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Tuberculosis without microbiological confirmation

Salomé Bellido-Calduch* and Zoran Stojanovic

Department of Pulmonology, University Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

ABSTRACT

A considerable proportion of tuberculosis (TB) cases are diagnosed without microbiological confirmation, particularly in early or paucibacillary disease. This review explores the diagnostic and therapeutic approach to non-microbiologically confirmed TB, integrating evidence from recent studies and international guidelines. Patients without microbiological confirmation often have milder symptoms and less extensive radiological findings, reflecting an early stage of disease with lower bacterial load and transmission risk. Radiological tools, mainly chest X-ray and computed tomography, remain essential but lack specificity, emphasizing the need for careful clinical correlation. Empiric anti-TB therapy should be initiated in cases with strong clinical and radiological evidence, followed by close monitoring to confirm response and exclude alternative diagnoses. Emerging technologies, including computer-aided radiological detection and blood-based biomarker assays, may improve diagnostic accuracy in smear-negative or immunocompromised patients. Early recognition and prompt treatment are crucial to reduce morbidity, mortality, and transmission, supporting global TB elimination goals.

Keywords: Tuberculosis. Clinical diagnosis. Empirical treatment.

***Correspondence to:**
Salomé Bellido-Calduch
E-mail: sbellidoc.germanstrias@gencat.cat

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INTRODUCTION

Tuberculosis (TB) is one of the oldest infectious diseases known to humanity. It is primarily a pulmonary disease, transmitted through airborne particles, but it can also present in extrapulmonary forms. Robert Koch identified its causative agent, *Mycobacterium tuberculosis* (MTB), in 1882. Yet only since 1940s, we have available first effective treatments. Even today, it remains a major global health challenge, particularly in low- and middle-income countries. With a total number of 10.8 million newly diagnosed in 2023, it is among top 10 causes of death worldwide and first of all infectious diseases, causing 1.09 million deaths in 2023. Almost double than caused by human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome[1].

Rapid and accurate diagnostic testing is of great importance because it ensures the most effective treatment regimen (depending on the pattern of drug resistance) as early as possible. Conventionally, TB diagnostic relied on more traditional methods such as smear microscopy and bacterial culture, which can take up to 2 months until having the result. In recent years, diagnostic tests for TB disease have improved substantially since rapid molecular tests and lateral flow urine lipoarabinomannan (LF-LAM) assays were introduced. People diagnosed by any of them are considered as "bacteriologically confirmed" cases of TB, nevertheless, of the 6.9 million people diagnosed with pulmonary TB worldwide in 2023, only 62% were bacteriologically confirmed[2]. Although it was significant improvement compared to the past decade, approximately 20–30% of patients with TB are found to lack culture confirmation and are diagnosed clinically in areas with sufficient resources and high levels of experience[2,3].

TB is now understood as a spectrum ranging from latent infection, through incipient and subclinical stages, to active disease. Progression along this continuum depends on host immune status, genetics, and comorbidities. While latent infection is asymptomatic and non-contagious, detectable with interferon-γ release assay (IGRA) or purified protein derivative–tuberculin skin test (TST), active TB presents with symptoms (cough, fever, weight loss, and night sweats), making a bacteriological confirmation through sputum tests more probable. Subclinical TB, lying between latent infection and active disease, is asymptomatic but can be identified radiologically and/or microbiologically, although the second one is less probable[4]. People diagnosed with TB in the absence of bacteriological confirmation are classified as "clinically diagnosed tuberculosis," which refers to a diagnosis of active TB made on the basis of clinical, radiographic, or other evidence of disease, in the absence of microbiological confirmation[1,5]. Intervention at the earliest possible state and a close follow-up will reduce morbidity for the individual and transmission for the community.

Outcomes for clinically diagnosed cases are generally comparable to bacteriologically confirmed cases, but mortality is higher, underscoring the need for systematic screening, better diagnostic methods, and management of comorbidities, other infections and unrecognized non-infectious diseases mimicking TB[2]. The goal of this review is to explore the approach to non-microbiologically confirmed TB.

DIAGNOSIS CHALLENGES

Clinical presentation

TB natural history is related with the concept of the TB disease spectrum, recognizing that human TB infection, from latent infection to active disease, exists within a range of manifestations derived from metabolic bacterial activity and antagonistic immunological responses. Therefore, patients with TB infection have no clinical, radiological, or microbiological evidence of active TB disease. In case of incipient infection, TB signs or symptoms of disease are absent but the bacteria are alive and replicating. Individuals with subclinical TB do not have symptoms but may have radiological or/and microbiological evidence of TB disease, and finally, patients with TB disease have classical signs and symptoms: cough, sputum production, weight loss, fever, and hemoptysis so the diagnosis is based on clinical and radiological findings, and confirmed by microbiological tests[6].

The above listed classical symptoms are the most common clinical presentation of clinically diagnosed TB, but they are less pronounced than those of microbiologically confirmed TB. For that reason, these patients with this presumed TB can be construed as an early disease state with less sings, symptoms, and a probably low mycobacterial burden and transmission risk[7].

Role of radiology

Chest radiography, or chest X-ray (CXR), is a rapid imaging technique that allows lung abnormalities to be identified. CXR is used to diagnose conditions of the thoracic cavity, including the airways, ribs, lungs, heart, and diaphragm. It has become an important tool for triaging and screening for pulmonary TB, and in combination with clinical assessment, CXR may provide important circumstantial evidence when pulmonary TB cannot be confirmed bacteriologically[8,9].

Patients with clinically diagnosed TB typically exhibit less extensive pulmonary involvement, characterized by a lower prevalence of cavitary lesions and more subtle radiographic infiltrates. The reduced intensity of clinical symptoms and imaging abnormalities, relative to bacteriologically confirmed cases, aligns with the concept of a disease continuum in TB pathogenesis representing an earlier stage of active disease[10].

While CXR is highly sensitive and useful for identifying abnormalities suggestive of TB, its specificity is limited. Pulmonary TB can share many radiological findings from other relevant respiratory diseases, which may include lung cavities from other non-TB infections, airflow obstruction diseases (such as chronic obstructive pulmonary disease or asthma), bronchiectasis, occupational lung diseases (such as silicosis), or neoplasms (such as lung cancer or pulmonary metastasis). Extrapulmonary TB also shows a wide range of imaging features, often requiring high suspicion and further diagnostic workup. As a result, availability of additional radiological diagnostic tools, such as computed tomography (CT), are needed to facilitate the recognition of non-confirmed TB, early TB states, and other non-TB disease so that no disease is left untreated[8,10].

CT imaging plays a valuable role in improving the diagnostic accuracy of pulmonary TB, particularly in cases with minimal radiographic abnormalities or lacking microbiological confirmation. The extent of CT findings correlates with sputum test results. In patients with negative microbiological findings or early-stage disease, CT typically reveals a lower overall lesion burden, often characterized by small centrilobular nodules with a predominantly peripheral distribution[11].

Microbiological studies

The microbiological tests used in the clinical diagnosis of TB include acid-fast bacilli (AFB) smear microscopy, mycobacterial culture (both liquid and solid media), and nucleic acid amplification tests (NAATs)[12].

AFB smear microscopy provides rapid information about infectiousness, though it cannot differentiate between viable and non-viable organisms, nor can it distinguish MTB from non-tuberculous mycobacteria, so its sensitivity and specificity are limited. The Ziehl–Neelsen stain remains the standard method for direct smear microscopy, although the more sensitive Auramine–Rhodamine fluorochrome technique is technique which is increasingly employed in high-throughput or low-resource laboratories, particularly for samples with low numbers of bacilli. Mycobacterial culture is considered the gold standard for diagnosis, and both liquid and solid cultures are recommended for all specimens to maximize sensitivity. Cultures allow for definitive identification of MTB and enable drug susceptibility testing, which is essential for guiding therapy. NAATs provide rapid detection and can confirm the presence of *M. tuberculosis complex*, especially useful in smear-positive cases[13].

Prevention recommends that AFB smear microscopy be performed in all patients suspected of having pulmonary TB, as it provides simple and rapid information about infectiousness, though its sensitivity and specificity are limited and a negative result does not exclude TB. Mycobacterial culture remains the reference standard for diagnosis, with liquid media offering faster and more sensitive detection than solid media. However, culture requires several weeks for definitive results and may be negative in extrapulmonary or paucibacillary cases[14]. Negative results also include inadequate sputum specimens, temporal variations in the number of expelled bacilli, overgrowth of cultures with other microorganisms, and errors in specimen processing[15].

Rapid molecular NAATs, such as the Xpert MTB/RIF and Xpert MTB/RIF Ultra assays, have demonstrated superior sensitivity and specificity compared to smear microscopy. These assays can detect *M. tuberculosis* DNA and rifampin resistance within hours, facilitating rapid clinical decision-making and targeted therapy, particularly in patients with paucibacillary disease and in those who are immunocompromised. Previous studies showed variable results of sensitivity of Xpert MTB/RIF ranging from 47% to 87% for smear-negative[16], that's the reason why NAATs are the ones recommended on the initial diagnostic moment. However, a negative NAAT does not exclude TB in smear-negative patients

with high clinical suspicion. Therefore, additional bacteriological testing may be required after a negative initial test result if there is still clinical TB suspicion. Induced sputum (though very low-quality evidence), flexible bronchoscopy sampling, such bronchoalveolar lavage or even bronchial/transbronchial biopsy, gastric aspiration, and fine-needle aspiration of lymph nodes can be employed to improve diagnostic yield. Nevertheless, its interpretation requires caution due to its reduced sensitivity in non-sputum samples, indicating higher false negative rates[12]. Besides, antigen detection in other clinical samples offers a faster alternative to culture-based methods without the need for sputum culture. The LF-LAM test, a major glycolipid component of the *M. tuberculosis* cell wall shed by metabolically active TB, can be detected in urine, making it a valuable biomarker that provides additional diagnostic options for disseminated TB in immunocompromised patients, especially in HIV-infected patients with low CD4+ counts. Likewise, the lack of material and diagnostic resources in high-burden, low-resource settings remains a significant contributing factor to the absence of microbiological confirmation in many TB cases[13,14,16].

Culture-negative pulmonary TB is likely an early disease state on the continuum between TB infection and disease. If left untreated, this form can progress to more advanced, transmissible stages. Careful characterization of its clinical and radiological features may facilitate early recognition and prompt initiation of treatment, thereby reducing the risk of disease progression and limiting transmission.

MANAGEMENT

Decision to treat and main treatment goals

The decision to promptly initiate empiric TB treatment is based on clinical, radiographic, patient severity, and public health factors, even before the results of AFB smear microscopy, molecular tests, and mycobacterial culture are known. However, it can carry the risk of adverse drug effects, increased antimicrobial resistance, and unnecessary administration of anti-TB drugs, which could cause delays in the diagnosis of conditions other than TB[17].

The primary aim of TB treatment is to reduce the number of actively replicating bacilli as quickly as possible, which helps lessen the severity of the disease, prevent death, and interrupt the transmission of *M. tuberculosis*. At the same time, therapy seeks to eliminate persistent bacterial populations to ensure a long-lasting cure and minimize the risk of relapse after treatment is completed. An equally important goal is to prevent the emergence of drug resistance throughout the course of therapy[18].

Empiric treatment and follow-up

It is recommended to start empiric treatment with the standard four-drug regimen: isoniazid, rifampin, pyrazinamide, and ethambutol. This approach is especially important for patients who are seriously ill. In less severe cases, if there is clear improvement in symptoms or imaging after the initial 2-month

intensive phase, the next phase of treatment (with just isoniazid and rifampin) can sometimes be shortened to another 2 months. As a result, patient adherence, drug adverse effects, and reducing transmission would also improve. However, for most patients, the full 6-month treatment still remains the best option. For possible extrapulmonary TB (when the infection is outside the lungs), the same general treatment principles apply. The continuation phase with isoniazid and rifampin may last 6–9 months, depending on the site of infection and how the patient responds. One important exception is tuberculous meningitis, which requires a 12-month treatment course[19].

Therefore, in the absence of microbiological confirmation, but with strong clinical and radiographic evidence of active TB, empiric treatment should be initiated without delay. Close follow-up is essential to assess clinical or radiographic improvement and to ensure that an alternative diagnosis has not been missed. Follow-up should involve repeated clinical evaluation and radiological imaging. Cough remains the primary symptom to monitor during the course of therapy. If there is clear clinical or radiographic improvement consistent with a therapeutic response to TB, the current treatment regimen should be continued to complete the standard duration[5,13]. Conversely, in patients who experience clinical deterioration or show no radiographic improvement after 2 months of therapy, repeat microbiological testing for *M. tuberculosis* should be pursued, alongside investigations for alternative diagnoses. In such cases, if the IGRA or the TST is positive, consideration should also be given to the possibility of latent TB infection and its appropriate management[19,20]. Table 1 summarizes the diagnostic and management for clinically diagnosed TB.

Evidence from the literature indicates that survival rates among patients receiving empirical TB treatment are significantly lower compared to those with microbiologically confirmed disease. However, other treatment outcomes appear to be comparable between the two groups. To minimize diagnostic delays and improve clinical management, it is recommended accurate detection of comorbid conditions, systematic screening for active pulmonary TB in a predetermined target group and timely initiation of appropriate therapies in patients with clinical diagnosed TB[2,21].

FUTURE DIRECTIONS

The End TB Strategy, launched by the World Health Organization (WHO), established ambitious global targets for the period 2020-2035. These include a 20% reduction in TB incidence and a 35% reduction in TB-related mortality by 2020, as well as a 90% reduction in TB incidence and a 95% reduction in TB mortality by 2035, relative to 2015 baseline levels[22]. In support of these goals, the WHO recommends the systematic screening of high-risk populations for active TB. Screening strategies may involve symptom-based tools, chest radiography, and NAATs. Specifically, the WHO four-symptom screening tool-which assesses for current cough, fever, weight loss, and night sweats-is recommended for active TB case finding among endemic TB areas, people living with HIV and other targeted high-risk groups, and household or close

Table 1. Diagnostic and management for clinically diagnosed tuberculosis

Clinically diagnosed tuberculosis	Description	Supporting details
Clinical presentation	Symptoms include cough, sputum, weight loss, and fever (less pronounced than in microbiologically confirmed TB)	Represents an early disease state with lower mycobacterial burden and transmission risk
Radiology–CXR	First-line imaging; identifies lung abnormalities and supports diagnosis	Patients often show less extensive disease (fewer cavities, subtle infiltrates). High sensitivity, limited specificity. Must distinguish from COPD, asthma, cancer, etc
Radiology–CT	Provides more detail, improves diagnostic accuracy in early or smear-negative disease	Typically shows small centrilobular nodules, peripheral distribution, and correlates with sputum test results. Consider TC
Microbiological tests	Includes AFB smear microscopy, mycobacterial culture, NAATs (e.g., Xpert MTB/RIF and Xpert Ultra)	Smear microscopy: quick but low sensitivity. Culture: gold standard but slow; may be negative in paucibacillary disease NAATs: faster, detect MTB DNA & rifampin resistance Negative test doesn't rule out TB
Additional diagnostic techniques	Used to increase yield when sputum is negative	Induced sputum, bronchoscopy (BAL, biopsy), gastric aspiration, and lymph node FNA. Lipoarabinomannan (LAM) urine test useful in immunocompromised patients
Decision to treat	Empiric treatment initiated based on clinical, radiological, and public health factors before microbiological confirmation	Must balance early treatment against risks of drug toxicity, possible resistance, and misdiagnosis
Empiric treatment regimen	Standard 4-drug therapy: isoniazid (H), rifampin (R), pyrazinamide (Z), ethambutol (E)	Intensive phase: 2 months HRZE; continuation: 4 months HR (total 6 months). Adjust for extrapulmonary TB: 6-9 months; meningitis: 12 months
Monitoring & follow-up	Clinical and radiological reassessment is crucial	Improvement in cough, weight, and imaging supports TB diagnosis. Lack of improvement requires repeating microbiological testing, reassess for alternative diagnoses. Evaluate the results of the IGRA and the TST
Alternative diagnoses to exclude	COPD, asthma, bronchiectasis, silicosis, lung cancer, metastasis, and other infections	Especially important in atypical cases or non-improvement during follow up

AFB: acid-fast bacilli; CT: computed tomography; CXR: chest X-ray; COPD: chronic obstructive pulmonary disease; IGRA: interferon-γ release assay; HR: isoniazid + rifampin; HRZE: isoniazid + rifampicin + pyrazinamide + ethambutol; NAAT: nucleic acid amplification tests; TB: tuberculosis; TST: tuberculin skin test.

contacts of confirmed TB cases[1,13,23]. Despite the significant progress that has been made in TB diagnosis over the past few decades, transformational and novel approaches may be necessary to overcome limitations in diagnosing non-confirmed TB.

Chest radiography is sometimes the main but the only method available for investigating patients with possible pulmonary TB with negative sputum smears. Nevertheless, its interpretation in this context lacks specificity for pulmonary TB, then innovative and transformative strategies may be required to address the limitations associated with the clinical diagnosis of TB. One such approach involves the use of computer-aided detection (CAD) software for automated radiological analysis, which may enhance the utility of CXR in TB diagnosis. Deep learning-based CAD systems could show potential in evaluating CXRs among individuals self-presenting with symptoms of pulmonary TB who have negative sputum smear results, as well

as among people living with HIV. These CAD tools may achieve diagnostic performance comparable to human interpretation of CXRs, while also improving the consistency and reliability of image assessment by mitigating intra- and inter-observer variability. Furthermore, CAD systems are not subject to reader fatigue, a factor that can significantly affect diagnostic accuracy in overburdened healthcare systems. Consequently, deep learning-based CAD for CXR analysis holds promise as a high-sensitivity rule-out test for TB, particularly in high-burden settings[24-26].

Emerging evidence highlights the potential of positron emission tomography combined with CT (PET/CT) in the evaluation of early TB stages. PET/CT can detect metabolically active lesions that are not visible on conventional radiography, offering insights into pre-clinical infection phenotypes and enabling risk stratification for disease progression and relapse. The integration of metabolic and anatomical data has deepened our understanding of the dynamic and heterogeneous pathophysiology of TB across its clinical spectrum. Potential applications include assessing treatment response, identifying individuals at higher risk of relapse, and evaluating extrapulmonary disease extent. Notably, the detection of residual lesions without metabolic activity may indicate a lower likelihood of recurrence. However, limited specificity, high cost, and technical requirements currently preclude its routine use in TB management, particularly in resource-limited settings. Further studies are needed to define its role in research and targeted clinical applications before its widespread adoption can be recommended by international health organizations[27].

In addition, blood-based diagnostic methods – such as enzyme-linked immunosorbent assay, polymerase chain reaction, and mass spectrometry – offer the advantage of delivering results within hours, thereby improving diagnostic sensitivity and facilitating earlier initiation of treatment. The integration of multiple biomarkers associated with active TB (e.g., cytokines, gene expression profiles, and metabolic signatures) has the potential to enhance diagnostic accuracy and specificity. This approach is particularly valuable in cases with low mycobacterial burden and in clinically diagnosed TB, where conventional diagnostic tools may fall short. Emerging evidence supports the potential of non-sputum-based point-of-care triage tests for symptomatic pulmonary TB. However, additional research is necessary to validate their diagnostic performance and operational feasibility in diverse clinical and epidemiological settings[28,29].

CONCLUSION

TB remains a major global health burden, and a significant proportion of TB cases, particularly in early or paucibacillary stages, are diagnosed without microbiological confirmation, posing diagnostic and therapeutic challenges. Radiological tools – especially CXR and CT – remain essential, and emerging technologies like deep learning-based CAD systems offer promising improvements in diagnostic accuracy and consistency. In addition, non-sputum-based tests, such as blood-based biomarker panels, show potential in enhancing early detection, particularly in smear-negative or immunocompromised populations. Empiric treatment based on

clinical and radiological evidence remains appropriate in high-suspicion cases, but requires careful follow-up to ensure therapeutic response and rule out alternative diagnoses. To achieve global TB elimination targets, systematic screening of high-risk groups and expanded access to advanced diagnostics are urgently required.

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CONFLICTS OF INTEREST

None declared.

ETHICAL CONSIDERATIONS

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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REFERENCES

1. World Health Organization. 2024 Global Tuberculosis (TB) Report. Geneva: World Health Organization; 2024.
2. Freitag B, Sultanli A, Grilli M, Weber SF, Gaeddert M, Abdullahi OA, et al. Clinically diagnosed tuberculosis and mortality in high burden settings: a systematic review and meta-analysis. EClinicalMedicine. 2025;84:103251.
3. Nguyen MV, Levy NS, Ahuja SD, Trieu L, Proops DC, Achkar JM. Factors associated with sputum culture-negative vs culture-positive diagnosis of pulmonary tuberculosis. JAMA Netw Open. 2019;2:e187617.
4. Teo AK, Maclean EL, Fox GJ. Subclinical tuberculosis: a meta-analysis of prevalence and scoping review of definitions, prevalence and clinical characteristics. Eur Respir Rev. 2024;33:230208.
5. Maze MJ, Nyakunga G, Sakasaka PA, Kilonzo KG, Luhwago E, Chelangwa M, et al. Etiologic investigation of patients diagnosed with bacteriologically unconfirmed tuberculosis in Tanzania. Am J Trop Med Hyg. 2023;109:733-9.
6. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG. Crossm incipient and subclinical tuberculosis : a clinical review of early stages and progression of infection the spectrum of tuberculosis infection to disease. Clin Microbiol Rev. 2018;1-24.
7. Jayasooriya S, Dimambro-Denson F, Beecroft C, Balen J, Awokola B, Mitchell C, et al. Patients with presumed tuberculosis in Sub-Saharan Africa that are not diagnosed with tuberculosis: a systematic review and meta-analysis. Thorax. 2023;78:50-60.
8. WHO. Chest Radiography in Tuberculosis. Geneva: WHO; 2016. p. 1-44.
9. Gilpin C, Korobitsyn A, Migliori GB, Raviglione MC, Weyer K. The world health organization standards for tuberculosis care and management. Eur Respir J. 2018;51:180098.
10. Nguyen MV, Jenny-Avital ER, Burger S, Leibert EM, Achkar JM. Clinical and radiographic manifestations of sputum culture-negative pulmonary tuberculosis. PLoS One. 2015;10:e0140003.
11. Lee HN, Kim JI, Kim YH. Clinical and CT characteristics of Xpert MTB/RIF-negative pulmonary tuberculosis. PLoS One. 2021;16:e0250616.
12. Lewinsohn DM, Leonard MK, Lobue PA, Cohn DL, Daley CL, Desmond E, et al. Official American thoracic society/infectious diseases society of america/centers for disease control and prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017;64:111-115.
13. Kontsevaya I, Cabibbe AM, Cirillo DM, DiNardo AR, Frahm N, Gillespie SH, et al. Update on the diagnosis of tuberculosis. Clin Microbiol Infect. 2024;30:1115-22.
14. Mao X, Wang J, Xu J, Xu P, Hu H, Li L, et al. Current diagnosing strategies for *Mycobacterium tuberculosis* and its drug resistance: a review. J Appl Microbiol. 2025;136:Lxaf100.
15. Ho J, Marks GB, Fox GJ. The impact of sputum quality on tuberculosis diagnosis: a systematic review. Int J Tuberc Lung Dis. 2015;19:537-44.
16. Li S, Liu B, Peng M, Chen M, Yin W, Tang H, et al. Diagnostic accuracy of Xpert MTB/RIF for tuberculosis detection in different regions with different endemic burden: a systematic review and meta-analysis. PLoS One. 2017;12:e0180725.
17. Abdullahi O, Moses N, Sanga D, Annie W. The effect of empirical and laboratory-confirmed tuberculosis on treatment outcomes. Sci Rep. 2021;11:14854.
18. Ebert RH. Treatment of Tuberculosis. Disease-a-Month. Vol. 2. Geneva: World Health Organization; 1956. p. 1-39.
19. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, 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:e147-95.
20. Duarte R, Munsiff SS, Nahid P, Saukkonen JJ, Winston CA, Abubakar I, et al. Updates on the treatment of drug-susceptible and drug-resistant tuberculosis an official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2025;211:15-33.

21. WHO. Operational Handbook on Tuberculosis. Geneva: WHO; 2022.
22. WHO. The End Strategy TB. Vol. 53. Geneva: WHO; 2015. p. 1689-99.
23. Marks GB, Nguyen NV, Nguyen PT, Nguyen TA, Nguyen HB, Tran KH, et al. Community-wide screening for tuberculosis in a high-prevalence setting. N Engl J Med. 2019;381:1347-57.
24. Bruno MA, Walker EA, Abujudeh HH. Understanding and confronting our mistakes: the epidemiology of error in radiology and strategies for error reduction. Radiographics. 2015;35:1668-76.
25. Pinto LM, Dheda K, Theron G, Allwood B, Calligaro G, Van Zyl-Smit R, et al. Development of a simple reliable radiographic scoring system to aid the diagnosis of pulmonary tuberculosis. PLoS One. 2013;8:e54235.
26. Tavaziva G, Harris M, Abidi SK, Geric C, Breuninger M, Dheda K, et al. Chest X-ray analysis with deep learning-based software as a triage test for pulmonary tuberculosis: an individual patient data meta-analysis of diagnostic accuracy. Clin Infect Dis. 2022;74:1390-400.
27. Santos AP, Rodrigues RS, Aarntzen EH, Castro PH, Magis-Escurra C, de Queiroz Mello FC. Review F-fluorodeoxyglucose PET / CT scans for thoracic tuberculosis : current evidence and future perspectives. Eur Respir Rev. 2025;34:240289.
28. Yang Z, Li J, Shen J, Cao H, Wang Y, Hu S, et al. Recent progress in tuberculosis diagnosis: insights into blood-based biomarkers and emerging technologies. Cell. Infect. Microbiol. 2025;15:1567592.
29. Sutherland JS, Van Der Spuy GD, Shaw JA, Richardson T, Tjon Kon Fat EM, Gindeh A, et al. Performance of 2 finger-stick blood tests to triage adults with symptoms of pulmonary tuberculosis: a prospective multisite diagnostic accuracy study. Clin Infect Dis. 2025;16:ciaf105.