[1] Division of Infectious Diseases, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

[2] Universidad de Guayaquil, Guayaquil, Ecuador

[3] Division of Pediatric Infectious Diseases, University of Alberta, Edmonton, Canada

[4] Wadhani Institute for Artificial Intelligence, Mumbai, India

[5] Survivors Against TB, India

Correspondence to RR Nathavitharana
rnathavi@bidmc.harvard.edu

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RATIONAL TESTING

Diagnosing active tuberculosis in primary care

Ruvandhi R Nathavitharana, [1] Dolores Freire Jijon, [2,3] Pankaj Pal, [1] Saurabh Rane[4,5]

What you need to know

- Consider active TB disease in patients with cough, fever, night sweats, weight loss, or fatigue in settings with a high incidence of disease, or in patients without symptoms who have epidemiological risk factors such as HIV, particularly in countries with a high incidence
- Chest radiography is a valuable screening tool to determine which patients should be referred for TB diagnostic testing
- Testing for active TB should prioritise microbiological diagnosis with rapid, high sensitivity molecular tests, such as nucleic acid amplification assays (eg, Xpert MTB/RIF or Xpert Ultra). Mycobacterial culture remains the reference standard, but is slow to return results
- Smear microscopy has low sensitivity and should not be relied on if nucleic acid amplification tests or culture are available
- Refer patients to a TB specialist when concern for TB remains despite negative diagnostic test results, particularly in the absence of an alternative likely diagnosis

A 58 year old transportation worker in India with uncontrolled diabetes (HbA1c 97 mmol/mol) presents with a three month history of productive cough and decreased energy level. He has been treated empirically for community acquired pneumonia twice without improvement in symptoms.

A 24 year old student who arrived in Canada from the Philippines three years ago presents with a two month history of bilateral multiple enlargedcervical lymph nodes.

Of the 10 million people who develop active tuberculosis (TB) disease each year, approximately three million are not identified by national TB care programmes and many are undiagnosed.[1] Diagnostic delays are common in both low and high resource settings[2] and lead to worse individual outcomes and ongoing transmission.[3,4] Patients often see several healthcare providers before the disease is diagnosed.[5,6] TB most commonly presents with pulmonary involvement, but can present in a number of ways, most commonly lymphadenitis, pleural effusions, and osteomyelitis. Observational studies using standardised patients find major gaps between knowledge of TB and diagnostic practice in private sector primary care providers in India, including low utilisation of TB diagnostic tests endorsed by the World Health Organization.[7]

In low incidence countries, people who develop active TB disease most commonly do so because of reactivation of previously acquired latent TB infection. In high incidence countries, most people who develop active TB experience more rapid disease progression after recent infection, reflective of higher rates of community transmission.[8] TB detection efforts in countries with low incidence therefore often focus on migrants from countries with high incidence, who have the highest likelihood of prior exposure.[9] Once infected, risk factors for a patient progressing to active TB disease, such as HIV, TNF-α inhibition, or diabetes are the same regardless of geographical location (box 1).[10]

Box 1: Epidemiological risk factors for TB exposure to/infection with TB and host risk factors for progression to active TB*

Epidemiological risk factors for TB exposure to/infection with TB

- Household or other close/prolonged contacts
- People living with HIV and people attending HIV testing
- People with substance use disorders, including alcohol use disorder, and persons who inject drugs
- People in high risk congregate settings such as prisons, migrant workers, or those who are homeless
- People in mental health clinics or institutions
- Occupations such as health work, mining, prison staff
- Children (higher risk if <5 years)
- In low incidence countries, people who have moved from or spent time in a high incidence country†

Host risk factors for progression to active TB

- HIV (increased further if AIDS or low CD_4 cell count)
- Recent TB infection (highest risk in first two years)
- Children (higher risk if <5 years)
- Silicosis
- People previously treated for TB
- Abnormal chest radiograph showing fibronodular disease or granuloma
- People with chronic respiratory disease and smokers
- Diabetes mellitus
- Chronic renal failure (increased further if requiring dialysis)
- Alcohol and substance use disorders
- Transplantation (owing to immunosuppressive therapy)
- Treatment with glucocorticoids
- Treatment with tumour necrosis factor (TNF)-alpha inhibitors
- Malnutrition/low body weight
- Gastrectomy or jejunoileal bypass
- Head and neck cancer

*Adapted from WHO guideline on systematic screening for active tuberculosis.

†https://cdn.who.int/media/docs/default-source/hq-tuberculosis/who_globalhbcliststb_2021-2025_backgrounddocument.pdf?sfvrsn=f6b854c2_9

Obtaining a microbiological diagnosis of TB is critical to confirm the correct diagnosis, avoid unnecessary empiric treatment, and ensure that patients can receive prompt drug susceptibility testing. The importance of rapid, accurate TB diagnosis is even greater in the covid-19 era given the projected long term rise in TB incidence and mortality[11] and worse outcomes in patients with TB and covid-19.[12]

Clinical assessment of patients who may have active TB

Patients should be evaluated for symptoms, including cough, haemoptysis, fever, night sweats, weight loss, and fatigue.[13] Clinicians should have access to fitted filtering facepiece respirators.[14] Nonetheless, clinicians should be aware of the limited accuracy of symptom screening for identifying people who may have active TB. Estimates from pooled data show that the sensitivity and specificity of prolonged cough (more than two weeks) for the diagnosis of active TB disease are 42% and 94% compared with 51% and 88% for cough of any duration.[10] The sensitivity and specificity of any TB symptom (including cough, haemoptysis, fever, night sweats, weight loss) for active TB disease are 71% and 64%.[10] Data from prevalence surveys in multiple countries show that as many as 50% of people diagnosed with active TB disease do not report symptoms.[10] Hence, risk factors for TB (box 1) should also be elicited to guide the need for TB testing, rather than relying on patient reported symptoms alone, particularly in settings with a high incidence.

Assessment of risk factors aims to gauge the likelihood of exposure to persons with infectious TB (typically active pulmonary TB) and the presence of any clinical risk factors that would enable progression to active TB and worse outcomes (eg, HIV, immunomodulatory therapy). Assessing possible exposures includes inquiring about infected close contacts, occupational risks such as for healthcare work or mining, and determining epidemiological risks based on country of origin or prior residence for patients in low incidence settings.[15] WHO recommends that the following groups should always be screened for TB (irrespective of symptoms): people who have HIV, people who have had recent close contact with a person who has TB, and people who have silicosis. Also consider screening people with other risk factors for TB (box 1). When evaluating patients for TB and assessing TB risk factors, be aware that stigma remains a major barrier to high quality care.

What is the next investigation?[1]

There is an urgent need for a rapid, accurate, point-of-care screening or triage test that could help clinicians determine which patients with symptoms or risk factors for TB should be referred for diagnostic testing.[16] Chest radiography is commonly used in the initial evaluation for TB[17] in people with pulmonary symptoms or TB risk factors (fig 1). Chest radiography is recommended by the WHO as an initial screening or triage test to determine which patients need referral for TB diagnostic testing.[10] The sensitivity for active TB disease of detecting any abnormality on chest radiography is 94%,[10] which makes it sufficiently sensitive as a rule out test to determine that the majority of people with negative chest radiography are unlikely to have active pulmonary TB disease. The more variable specificity of chest radiography means that other infectious and non-infectious causes should be considered alongside TB as potential causes of imaging abnormalities[18]; however, the specificity of chest radiography improves when suggestive abnormalities such as pulmonary cavitation are detected.[10] However, the availability of chest radiography as a TB screening or triage test in primary healthcare in low resource settings is limited,[19] and it does not offer microbiological confirmation of an infectious cause.

A real time polymerase chain reaction (PCR) assay or nucleic acid amplification assay (NAAT) that simultaneously detects *Mycobacterium tuberculosis complex* (MTB) DNA and the presence of resistance to rifampicin in sputum is the initial diagnostic test of choice in all persons being evaluated for pulmonary TB[20] (eg, Xpert MTB/RIF or Xpert Ultra (Cepheid Inc., Sunnyvale, CA, USA)[21 22] and Truenat MTB or MTB Plus followed by Truenat MTB-RIF Dx if positive (Molbio Diagnostics, Goa, India)).[20 21] These tests can be performed with minimal technical training, and results may be available in less than two hours (although this does not reflect the time it takes for results to reach clinicians in practice). Xpert has an overall sensitivity of 85-88% (table 1) for pulmonary TB diagnosis, although this is higher (98%) for patients with smear-positive disease compared with those who are smear negative (67%).[22] Xpert has a high specificity of 96-98%.[22] Truenat MTB and MTB Plus have an overall sensitivity of 73-80% (table 1) for pulmonary TB diagnosis, which is higher (92-96%) for patients with smear-positive disease compared with those who are smear negative (39-46%).[20 21]

Mycobacterial culture is typically considered the reference standard for diagnosing active TB disease[16 24] as the approach with the lowest limit of detection for mycobacteria. However, mycobacterial culture may take 2-8 weeks for AFB growth and moreover requires technical expertise and robust laboratory infrastructure, therefore it is often not routinely accessible to patients in most settings with a high incidence of TB.

What about smear microscopy?

In contrast with WHO recommendations that prioritise the use of rapid molecular TB tests, in many places, acid-fast bacilli (AFB) smear microscopy is the initial or only microbiological test performed for the diagnosis of TB. Estimates for the sensitivity of smear microscopy vary from 32% to 94% (based on older heterogeneous studies that raise concerns for bias), with an average 10% increase when fluorescence microscopy is used.[23] The typically low sensitivity of smear—when used instead of rapid molecular TB tests—is one of the major drivers of TB under-diagnosis globally. In addition to difficulties patients face in producing adequate sputum specimens for testing, specimen transport from primary care clinics to testing centres can also prove to be logistically complex.

Further, AFB staining is not specific to MTB, so false positives can occur owing to the presence of non-tuberculous mycobacteria. Loopamp MTB assay (TB-LAMP) is a manual NAAT that can be used as a replacement or follow-on test to smear microscopy with a sensitivity of 78% and specificity of 98%, but should not replace the use of rapid molecular NAATs such as Xpert or Truenat, which also diagnose rifampicin resistance.[20]

How should I approach testing for extra-pulmonary TB?

Extra-pulmonary TB presents additional diagnostic challenges. A high clinical index of suspicion coupled with microbiological testing is important. Obtaining specimens is challenging because tissue biopsies and cerebrospinal or pleural fluid sampling require invasive procedures. The sensitivity of all aforementioned tests—microscopy, NAATs, TB PCR, and culture—is lower for extra-pulmonary TB[26] because of lower bacterial quantities in obtained samples. That

said, molecular diagnostic testing (currently Xpert MTB/RIF or Xpert Ultra) is the initial diagnostic test recommended by the WHO for the initial evaluation of TB meningitis and should also be considered for the diagnosis of other forms of extra-pulmonary TB.[20 21] We note that access to molecular testing may be limited, and suggest that other available TB PCR tests should be considered as an alternative, in addition to mycobacterial culture, given the lower diagnostic sensitivities of all of these tests for extra-pulmonary TB, compared to pulmonary TB.

Diagnostic testing considerations for people with HIV

The sensitivity of Xpert is lower among people with HIV (81%) than in those without (88%).[22] Nonetheless, NAAT/TB PCR remain the test of choice in people with HIV, as people with HIV are more likely to have AFB smear-negative TB and the sensitivity of chest radiography in this group is also reduced.[27] Typical TB findings on chest radiography such as cavitary disease, upper lobe disease, or fibrosis are less common as CD_4 cell count declines, and approximately 20% of people with HIV and TB have a normal chest radiograph.[28] At the same time, other findings such as adenopathy and pleural effusion may be more common in those with HIV.[28] Thus, in settings with high HIV prevalence, non-site-specific TB diagnostic tests including the point-of-care urine lipoarabinomannan (LAM) test may be helpful. LAM has a low sensitivity in the general population[25] but is recommended by the WHO as an add-on test (eg, in combination with NAAT and culture) to assist with TB diagnosis in adults or children with HIV who either have signs or symptoms of TB or are seriously ill (at any CD_4 cell count), or those who have a CD_4 cell count of less than 100 cells/mm^3, irrespective of signs and symptoms.[29] As LAM is a point-of-care test, a positive result can facilitate rapid diagnosis and treatment for people with HIV who are sick with TB and may not be able to produce sputum. Nonetheless, LAM sensitivity even in patients with HIV is insufficiently high to rule out TB and a negative test should be interpreted with caution.

What if these tests are negative but I am still concerned about TB?

In patients with negative TB diagnostic test results but ongoing suspected TB, consider additional and/or longitudinal testing, assessment of the likelihood of alternative diagnoses, and referral to TB specialists. The sensitivity of smear microscopy and urinary LAM testing is not high enough for these assays to be considered "rule out tests" (ie, a negative test does not exclude a diagnosis of active TB). Even Xpert and other NAATs have an overall sensitivity of less than 90% given worse performance in people with smear-negative or paucibacillary disease. Mycobacterial culture has the lowest limit of detection but may miss up to 20% of patients with TB[24] because of specimen sampling or paucibacillary disease, particularly for extrapulmonary TB. Consider the results of these tests in the context of adjunctive clinical information and the overall likelihood of active TB compared with alternative diagnoses.

Histopathological evidence of necrotising granulomas, or immunological evidence of TB infection (eg, positivity on tests used for latent TB diagnosis such as tuberculin skin testing or interferon gamma release assays[30]) may lend support towards a diagnosis of TB (although these tests do not distinguish latent from active TB). The practice of giving empiric broad-spectrum antibiotics to symptomatic patients with negative TB testing, in order to distinguish TB from other infectious causes, has a weak evidence base, with a sensitivity of 67% (95% CI 42 to 85) and specificity 73% (95% CI 58 to 85) compared with mycobacterial culture, and raises concerns for delayed and missed TB diagnoses as well as antimicrobial resistance.[31] While common, clinicians should try to avoid making a clinical diagnosis of TB without microbiological testing and consider referring patients to a TB specialist when concern for TB remains despite negative testing, particularly in the absence of an alternative diagnosis.

Patients diagnosed with TB who are not responding to TB treatment warrant additional investigation for drug resistance (culture based or molecular drug susceptibility testing) and referral to a TB specialist.

Outcomes for case vignettes

The first patient underwent chest radiography, which showed bilateral patchy nodular opacities. Sputum testing for Xpert was positive for MTB without evidence of rifampicin resistance, and subsequent mycobacterial culture confirmed a fully drug susceptible strain.

The second patient underwent lymph node biopsy. Pathological examination revealed granuloma and mycobacterial culture was subsequently positive for MTB without evidence of drug resistance.

Both patients were HIV negative. Both were treated with first line therapy comprising rifampicin, isoniazid, pyrazinamide, and ethambutol for two months followed by rifampicin and isoniazid for four months, with resolution of symptoms.

Rational testing into practice

- What is your access to WHO endorsed diagnostic tests for TB, in particular nucleic acid amplification tests, such as Xpert MTB/RIF or Ultra or Truenat MTB?
- Reflect on the last time you cared for someone presenting with symptoms of TB. Would the recommendations in this article change your management plan?

Sources and selection criteria

This article is based on targeted search of online publication databases (https://www.nlm.nih.gov/) and World Health Organization guidelines examining the topic areas listed in the article, including

- TB screening
- TB diagnosis
- Clinical presentation of pulmonary and extrapulmonary TB.

Secondary references were identified originating from those identified above, in addition to those identified through personal and professional networks (including grey literature, such as professional guidelines), and throughout the review process.

A patient's perspective, by Saurabh Rane

While working in my internship, I started to have fever, anorexia, and fatigue. These symptoms worsened despite me receiving antibiotic treatment. I then developed weight loss, cough, chest pain, and eventually breathlessness. I was rushed to the hospital, and a doctor said my chest x ray was suggestive of TB. The doctor sent a sample for testing and started me on first line TB treatment. I asked for a culture or drug susceptibility test, but these were not undertaken.

I had jaundice, weight loss, and high fever. My drug regimen was changed without testing, yet I slowly continued to become sicker. Finally, after extensive investigations that included culture and drug susceptibility testing, I was diagnosed with drug resistant TB. Despite faithfully taking six months of treatment, I was looking at another 24 months of multiple antibiotics with a range of toxic side effects.

If I had had access to rapid, accurate molecular diagnostic testing for first line resistance with prompt follow-up drug susceptibility testing, I could have avoided the physical and mental turmoil I later faced.

Improving access to high quality WHO endorsed TB diagnostic tests for all people being evaluated for TB is an urgent priority.

How patients were involved in the creation of this article

The cases provided are fictitious but based on commonly encountered clinical scenarios. This article was reviewed by an individual who has had TB who provided feedback based on their patient experience.

Contributors: RRN was responsible for the idea and conception of the article. RRN and PP did the literature review and analysis. RRN, PP, DF, and SR drafted the article. All authors revised the article critically for important intellectual content. All authors reviewed and approved the final version to be published. RRN is guarantor.

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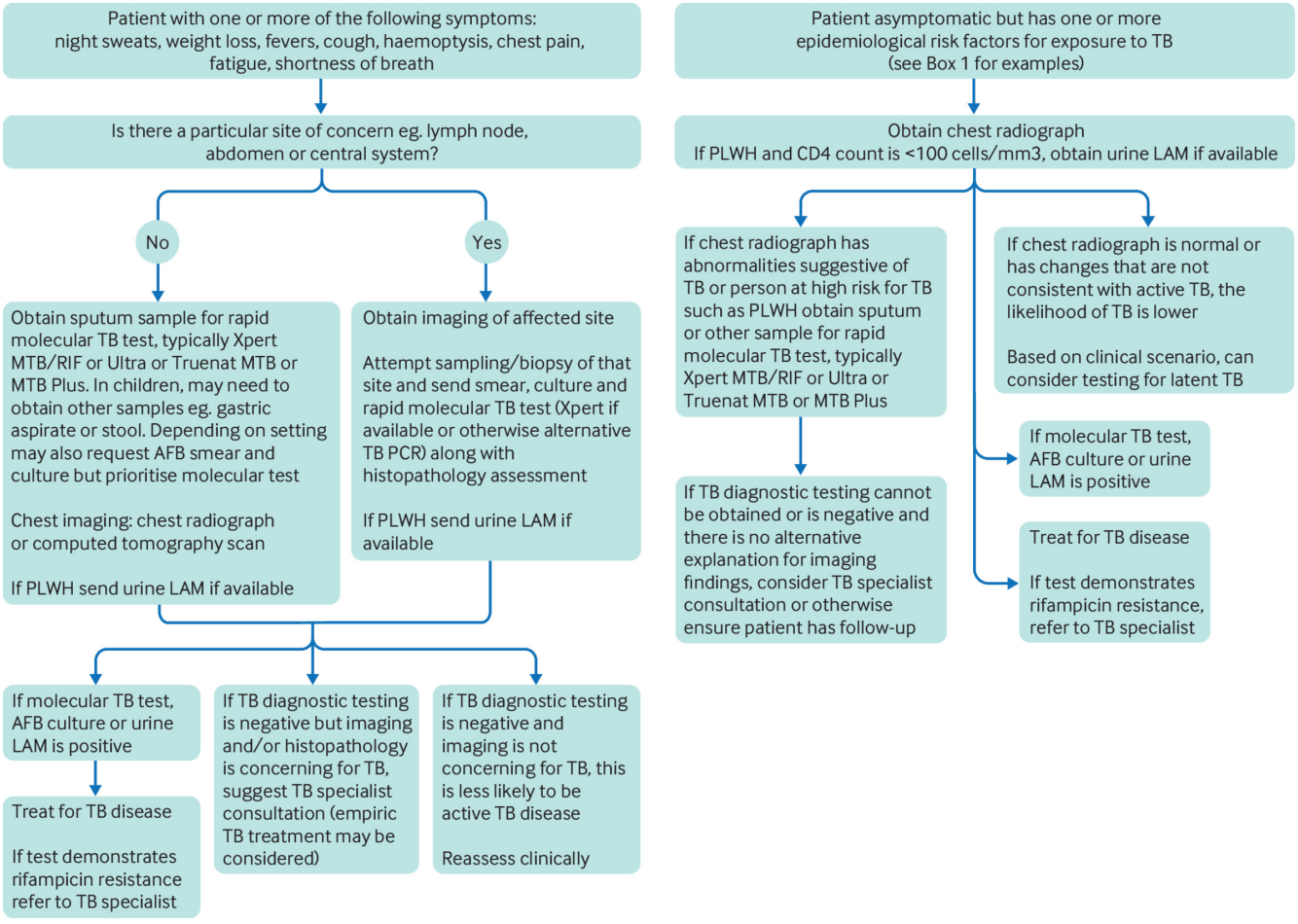

Fig 1 | A suggested diagnostic algorithm to assist clinicians with diagnostic reasoning when evaluating patients for TB

Table 1 | WHO endorsed tests for diagnosing active pulmonary and extrapulmonary TB in primary care

Radiographic test					
Test	**Site**	**Sensitivity**	**Specificity**	**Turnaround time and infrastructure**	**Other considerations**
Chest radiograph	Chest	94%[10] (if any abnormality identified)	89%[10] (if any abnormality identified)	Same day. Requires radiography equipment. Trained radiologist needed for interpretation	Evaluation of pulmonary or pleural TB only
Microbiological or molecular tests					
Test	Specimen	Sensitivity	Specificity	Turnaround time and infrastructure	Other considerations
Microscopy for AFB smear: a) Conventional—acid fast stain, b) Fluorescence—acid fast fluorochrome dye	Any	a) 20-80% in pulmonary TB, b) 10% higher sensitivity.[23] Lower in PLWH	a) 89%, b) no change[23]	Same day. Requires trained technicians and microscopy equipment	Unable to differentiate TB from non-tuberculosis mycobacteria. Two sputum smears (spot and morning) often recommended to improve sensitivity
AFB culture	Any	~81-85%,[24]* a) 89% for smear positive, culture positive patients, b)73% for smear negative, culture positive patients	~99%[24]	2-8 weeks. Requires trained technicians, equipped laboratory, proper ventilation	Reference standard, despite imperfect sensitivity
a) Xpert MTB/RIF, b) Xpert Ultra NAAT. Detect MTB and rifampicin resistance	Any, but most commonly done on sputum or respiratory specimens	TB detection[22] a) 85% b) 88%. Rifampicin resistance a) 96% b) 95%	TB detection,[22] a) 98% b) 96%. Rifampicin resistance a) 98%, b) 98%	Same day. Automated platform. Results in 1-2 hours. Requires stable electrical supply, temperature control	Xpert and non-Xpert NAATs or PCRs for TB detection can be sent from extrapulmonary samples
a) Truenat MTB, b) Truenat MTB Plus, NAAT, Detect MTB, c) Truenat MTB-RIF Dx, NAAT. Detects rifampicin resistance	Sputum or respiratory specimens	TB detection,[20] a) 73% b) 80%. Rifampicin resistance c) 84%	TB detection,[20] a) 98% b) 96%. Rifampicin resistance c) 97%	Same day. Automated platform. Results in <1 hour. Battery operated. Can be performed at field site	Truenat assays are not currently recommended for extrapulmonary TB diagnosis
Loopamp Mycobacterium tuberculosis complex assay (TB-LAMP), NAAT. Detects MTB	Sputum specimens	TB detection 78%. Lower in PLWH	TB detection 98%	Same day. Manual assay that can be read with the naked eye under ultraviolet light. Results in <1 hour	Should not replace the use of rapid molecular tests to detect TB and rifampicin resistance. May be used as a replacement or follow-on test for smear microscopy
Urine lipoarabinomannan (LAM). Detects MTB cell wall component. Lateral flow assay	Urine	42% in symptomatic PLWH[25]	91% in symptomatic PLWH[25]	Same day POC test. Automated platform	Studied in PLWH, sensitivity too low for general population. Facilitates diagnosis if sputum not produced. In symptomatic patients with 10% prevalence-8% false positives, 6% false negatives[25]

AFB=acid fast bacilli; PLWH=people living with HIV; NAAT=nucleic acid amplification test; POC=point of care

* Data are for liquid culture using BACTEC 960/MGIT and BACTEC 460TB compared with a reference standard which was defined as a positive culture with at least one of the three culture systems used (BACTEC 960/MGIT, BACTEC 460TB and/or solid culture media)