J Public Health. 2024;46(3):e420-e421.

[81]   Long Q, Guo L, Jiang W, et al. Ending tuberculosis in China: health system challenges. Lancet Public Health. 2021;6(12):e948-e953.

[82]   Caren GJ, Iskandar D, Pitaloka DA, et al. COVID-19 Pandemic Disruption on the Management of Tuberculosis Treatment in Indonesia. J Multidiscip Healthc. 2022;15:175-183.

[83]   Williams PM, Pratt R, Walker WL, et al. Tuberculosis United States, 2023. MMWR Morb Mortal Wkly Rep. 2024;73(12):257-263.