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Incipient and subclinical tuberculosis: a narrative review

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Abstract

Mycobacterium tuberculosis has been known to infect humans for eons. It is an airborne infectious disease transmitted through droplet nuclei of 1 to 5 μm in diameter. Historically, tuberculosis (TB) was considered a distinct condition characterized by TB infection and active TB disease. However, recently, the concept of a dynamic spectrum of infection has emerged, wherein the pathogen is initially eradicated by the innate or adaptive immune system, either in conjunction with or independently of T cell priming. Other categories within this spectrum include TB infection, incipient TB, subclinical TB, and active TB disease. Various host- and pathogen-related factors influence these categories. Furthermore, subclinical TB can facilitate the spread of infection within the community. Due to its asymptomatic nature, there is a risk of delayed diagnosis, and some patients may remain undiagnosed. Individuals with subclinical TB may stay in this stage for an indeterminate period without progressing to active TB disease, and some may even experience regression. Early diagnosis and treatment of TB are essential to meet the 2035 targets outlined in the end-TB strategy. This strategy should also include incipient and subclinical TB. This review will focus on the definition, natural history, burden, trajectory, transmissibility, detection, and management of early-stage TB.

Key words: *Mycobacterium tuberculosis*, transmission, incipient TB, subclinical tuberculosis, early-stage TB.

Introduction

Traditionally, TB has been classified as a binary paradigm consisting of TB infection and active TB disease. However, recent advances in our understanding of the natural history of TB have led to a more nuanced perspective. TB is now thought of as a continuous spectrum with multiple stages [1,2]. This spectrum includes individuals who have successfully eliminated TB infection, those with TB infection, incipient TB, subclinical TB, and active TB disease [3,4]. Nonetheless, there are disparities in nomenclature, diagnostic standards, and definitions for various states of TB [5]. Latent TB infection is defined as an asymptomatic state of infection with *Mycobacterium tuberculosis*. The infection is demonstrated by a positive response to in vivo or in vitro stimulation with *Mycobacterium tuberculosis* antigens, such as tuberculin skin test (TST) or interferon gamma release assay (IGRA) [6]. Since the TST or IGRA tests cannot distinguish between individuals who have cleared *Mycobacterium tuberculosis* with activation of T-helper memory cells and those who harbor latent TB bacilli, the more accurate terminology should be TB infection and not latent TB infection. Incipient TB is defined as an asymptomatic, early preclinical disease state during which pathology evolves, including mycobacterial replication or an inflammatory response [6]. There are no clinical signs or symptoms present, and radiographic or microbiological evidence of active TB disease is lacking [3]. Frascella et al. described incipient disease as a transition between minimal disease and subclinical disease, indicating that incipient TB is not considered a distinct disease state [7]. Individuals with incipient TB are likely to progress to subclinical TB or active TB disease in the absence of further intervention [3]. An individual with incipient TB infection has viable TB bacilli characterized by slow metabolic activity and replication, with the bacilli alternating between periods of dormancy and metabolic activity [8]. These patients are likely not infectious, and there are currently no validated diagnostic tools available for diagnosing incipient TB patients. The exact incidence of incipient TB is unknown; however, active TB progresses through an incipient state. Additionally, individuals with incipient TB may experience spontaneous resolution, suggesting that the incidence of incipient TB is likely to be higher than that of active TB disease. The TST and IGRA tests are positive in patients with incipient TB. Drain et al. defined subclinical pulmonary TB as a state of disease due to viable *Mycobacterium tuberculosis* that does not cause TB-related symptoms but does result in other abnormalities detectable through existing radiologic or microbiologic assays [3]. Patients with subclinical TB disease are asymptomatic upon symptom screening [3]. Therefore, they may remain undiagnosed in a symptom-based TB screening program and continue to transmit the infection, as the bacilli are replicating and metabolically active [4]. The International Consensus for Early TB (ICE-TB)

group, through a Delphi exercise involving 71 participants, classified both active TB and subclinical TB into two stages: infectious and non-infectious [5]. This classification was based on three parameters: the presence of macroscopic TB pathology, the infectiousness of the host, and the symptoms or signs of TB. Individuals with non-infectious subclinical TB exhibit macroscopic pathology. Consequently, imaging is the only technique that can identify this stage. Individuals with an infectious form of subclinical TB also exhibit macroscopic pathology. Either these states may be asymptomatic or have symptoms or signs that go unrecognized or unacknowledged [5]. Moreover, the symptoms may not be sufficient to drive them to seek medical care. The TST and IGRA tests are also positive in patients with subclinical TB. Early detection of subclinical TB and the timely initiation of effective chemotherapy can interrupt the transmission of infection, prevent future infectiousness, mitigate extensive lung damage, and reduce the subsequent risk of post-TB sequelae [5,9].

Although subclinical TB is often described as an asymptomatic state, individuals with this condition are not always truly asymptomatic. In prevalence surveys, subclinical TB has frequently been defined as any case of TB without the typical symptom of a cough persisting for 2 weeks or more. For instance, in a prevalence survey conducted in Zambia, 40.5% of 257 confirmed TB patients reported no history of cough [10]. However, TB patients without a history of a cough lasting two weeks or more also reported other symptoms such as chest pain (46.2%), fever (24%), night sweats (27.9%), and weight loss (38.5%). Approximately 12% of individuals had no cough, fever, night sweats, or weight loss. Therefore, evaluating other TB-related symptoms is also crucial. Patients with subclinical pulmonary TB who are bacteriologically positive can transmit infection intermittently or persistently through symptoms they are unaware of, do not acknowledge, or attribute to alternative conditions [11]. Kendall et al. described these symptoms as too subtle to warrant medical attention or too nonspecific to prompt a clinical TB workup [12]. The subtle symptoms are usually more frequent than the classical symptoms of TB. Healthcare professionals can elicit these milder symptoms through targeted questioning; the process has not been entirely standardized. For example, patients may develop unrelated coughs due to factors such as air pollution, weather, alternative respiratory diseases, viral infection, and smoking. Moreover, patients may not recognize when their cough frequency exceeds normal. Sometimes, patients experience fleeting symptoms, which they don't consider unusual. These symptoms can be detected using a wearable cough monitor or a cough diary. Chronic or acute cough unrelated to TB pathology may also contribute to the transmission of subclinical TB. In patients with subclinical TB, chronic cough may be attributed to non-TB conditions such as chronic bronchitis and

bronchiectasis, which can obscure the symptoms of TB. Individuals may transmit the infection due to their habitual coughing. Furthermore, the likelihood of transmission increases because these patients continue to participate in regular social activities [13,14]. Chronic cough is not uncommon in the community. In a systematic review and meta-analysis, Song et al. reported an overall global prevalence of chronic cough of 9.6% (95% CI 7.6–11.7%) [15]. Sometimes, a viral acute respiratory infection may induce coughing and facilitate the transmission of underlying subclinical TB [14]. Smoking, which can lead to chronic cough, may also mask the TB symptoms [13]. Lin et al. assessed the prevalence and duration of cough following H1N1 influenza infection, enrolling 141 influenza cases, and found cough in 97.2% of cases [16]. The incidence of coughs between 1-3 weeks and 3 weeks was 7.8% and 8.5%, respectively. Patterson et al. suggested that coughing is not the sole mechanism for TB transmission [17]; TB can also be transmitted through tidal breathing, sneezing, talking, singing, yawning, and during lung function testing. An important mechanism for aerosol production is the bronchiole fluid film burst mechanism. During expiration, the small airways are filled with fluid. Early in inspiration, the bursting of the bronchiole fluid film occurs, creating an aerosol. Table 1 shows the definition of various spectrums of TB. Figure 1 shows the characteristic features of various stages of TB.

Epidemiology and risk factors

The high burden of undiagnosed TB has significant potential to fuel the global TB burden. The large pool of subclinical TB is one example of undiagnosed TB. Frascella et al. reported that subclinical TB accounts for 36.1% to 79.7% (median, 50.4%) of the bacteriologically confirmed cases of prevalent TB [7]. The prevalence in African and Asian countries was 49.4% [interquartile range (IQR), 38.8% – 52.4%] and 56.4% (IQR, 42.8% – 68.5%), respectively. They could not find any association with human immunodeficiency virus (HIV) prevalence. Chest radiography identified the majority of bacteriologically confirmed TB cases, including subclinical TB (median, 89%; range, 73%–98%). As a result, the current TB screening approach should include chest radiography. Stuck et al. in a meta-analysis estimated the prevalence of subclinical TB based on three case definitions [18]: 1) sputum-culture-positive TB but without a self-reported cough lasting 2 weeks or more, irrespective of other symptoms, 2) sputum culture positive TB but without any self-reported cough of any duration or 3) sputum culture positive TB in the absence of cough, fever, night sweats, weight loss, or chest pain, regardless of the duration of symptoms. The estimated unadjusted proportion of subclinical TB was 59.1% [95% confidence interval (CI), 55.8–62.3] for individuals with no persistent cough and 39.8% (95% CI, 36.6–43.0) for those with

no cough of any duration. The adjusted proportions were 82.8% (95% CI, 78.6–86.6) for individuals with no persistent cough and 62.5% (95% CI, 56.6–68.7) for those with no cough at all. Among participants with TB, 29.1% (95% CI 25.2–33.3) of those without a persistent cough and 23.1% (95% CI 18.8–27.4) of those without any cough had positive smear examinations. Consequently, a sizable proportion of cases of TB will remain undiagnosed if the diagnosis is solely based on symptoms. Hamada et al. conducted a meta-analysis of 16 national and sub-national TB prevalence surveys that included data from Asian and African countries [19]. The prevalence of subclinical TB ranged from 15.1% to 56.7%, with a median of 38.1%. On multivariate analysis, current smoking was associated with both subclinical [Odds ratio (OR) 1.67, 95% CI, 1.27–2.40] and symptomatic TB (OR 1.49, 95% CI, 1.34–1.66). However, self-reported diabetes was not found to be associated with subclinical TB (OR 0.92, 95% CI, 0.55–1.55). Therefore, regardless of age or gender, current smokers are more likely to have subclinical TB and should be given priority for intensive TB screening, including chest X-rays. The results of national TB prevalence surveys in 12 Asian countries (1990 to 2012) indicated that 40% to 79% of bacteriologically positive TB cases reported absence of TB symptoms during screening [20]. Additionally, five regional TB surveys from Tamil Nadu reported a crude median prevalence of subclinical TB of 43.1% (IQR 36–55%) [7]. The Indian National TB Prevalence Survey (2019-2021) was a population-based cross-sectional study that revealed poor healthcare-seeking behavior among many symptomatic patients, with 63.6% not seeking care. Furthermore, without chest X-rays, 42.6% of the TB cases identified in the survey would have gone unnoticed [21]. Oni et al. evaluated the prevalence of subclinical TB disease and its outcomes among 274 asymptomatic, treatment-naïve individuals infected with HIV-1 in Cape Town, South Africa [22]. The prevalence of subclinical TB disease was found to be 8.5% (95% CI, 5.1% to 13.0%). The majority of patients with subclinical TB were diagnosed on the basis of positive cultures. Approximately 70% of subclinical TB patients were smear negative, compared to 16% of patients with symptomatic TB ($P<0.001$), indicating a lower bacterial burden in the subclinical group. Gunasekera et al. estimated the burden and risk factors for subclinical TB within the South African communities participating in the Zambia, South Africa Tuberculosis and AIDS Reduction trial [13]. They reported a crude prevalence of TB at 2222.1 cases per 100,000 population (95% CI 2053.4–2388.5), with 44.7% of these cases being subclinical. A significant association was found between current tobacco smoking (OR 2.37, 95% CI 1.41–3.99) and HIV-positive status (OR 3.26, 95% CI 2.31–4.61) with subclinical TB. The Indian TB prevalence survey identified several risk factors for TB, including low body mass index (BMI), alcohol use, smoking, older age groups,

male gender, and diabetics [21]. Subclinical TB is a subset of active TB without symptoms and shares the same risk factors. Tang et al. conducted a retrospective study in China and found that out of 380 patients, 81.8% had active TB, and the remaining 18.2% had subclinical TB cases [23]. Younger individuals were shown to have a higher risk of having subclinical tuberculosis [23]. The sensitivity for detecting subclinical TB cases was 33.3% when combining culture and Xpert MTB/RIF assay. Additionally, a lower neutrophil-to-lymphocyte ratio and a significantly reduced prevalence of the Beijing genotype were observed in the subclinical TB group. However, the study was conducted in a low-prevalence setting. Bajema et al. reported that subclinical TB accounted for 23% of all TB cases among patients with untreated HIV in South Africa [24]. Patients with subclinical disease exhibited an intermediate degree of immunosuppression, with a median CD4 count of 136 (range: 72–312) cells/mm^3. In a non-HIV population in South Korea, nearly 20% of TB patients were found to have subclinical TB. Multivariable analysis indicated that being under 65 years of age was the only variable significantly associated with subclinical disease [25]. The authors noted a significantly lower proportion of smear positivity, culture positivity, and multiple lobe involvement in patients with subclinical disease compared to those with active TB. However, the treatment outcomes for subclinical TB were not significantly different from those for active disease. Carter et al. estimated the prevalence of subclinical pulmonary TB among household contacts (HHCs) of index TB patients in two South African provinces [26]. They reported a higher prevalence of subclinical pulmonary TB compared to clinical pulmonary TB, with rates of 2.3% (95% CI 1.7–3.1%) for subclinical TB and 1.0% (95% CI 0.6–1.5%) for symptomatic pulmonary TB. The prevalence of subclinical TB was notably higher in HIV-infected patients compared to HIV-uninfected patients. (4.0% versus 1.9; p = 0.018). Mtei et al. screened 498 HIV-1-infected individuals in Tanzania for active TB and reported the prevalence of active TB and subclinical TB as 71% and 29%, respectively [27]. The majority of patients with subclinical TB had initially received isoniazid preventive therapy. As a result, a high level of clinical suspicion for subclinical TB must be considered, especially in HIV-infected individuals and smokers, and appropriate investigations should be conducted before initiating TB preventive therapy. Rickman et al. [28], in the Tshepiso Study conducted in Soweto, South Africa, assessed the prevalence and impact of subclinical TB on maternal and pediatric outcomes in 235 HIV-infected pregnant women with TB, compared to matched HIV-positive, TB-negative pregnant women. They reported a 4.3% prevalence of subclinical TB among 162 women initially recruited as TB-negative controls. The risk of adverse effects was higher in infants born to HIV-infected mothers with subclinical TB compared to those born to TB-negative mothers. A TB prevalence survey from South Africa

identified 234 patients as having bacteriologically confirmed pulmonary TB. Among these patients, approximately 57.7% exhibited no symptoms and were identified as positive solely through chest X-rays. Therefore, chest X-rays should be included as part of routine TB screening, alongside other diagnostic criteria [29]. A variety of factors contribute to the high prevalence of subclinical TB. These factors include individuals with a history of TB, smokers, HIV-positive people, especially those who are treatment-naïve, pregnant or postpartum period, and concomitant non-communicable diseases such as household contacts, prisoners, and miners [3]. The national prevalence-to-notification ratio for TB in India is 2.84:1 [19]. The prevalence surveys encompass both subclinical and clinical TB disease cases, while patients with symptomatic TB typically seek treatment at clinics and are subsequently notified. In 2021, an average of 1.9 million new TB patients (including both new and relapsed cases) were notified in India. This indicates a total prevalence of 5.3 million TB cases. If the global median prevalence is 50% [7], the median prevalence of subclinical TB in India is substantial, estimated at around 2.5 million cases. *Supplementary Table 1* shows the various studies on early-stage TB

Trajectory of subclinical tuberculosis

The natural history of subclinical tuberculosis is heterogeneous, with distinct trajectories noted in various groups. Kendall et al. identified three trajectories of TB in the absence of treatment [12]. Immunocompromised individuals and patients at the extremes of age typically exhibit rapid progression. Identifying these individuals during the subclinical stage may help prevent morbidity and mortality, although the window for intervention is limited. Other categories include slow progression with intermittent containment and spontaneous resolution. Individuals in these categories may remain infectious for a longer duration. Since they are generally recognized only after years of infection, those with slow progression have a higher chance of transmitting the infection. In a modeling study, Ryckman et al. examined the future trajectories of TB patients, including those who are smear-positive/negative and symptomatic/subclinical [30]. The anticipated duration of illness for patients with smear-negative subclinical TB at baseline was 4.8 (95% CI, 3.3 to 8.4) months, and 86% to 89% of them had spontaneous resolution. Patients with smear-positive subclinical TB before diagnosis had an anticipated duration of illness of 15.9 (95% CI 11.1 to 23.5) months. Nearly all patients (96%) developed symptoms. Ultimately, 71% (range: 49 to 87%) received treatment, while 17% (range: 8 to 28%) succumbed to TB. Only 9% to 16% of future transmission events were caused by smear-negative subclinical TB, while 35% to 51% were caused by smear-positive subclinical TB. Ku et al. estimated the duration of asymptomatic,

symptomatic, and care-seeking phases of TB disease based on data from 11 national datasets across Asia and Africa [31]. The duration of asymptomatic bacteriologically positive TB ranged from 4 to 8 months in African nations, while it exceeded one year in three Asian countries: Cambodia, Lao PDR, and the Philippines. People living with HIV have been observed to have a shorter duration. In Blantyre, Malawi, the duration of asymptomatic TB was 1.3 months (95% credible interval: 0.3–3.0) and 8.5 months (95% credible interval: 5.0–12.7) for HIV-positive and HIV-negative individuals, respectively. This finding is not surprising, as it is a well-known fact that TB disease progression is faster in cases of HIV-associated TB. In high-TB burden settings, where subclinical TB is common and there is a delay in healthcare-seeking behavior, active approaches to TB screening and case-finding should be considered as early detection could help avoid unfavorable consequences. In patients with subclinical TB, progression to active disease is not an inevitable or irreversible phenomenon. It can progress, regress, or even remain in a chronic disease state. Richards et al. in a systematic review assessed the outcome of untreated TB disease among the following three states [32]: minimal (non-infectious), subclinical (asymptomatic but infectious), and clinical (symptomatic and infectious). After 5 years, 40% [95% uncertainty intervals (UIs) 31.3–48.0] of those with subclinical disease at baseline had recovered, while 18% (95% UI 13.3 to 24) died from TB. About 14% (9.9–19.2) of individuals with subclinical disease at baseline still had infectious disease, and at five years, approximately 25% of patients with subclinical TB advanced to active disease. Moreover, among patients with subclinical disease at baseline, 50% (40·0–59·1) will never develop symptoms over five years. Spontaneous resolution is due to the self-clearance of *Mycobacterium tuberculosis* bacilli. Lawn et al. identified 16 patients with subclinical TB who were culture-positive from Cape Town, South Africa [33]. They found that 75% of these patients developed TB symptoms between 5 days and 2 months of follow-up.

Transmission dynamics of subclinical tuberculosis

Subclinical TB can be smear negative and culture positive, smear negative and molecular test positive, or smear positive. Subclinical TB can also be positive only on chest x-ray. Patients with chest x-ray suggestive of active TB with an initial microbiologically negative disease had approximately 10% annual risk of progression to microbiologically positive disease [34]. Cough has long been associated with the production of infectious aerosols and subsequent transmission of TB. Other aerosol-generating maneuvers, such as sneezing, singing, tidal breathing, and talking, may also contribute to aerosol-generation [35,36]. Patients with active TB disease can produce

bioaerosols during normal tidal breathing, with particle sizes ranging from 0.5 and 5 μm, which facilitate transmission. Dinkele et al. assessed bioaerosols and viable *Mycobacterium tuberculosis* from 38 people with treatment-naive, Xpert-positive pulmonary TB during three separate respiratory maneuvers: tidal breathing, forced vital capacity (FVC), and cough [37]. They reported 4.8-fold greater total particle counts in cough samples than either tidal breathing or FVC. However, all three maneuvers showed similar rates of positivity for viable *Mycobacterium tuberculosis*. Further modeling revealed that tidal breathing produced more than 90% of the daily aerosolized *Mycobacterium tuberculosis* among symptomatic TB patients, regardless of cough frequency. This is because an individual takes on average 22,000 breaths per day, compared to an upper quartile of 550 coughs in the same period. Furthermore, individual differences in bioaerosol generation outweigh the variability in bioaerosol production caused by respiratory maneuver types. Emery et al. estimated the contribution of subclinical TB to population-level TB transmission in a modeling study [38]. They collected data from 414 index cases and 789 household contacts from three prevalence surveys (Bangladesh, Philippines, and Viet Nam) and one case-finding trial in Viet Nam. About 68% (95% prediction interval, 27-92%) of global *Mycobacterium tuberculosis* transmission was due to prevalent subclinical TB, although the confidence intervals were wide. The transmission rate was 45% (95% prediction interval, 19%-76%) in Nigeria and 84% (95% prediction interval, 60%-95%) in Mongolia. The per unit time infectiousness of subclinical TB relative to clinical TB was 1.93 (95% prediction interval, 0.62-6.18). Therefore, subclinical TB contributes significantly to TB transmission and is similar in infectiousness to active clinical TB. Xu et al. measured TB transmission by using whole genome sequencing (WGS) from TB clusters in Valencia Region, Spain [39]. They found that 35.7% of TB transmission occurred well before symptom onset and when the patients were largely sputum negative. This clearly supports the concept of transmission in patients with subclinical disease. Naidoo et al. assessed the incidence, progression, and outcome of subclinical TB in 402 individuals living with HIV in South Africa [40]. Clinical-radiological-bacteriological screening for TB was done for 36 months. Forty-eight patients had bacteriologically-confirmed recurrent TB, and out of this, 35.4% had subclinical TB. Furthermore, there was spontaneous resolution of subclinical TB in 35.3% of subjects who had bacteriologically confirmed TB. The majority of subclinical TB patients (82.3%) had positive cultures but negative smear results. While a low smear-positivity incidence suggests a lower bacillary burden, subclinical and clinical TB showed similar time to culture-positivity. This suggests a comparable bacterial burden and potential for transmission. Houben et al. described three stages of progression following TB infection [11]. In

classical TB, both the incubation and pre-infectious period progress into clinical disease and infectiousness simultaneously. In the case of subclinical TB, the infectious period predates clinical TB. Subclinical TB may undergo self-cure or may enter a non-progressive stage. This will lead to a discrepancy between prevalence and estimated incidence. Based on multivariate analysis of data from Vietnam, Nguyen et al. estimated the adjusted risk ratio of TST positivity of 2.26 (95% CI: 1.03-4.96) in children living with patients of subclinical TB after adjusting for index smear status [41].

Pathogenesis of early tuberculosis

The concept of early TB disease is not new. In a necropsy study involving 1225 patients with sudden and unexpected death due to non-TB causes, Medlar demonstrated active minimal TB in 96 lesions. The disease showed a predilection for the right apical posterior segment [42]. The pathogenesis of incipient and subclinical TB may be influenced by various factors, such as strain variation, different infection sites, diverse immunological milieu, and bacterial heterogeneity. A deeper understanding of the pathogenetic events in the early subclinical phase of TB will be facilitated by the development of novel diagnostics for subclinical TB. Esmail et al. conducted a whole genome transcriptomic analysis in 10 HIV-infected individuals with radiological evidence of subclinical TB and 15 active TB patients [43]. They found abundant expression of the classical complement pathway and Fcγ receptors during the subclinical stage of the disease. They also noted increased levels of the circulating immune complex. The findings showed that antigen levels were found even in the early-stages of paucibacillary disease. Moreover, transcripts associated with the Fcγ receptors in the classical complement pathway increased in HIV-negative patients 12 months prior to the onset of illness. This insight has the potential to pave the way for developing newer therapies and diagnostics in the future. The *Mycobacterium tuberculosis* lineages are also important since they typically exhibit distinct traits, including virulence, transmissibility, and disease severity [44].

Radiological features of early-stage pulmonary tuberculosis

Among newly diagnosed HIV-negative patients with active subclinical TB, 68.2% showed typical adult-type pulmonary TB imaging abnormalities [45]. Other findings are intrathoracic lymph node enlargement (3.1%), bilateral disease (24.5%), cavitation (6.6%), and acinar shadows (7.1%), respectively. However, 17.5% of patients had a normal chest X-ray. Typically, cavities are small and often single. Compared to chest X-rays, computed tomography (CT) scans were 4.77 times

(95% CI, 1.95–11.66), 19.36 times (95% CI, 8.05–46.52), and 3.23 times (95% CI, 1.66–6.30) more likely to show lung cavitation, endobronchial spread, and moderate/far-advanced parenchymal disease. Thus, CT scans are more effective in identifying TB in its early stages. In a retrospective study, Lau et al. reported subclinical TB in approximately 20% of patients with culture-positive pulmonary TB [46]. In comparison to patients with clinical disease, subclinical pulmonary TB also has a higher prevalence among foreign-born individuals (90.2% vs. 79.6%), a higher likelihood of having smear-negative TB (88.2% vs. 43.5%), and a longer median time for culture positivity (18 days [IQR, 14-25 days] vs. 12 days [IQR, 7-17 days]). In asymptomatic patients, chest X-ray is a crucial tool in active TB diagnosis as it guides subsequent microbiological testing. However, in this study, 86.4% of patients had either no or minimal parenchymal abnormalities. In comparison to the panel of expert radiologists, Long et al. found that field radiologists were less likely to report cavitation, a typical pattern, and parenchymal disease (74.9% vs. 81.3%, 62.4% vs. 70.0%, and 3.4% vs. 7.6%, respectively) in patients with subclinical pulmonary TB [47]. In Alberta, Canada, Heffernan et al. [48] evaluated the frequency of subclinical TB in patients with peripheral lymph node TB. About 12.9% of patients with no symptoms and normal lung parenchyma and 66.7% of individuals with both had positive sputum cultures. About 50% of individuals with a normal chest x-ray but a positive culture also had a normal CT thorax. As a result, pulmonary TB linked to peripheral lymph nodes may be subclinical. Since chest radiography is frequently recommended, widespread TB preventative therapy may also identify a significant proportion of people with subclinical TB. Ryckman et al. demonstrated that symptoms-based active case finding (ACF) will only prevent less than 50% of future transmission [30]. However, 62 to 78% transmission may be avoided if patients with baseline bacterial burdens were identified. Therefore, even though they may burden healthcare in settings with limited resources, additional tests such as bacteriological investigations should be done. Han et al. evaluated the radiological features in 66 HIV-negative patients with bacteriologically proven early TB and reported well-defined solid nodules in the upper lobes and superior segments of the lower lobe as the most common imaging findings [49]. The adjusted OR for the progression to active TB in the presence of risk factors was 8.59. Positron emission tomography in conjunction with CT (PET-CT) is one option that can pick up early-stage TB. Increased 2-deoxy-2-[18F]fluorodeoxy-glucose (FDG) PET-CT scan in TB are caused by metabolically active cells such as macrophages and neutrophils [50]. Esmail et al. evaluated 35 asymptomatic, treatment-naïve, HIV-1-infected individuals with PET-CT scan [51]. These individuals had latent TB based on a positive QuantiFERON-TB Gold in tube test. The patients had culture negativity, no abnormalities

on chest X-rays, and CD4 T cell counts of 350/mm^3. The patients with subclinical TB had significantly more likely to have abnormal FDG uptake within the mediastinal lymph nodes as compared to 25 participants without subclinical TB (80% versus 32%; P = 0.022).

Community-based screening

Community-based screening would be the most effective method to diagnose subclinical TB. According to the World Health Organization (WHO) consolidated guideline on systematic TB screening, in regions where the TB prevalence is 0.5%, the general population should be subjected to systematic screening. Symptom-based screening, chest x-rays, and rapid molecular diagnostic tests are the tools used in systematic screening. Computer-aided detection (CAD) can be can be applied to the interpretation of chest x-ray images [52]. In a systematic review of community-based ACF, Burke et al. found that ACF could be effective in modifying TB epidemiology if implemented with high coverage and intensity [53]. In the cluster-randomized trial conducted over three years in Vietnam, Marks et al. compared active community-based screening with passive case detection [54]. There were 42,150 participants in the intervention group and 41,680 participants in the control group. In the interventional arm, they screened the population with Xpert MTB/RIF and chest x-rays. They observed a reduction in the prevalence of Xpert test-positive, culture-confirmed pulmonary TB from the first year to the fourth year by 64%. In the DETEC TB trial, the mobile van approach was found to be more effective in detecting previously undiagnosed smear-positive TB than screening by door-to-door visits at 6-month intervals (adjusted risk ratio 1.48, 95% CI 1.11–1.96, p = 0.0087) [55]. In a modeling study, Dowdy et al. assessed the effects of various TB case-finding strategies on subclinical, pre-diagnostic disease, and clinical phases at the population level [56]. In the pre-diagnostic phase, symptoms exist, but a diagnosis was not established. By year 10, the passive strategy will reduce the incidence of TB by 18% if the subclinical phase is disregarded, compared to 23% for the enhanced strategy and 18% for the active strategy. However, after incorporating the subclinical phase, the corresponding figures for the passive, enhanced, and active strategies were 11%, 6%, and 16%, respectively. Subclinical TB has the potential to reduce the current TB detection strategies, and an active strategy is better for TB detection at the population level.

In a cluster-randomized trial, Martinson et al. showed that targeted universal testing for TB (TUTT) in high-risk groups diagnosed more patients with TB per month compared to the current standard of care (SoC) symptom-directed TB testing [57]. They provided sputum Xpert Ultra and culture to individuals who were HIV-positive, HHCs with TB, or prior TB. By direct comparison, there was

no increase in the number of TB patients diagnosed. However, compared to the previous year, the same clinic showed a 17% increment in TB patients diagnosed per month [incidence rate ratio (IRR) 1.17, 95% CI 1.14, 1.19, $p < 0.001$]. The tools available at present to detect subclinical TB are symptom screening, chest radiology, and molecular diagnostics. Houben et al. suggested additional sputum, induced sputum, bronchoalveolar lavage, bioaerosol sampling to detect additional infectious cases as they are also contributing to mycobacterial transmission [58]. TB transmission from millions of individuals with subclinical TB must be stopped. Without achieving this, the goal of end TB strategy by 2035 might not be met. In the future, we definitely need newer diagnostics that will meet the WHO-recommended target product profile (TPP). Based on the presently available tools, a large fraction of infectious TB will be missed. A delay in the diagnosis of subclinical TB may increase the risk of potential transmission of TB. Many new diagnostics are in the pipeline, particularly non-sputum-based ones [59].

Biomarker

In a systematic review and meta-analysis, the reported sensitivity of sputum culture, smear microscopy, TST/IGRA, and chest x-ray for diagnosing subclinical TB were 77 % (95 % CI:43–99 %), 15 % (95 % CI: 4–29 %), 64% (95 % CI: 33–90 %), and 53 % (95 % CI: 3–81 %), respectively [60]. Microbial tests are less sensitive as the bacterial burden is less in subclinical TB. As a result, there is enormous potential to develop diagnostic techniques that can identify TB in its early stages. Non-sputum-based assay such as host biomarkers, have a great potential. Currently, TST and IGRA tests are employed as host biomarkers in TB. The new biomarkers include the *Mycobacterium tuberculosis* specific T-helper cell activation assays, RNA signatures, proteins such as RISK 6, RISK 11 score. The potential of a biomarker-based diagnostic is enormous. However, the novel tests should meet the TPPs as recommended by the WHO [61]. The TPPs should have a sensitivity and specificity of at least 75% (minimum) to 90% (optimum) for predicting active disease progression over a period of two years. This would make the number needed to treat (NNT) about 10 to 25. Newer tests should have the following characteristics: First, it should be instrument-free or feasible with limited instrumentation. Secondly, the samples should be easily accessible, such as blood, urine, or breath. Moreover, it should be able to discriminate between different states of TB [62-64]. The TPP should also be able to detect individuals with incipient TB who are likely to develop clinical disease within the next two years and who would benefit from TB preventive therapy. Transcriptomes are helpful in identifying incipient TB. Sivakumaran et al. evaluated 35 incipient TB and 12 subclinical TB cases in Southern India, along

with corresponding household active TB cases (n=11) and household controls (n=39), using transcriptional and protein profiling [64]. An 11-gene signature (ABLIM2, C20orf197, CTC-543D15.3, CTD-2503O16.3, HLADRB3, METRNL, RAB11B-AS1, RP4-614C10.2, RNA5SP345, RSU1P1, and UACA) was found to have very good discriminatory power in differentiating between subclinical and incipient TB. They also identified eight protein signatures with good to moderate discriminatory power that might distinguish subclinical and incipient TB. In a systematic review and individual participant data meta-analysis, Gupta et al. evaluated 17 candidate mRNA signatures in a pooled dataset from four eligible studies comprising 1126 samples [65]. In this dataset, 183 samples from 127 incipient TB cases were included. They detected eight signatures comprising of 1-25 transcripts that discriminated subjects with incipient TB from controls and predominantly expressed interferon and tumor necrosis factor-inducible gene expression. Within a 2-year period, the eight signatures had similar diagnostic accuracy for incipient TB patients. The area under the ROC curve (AUC) ranged from 0·70 (95% CI, 0·64–0·76) to 0·77 (95% CI, 0·71–0·82). Unfortunately, none of the 24 signatures met the minimum WHO TPP for incipient TB biomarkers over a 2-year period, except when applied to 3–6-month intervals. The CORTIS trial used an RNA transcriptomic signature of TB known as RISK11 in order to predict the risk of future TB. Additionally, they assessed the three-month duration of weekly isoniazid and rifapentine (3HP) preventive treatment in South African volunteers who tested positive for RISK11. [66] In individuals with a positive and negative RISK-11 profile and without therapy, the prevalence of culture-positive illness was 4.1% and 0.78%, respectively. Over a period of 15 months, the incidence of TB in patients with a positive RISK-11 signature (3HP negative and without treatment) but no culture at baseline was 2.09/100 person years. In those who tested negative for RISK11, the comparable value was 0.80/100 person-years. The trial has shown good discriminatory power in detecting prevalent or incident TB disease over 15 months. The optimal capacity to predict progression to active TB disease was limited to a six-month timeframe. The test performed well in symptomatic prevalent TB, but its effect was less in asymptomatic prevalent TB (e.g., subclinical TB). Since asymptomatic prevalent TB has a limited specificity, people with a negative risk score may nonetheless be TB positive. However, the weekly 3HP regimen in RISK-11-positive individuals did not reduce the progression to TB. Zak et al. have found that blood RNA signatures can predict the progression of TB [67]. In the 12 months preceding TB diagnosis, they identified 16 gene signatures that predicted the disease progression with a sensitivity of 66.1% (95% CI, 63.2–68.9) and a specificity of 80.6% (79.2–82.0). The gene signature is known as Zak16. The Xpert MTB Host Response (MTB-HR) assay is a new point-of-care finger stick blood test that has

been developed by Cepheid. The messenger RNA (mRNA) expression of three genes-guanylate binding protein 5 (GBP5), dual specificity phosphatase 3 (DUSP3), and Krüppel-like factor 2 (KLF2) was used to generate a "TB score". Both GBP5 and DUSP3 mediate pro-inflammatory responses and are upregulated in TB. Sutherland et al. [68] compared the accuracy of the Cepheid GeneXpert MTB-HR prototype to the GeneXpert Ultra results and a composite microbiological score (GeneXpert Ultra and liquid culture) in adults with clinical TB in three African countries as well as Vietnam. Patients were classified as having TB or other respiratory diseases. When compared to GeneXpert Ultra, the Xpert-MTB-HR-Prototype TB score has an AUC of 0.94 (95% CI, 0.91 to 0.97) to distinguish between active TB and other respiratory diseases. The sensitivity and specificity were 87% (95% CI, 77-93%) and 94% (88-97%), respectively, independent of geographic area or HIV infection status. These assays met the WHO minimum TPP for a point-of-care triage test for TB. However, studies need to be done in subclinical TB when alterations in gene expression can be minimal. Wanchu et al. evaluated two biomarkers, Malate Synthase (MS) and MPT51, in both TB and HIV-TB coinfected patients in India and reported high sensitivity and specificity for TB diagnosis [69]. The presence of concurrent HIV infection, the location of TB infection, or the lack of pulmonary symptoms in HIV/TB patients do not affect the performance of these biomarkers. Results also demonstrate the potential of these biomarkers for identifying early TB in HIV-infected but TB-negative subjects at high risk for TB. Penn-Nicholson identified a host-blood transcriptomic signature known as RISK6 and reported a receiver-operating characteristic curve value over 85% for the diagnosis of subclinical and clinical TB disease in HIV-uninfected and HIV-infected persons, respectively. When the test was run on finger-prick capillary blood samples, it revealed no difference in performance between venous and capillary blood. In addition, RISK6 scores showed a correlation with lung immunopathology activity, tracked response, and predicted treatment failure [70]. The use of blood RNA signatures as a diagnostic modality is very promising. Moreover, it also has the potential to be a point-of-care test with rapid turnaround times. However, blood biomarker-based diagnostics do have several limitations. Mulega et al. demonstrated that viral infections can result in transient false-positive results from the RISK-11 whole-blood transcriptome signature, which may have impacted the clinical trial's outcome [71]. Both rhinovirus and coronavirus infections have been linked to this. Moreover, RISK11 signature scores are elevated in HIV infection [72]. A sizable fraction of patients with incipient disease may undergo self-regression. This will give rise to a false positive test [73]. In addition, the progression of early TB is quite variable. Some individuals might progress more slowly than others. Those who progress more quickly will be tested positive at the beginning of

clinical illness. Lastly, gene expression will be variable in early childhood diseases and immunocompromised hosts. The best indication of biomarker is the recent HHCs. Figure 2 shows the flow chart depicting the diagnostic approach to early-stage TB.

Computer-aided diagnostic

The WHO has recommended that CAD software programs may be used for the interpretation of digital chest X-rays in individuals 15 years of age and older for the purpose of TB screening [52]. Qin et al. assessed the efficacy of five artificial intelligence (AI) algorithms for triaging TB patients in Dhaka, Bangladesh, and reported that all five AI-based algorithms performed better than the radiologists [74]. Therefore, AI-based x-ray reading is accurate and can be implemented in high-burden settings. Increasing use of AI-based tools will identify a large number of bacteriologically negative TB. Patients with radiologically positive TB can progress from 30% to 50% over a period of 4–6 years to culture-confirmed TB [75,76].

***Mycobacterium tuberculosis* in aerosol**

The detection of *Mycobacterium tuberculosis* bacilli or DNA in aerosols belongs to the late prototype test category [57]. The bacilli or DNA are captured with capture filters, absorbent materials, or blow tubes with a capture filter. In a longitudinal study, Williams et al. detected Mycobacterium tuberculosis DNA in 86% of facemasks and 21% of sputum samples [77]. They performed an XpertMTB/RIF Ultra assay on the sputum and facemask samples. Patients who were tested positive for face masks but sputum negative were further assessed for 20 weeks using bronchoscopy, PET-CT, and sputum analysis. The exhaled DNA did not exhibit any diurnal pattern. Additionally, no association was observed between exhaled *Mycobacterium tuberculosis* in face masks and cough frequency, sputum bacillary content, or chest radiographic disease severity. *Mycobacterium tuberculosis* was found via facemask sampling four times more frequently than in sputum samples. Furthermore, it also aids in early diagnosis, up to six weeks before conventional sputum diagnosis. The mechanism of infected bioaerosol production can be cough-independent, which suggests the infectivity of subclinical TB [78]. Tidal breathing produces aerosols by the bronchiole fluid film burst mechanism [79]. Collecting samples from tongue swabs is an safe and easy-to-collect method for patients with pulmonary TB. The testing is done with the rapid molecular method. Using sputum Xpert Ultra as the reference standard, Andama et al. showed that tongue swabs Xpert Ultra had a sensitivity and specificity of 77.8% (95% CI 64.4–88.0) and 100.0% (95% CI, 97.2–100.0), respectively [80]. Using sputum Xpert

Ultra and sputum mycobacterial culture as microbiological reference standards, sensitivity was 72.4% (95% CI, 59.1–83.3) and specificity was unchanged. Further optimization of tongue swab analysis is needed to achieve parity with sputum-based molecular testing for TB. Sputum-free diagnostic methods look promising for future TB diagnostics. TB diagnostics can be useful for triaging or for confirmation of diagnosis. A triage test will guide us in determining who among the presumptive TB patients needs a confirmatory test [58].

Compounds in breath

Variations in the signatures of volatile organic compounds in exhaled breath can be analyzed to facilitate the detection of pulmonary TB using electronic nose devices or gas chromatography [81]. Mougang et al. assessed the efficacy of an electronic nose for the diagnosis of TB in a Cameroon hospital [82]. They noted 88% accuracy, 90.8% sensitivity, 85.7% specificity, and 0.88 AUC compared to healthy controls. Similarly, Saktiawati et al. from Indonesia reported sensitivity and specificity of 85% (95%CI: 75–92%) and 78% (95%CI: 70–85%), 55% (95%CI: 44–65%) and 42% (95%CI: 34–50%), in the calibration and validation phases, respectively [83]. The negative predictive value in the blind prediction model was reported by Teixeira et al. as 100% [84]. Therefore, the electronic nose can be used as a rule-out test in the future. Another non-sputum-based test is the lipoarabinomannan (LAM) in urine. A recent development is the Fujifilm SILVAMP TB-LAM, which showed higher sensitivity irrespective of HIV status. In HIV-infected and HIV-uninfected patients, Comella-del-Barrio found a sensitivity of 70% (95% CI 35–92) and 65.7% (95% CI 48–80), respectively [85]. The tuberculin test and interferon-gamma release assay (IGRA) have a low positive predictive value (PPV) for progression to active TB. Diel et al. in a meta-analysis of 28 studies including >30,000 individuals, found IGRAs to be more predictive than the TST for progression to active TB [86]. The pooled PPV for both IGRAs and TST is low; however, it is higher for IGRAs (2.7% (95% CI, 2.3%-3.2%) than TST (1.5% (95% CI, 1.2%-1.7%) ($P < .0001$). The negative PPV for IGRAs and TST were 99.7% (95% CI, 99.5%-99.8%) and 99.4% (95% CI, 99.2%-99.5%) respectively ($P < .01$). Moreover, in the high-risk group (recently infected or HIV-infected), the PPV for IGRAs rose to 6.8%, whereas it was only 2.4% for the TST. In children with subclinical TB, the best diagnostic outcome was noted when a combination of immunodiagnostic testing and imaging followed by culture and molecular testing were used (27.9%) [87].

Treatment of incipient and subclinical tuberculosis

Given the potential for transmission, implementing a prevention and treatment strategy for subclinical TB disease is a crucial public health intervention. It has the potential to prevent negative health impacts and poor outcomes. However, there are few studies that have evaluated preventive therapy, treatment, and outcomes in early TB. The CORTIS trial evaluated the weekly isoniazid and rifapentine (3HP) preventive therapy for three months in RISK11-positive participants in South Africa and reported negative results [66]. Patients with early-stage TB are not recruited in most clinical trials, making it difficult to study the effects of chemotherapy, vaccines, preventive therapy, and TB diagnostics on the subclinical and incipient stages of the disease. In order to fully understand and address subclinical and incipient TB, it is important to include both early-stage and clinical TB disease in research [11]. Currently, there is no specific guideline for managing subclinical TB. It may be challenging to offer the standard six-month treatment to asymptomatic patients, leading to issues with adherence [88]. The traditional regimens for latent TB infection may be useful for incipient TB as well, but there is a lack of evidence. Therefore, further trials are needed to evaluate the use of newer drugs, shorter-duration regimens, host-directed therapy, and therapeutic vaccines in treating early-stage TB [89]. The WHO has advised TB preventive therapy with isoniazid for 36 months for TB infection in HIV-positive individuals in TB-endemic countries, as this may serve as the initial stage of incipient TB [3,90]. In a prospective study conducted in South Korea, Min et al. assessed the treatment outcomes of subclinical TB disease among HIV-uninfected patients [91]. Of the 420 individuals enrolled, 19.2% were found to have subclinical disease. In comparison to active disease, subclinical disease showed a significantly reduced proportion of acid-fast bacilli smear and culture positivity, as well as multiple lobe involvement. Although the proportion of favorable outcomes was higher in patients with subclinical disease, the odds ratio was not statistically significant. Tan et al. evaluated the effectiveness of preventive therapy for subclinical TB among childhood HHCs in Lima, Peru [92]. They enrolled 793 TST-positive child HHCs (age 15) who underwent both symptom and chest x-ray screening and monitored them over the course of one year for the occurrence of TB disease. A normal chest X-ray was present in 784, and 451 received 6-month isoniazid preventive therapy. Preventive therapy was 72% effective in patients with normal chest x-rays, as incident TB occurred in 1.6% of those receiving preventive therapy versus 4.6% of those not receiving it. In those with abnormal chest x-rays, preventive therapy efficacy was 65%, with TB occurring in 17% of those receiving it and 59% not receiving it. This suggests that preventive therapy is effective even in patients with subclinical TB. In a prospective study, Ananda et al.

assessed the course and outcomes of TB disease diagnosed by a community-based ACF program that was mobile and located in Yogyakarta, Indonesia [93]. They reported that 41.9% of patients with bacteriologically confirmed TB had subclinical TB. Multivariate analysis revealed weak evidence of reduced unsuccessful outcomes in cases of symptomatic versus subclinical TB (aOR 0.6, 95% CI 0.36–0.998). The American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines recommended a 4-month treatment regimen for HIV-uninfected adult patients with AFB smear-and culture-negative pulmonary TB [94]. Until we have specific studies involving early-stage TB for prevention and management, the treatment of subclinical TB should follow guidelines for conventional drug-susceptible TB disease. Before starting treatment, concurrent comorbidities, HIV infection, and potential drug-drug interactions should be assessed. Newer drug trials should include early TB cases in order to develop more effective treatment strategies. The SWIFT trial is a prospective, open-label, multicenter randomized controlled trial dedicated to subclinical TB only [95]. The result is pending. Prior to initiating TB preventive therapy, active TB disease must be ruled out, and chest radiology should be routinely performed. Dowdy et al. [96], in a modeling study, have proposed a comprehensive approach to reducing the incidence of TB. Interventions such as preventive therapy, case finding and diagnosis, and airborne infection control measures will be helpful in reducing transmission.

Challenges and need for the future

There are several flaws in the diagnostic tests that are currently in use. Furthermore, a lack of awareness about early-stage TB is common in resource-poor settings. A major knowledge gap exists regarding diagnostic strategies and treatment of early-stage TB. Because of its cross-reaction with non-tuberculous mycobacteria and the BCG vaccination, TST has a limited specificity. Availability and high cost is a significant barrier to the IGRA's extensive application in resource-poor settings. Furthermore, there is no distinction made by these tests between TB infection and active TB disease. Chest x-rays have several limitations. Sputum culture can be positive in patients with normal chest X-rays. Therefore, relying on chest X-rays may underestimate subclinical TB by 10%. Chest x-rays have high sensitivity but poor specificity for pulmonary TB. In addition, there is significant intra- and inter-observer variability in the reading of chest x-rays [97]. Furthermore, screening for subclinical TB requires significant resources. There would be a US$ 22,278 incremental cost-effectiveness ratio for each new TB case detected on chest x-ray screening as compared to only symptom-based screening [98]. Performing ACF regularly in a populous country

is also a big challenge. Health care seeking behaviour is also poor in resource-poor settings. The sensitivity of microscopy is also low, particular in immunocompromised patients. Laboratory infrastructures lack adequate infrastructure and manpower in resource-poor settings. Laboratories are often not adequate to manage a high volume of patients. Additionally, access to advanced diagnostic techniques is often limited in resource-poor settings that poses a challenge in diagnosing early-stage TB. We need novel and accurate testing modalities to detect individuals who are diagnosed with incipient disease or subclinical TB. This area needs funding and research at a level similar to the COVID-19 pandemic. An innovative test should ideally address the existing shortcomings and ideally be a point-of-care exam. The test must be available and cost-effective for middle- and low-income countries. Additionally, it should fulfill the WHO's recommended TPP. Adoption of TB preventive therapy on a large scale will lessen the incidence of active TB, including subclinical and incipient disease. Epidemiological data and genetic sequencing are required for the identification of transmission events. Diagnosis of early-stage TB requires cheaper and more sensitive detection methods. There is an urgent need to study treatment in various subsets of subclinical TB patients with a particular emphasis on shorter treatment duration. Additionally, we must ascertain how early identification affects post-TB squeal.

Conclusions

Subclinical and incipient tuberculosis may contribute a substantial proportion of the global TB burden. Patients with early-stage tuberculosis also have the potential to spread the disease. However, the current method of symptom-based screening may not detect cases of early tuberculosis. As a result, patients with early TB will continue to add to the overall global burden of tuberculosis. Furthermore, existing laboratory tests for TB are not able to confirm all cases of tuberculosis bacteriologically. Early identification of subclinical TB can significantly reduce the burden of TB and its long-term effects. If we proactively use active case-finding strategies to screen individuals who do not exhibit symptoms, we can achieve significant progress. Similarly, a validated biomarker-based approach may also be helpful in the diagnosis of various spectrums of TB diseases. Chest imaging-based community-based screening is crucial for the early detection of subclinical TB. This will help tremendously in achieving the target of the end-TB strategy. There are still many gaps that need to be addressed in the future. The best screening technique and treatment plan for subclinical tuberculosis need to be identified. The biomarker-based tests have great potential for TB diagnosis in near future. The number of drugs and the duration of treatment

is not clear and needs future clinical trial. Further research and advancements in the future will provide us with the answers we need.

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Online supplementary material:
Supplementary Table 1. The various studies on early-stage tuberculosis.

Table 1. Definition of various spectrums of tuberculosis.

	Definition
Latent TB infection	Asymptomatic state of infection with *Mycobacterium tuberculosis* demonstrated by a response to in vivo or in vitro stimulation by *M. tuberculosis* antigens as identified by a positive TST or IGRA. [6]
Incipient TB	Incipient TB infection is an infection with viable *M. tuberculosis* bacteria that has not yet produced clinical symptoms, radiographic abnormalities, or microbiologic evidence consistent with active TB disease but is likely to progress to active disease in the absence of further intervention. [3]
	Incipient TB as an "asymptomatic, early preclinical disease state during which pathology evolves, such as mycobacterial replication or the inflammatory response. During this state, clinical signs of the disease, including TB-compatible symptoms, are still absent. Radiological abnormalities or positive microbiological tests may or may not be present. This state may either evolve and lead to symptomatic clinical TB or regress and remain asymptomatic." [6]
Subclinical TB	A state of disease due to viable *Mycobacterium tuberculosis* that does not cause TB-related symptoms but does cause other abnormalities that can be detected using existing radiologic or microbiologic assays. [3]
Clinical TB	Active symptomatic disease state as a result of the mycobacterial inflammation, with the presence of TB-compatible signs and symptoms, which can be demonstrated by radiological, pathological, and/or microbiological evidence. [6]

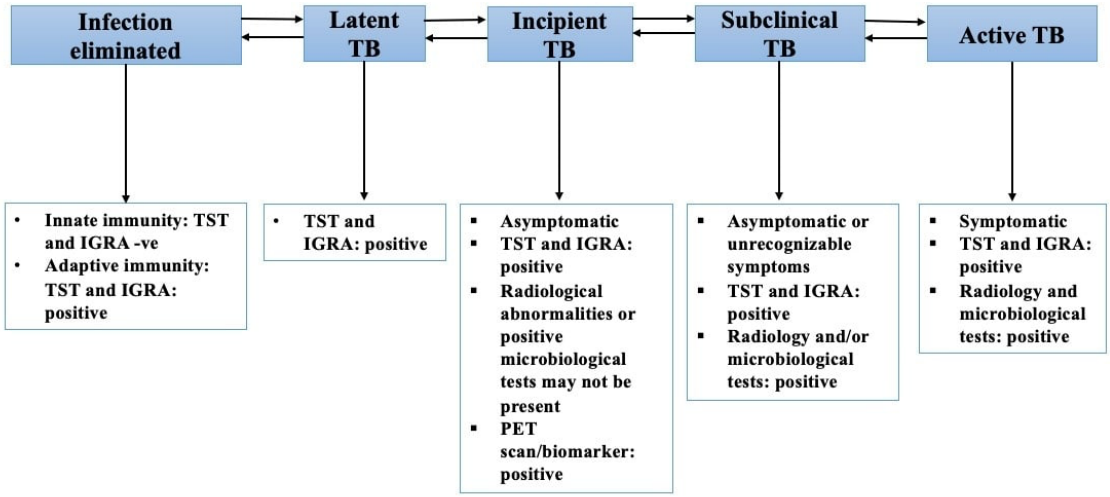

Figure 1. The various stages of tuberculosis TST, tuberculin test; IGRA, interferon γ release assay; PET, positron emission tomography.

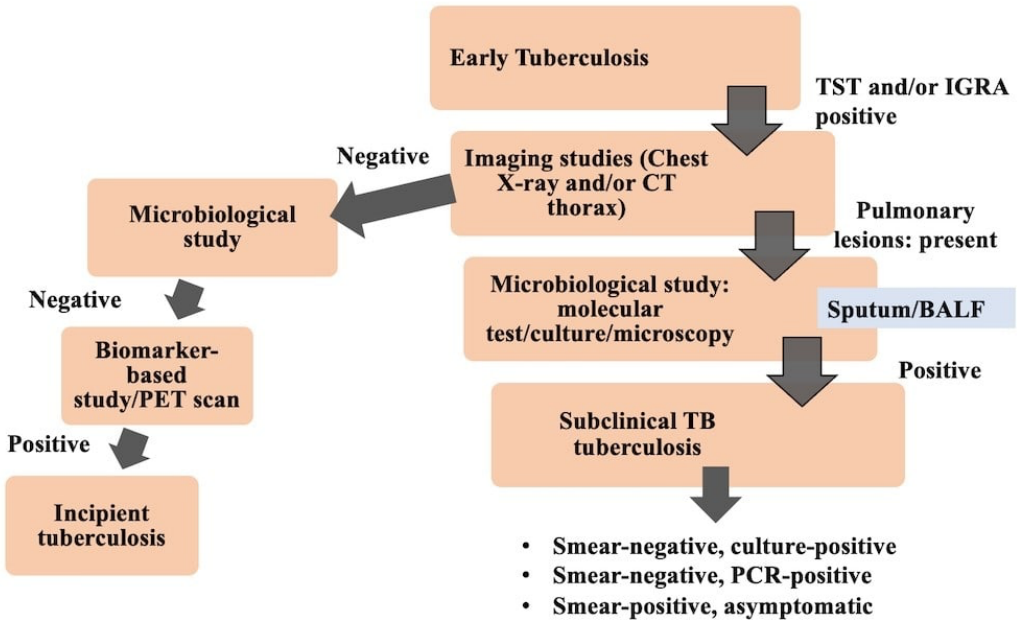

Figure 2. The flow chart depicting the diagnostic approach to early-stage tuberculosis. BALF, bronchoalveolar lavage fluid; PCR, polymerase chain reaction; CT, computed tomography.