Review Article

Subclinical Tuberculosis: Addressing the Hidden Threat to Tuberculosis Control and Disease Prevention

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Abstract

Subclinical tuberculosis (Subclinical TB) remains a significant yet frequently underdiagnosed contributor to the global TB burden. Due to its lack of noticeable symptoms and its potential for spreading pathogens, many subclinical TB patients face diagnostic delays and act as silent sources of infection. Consequently, subclinical TB is just as impactful as active TB in contributing to both individual health deterioration and the spread of TB within communities. Early identification and treatment of subclinical TB cases is essential for effective TB control and must be prioritized to make substantial progress toward TB elimination, especially in high-burden countries like Thailand. In addition to passive diagnostic systems, it is recommended that active case-finding strategies be proactively implemented within the population. These strategies would facilitate early diagnosis and prompt treatment, supporting secondary prevention by minimizing further damage to the patient's health. Furthermore, they would contribute to primary prevention by halting the spread of TB, ultimately reducing both the incidence and overall burden of the disease. This paper explores the classification, prevalence, diagnostic challenges, and clinical significance of subclinical TB, underscoring the need for proactive screening strategies to reduce the TB burden and help achieve elimination goals, both globally and in Thailand.

Keywords: subclinical tuberculosis, asymptomatic tuberculosis, TB transmission, TB control

Tuberculosis (TB) has long been a concern at both the international level and in Thailand, as evidenced by the UN resolution to end the global TB epidemic by 2035[1] and the 2023-2027 Thailand Operational Plan addressing this issue.[2] According to the WHO's Global Tuberculosis Report 2024, an estimated 10.8 million people had TB in 2023, equivalent to 134 incident cases per 100,000 population. There were 8.16 million new TB cases reported and 1.25 million deaths caused by TB in 2023. TB is not only a substantial public health issue worldwide, but it also remains a significant problem in Thailand, with an incidence of 157 per 100,000 population in 2023, placing Thailand among the 30 nations with the highest TB burden.[3]

In an effort to understand and control TB infection, subclinical tuberculosis (subclinical TB) was recently introduced as a new disease stage, expanding previous knowledge. TB can now be classified into latent TB infection, subclinical or asymptomatic TB, and clinical or active TB.[4] Among these classifications, subclinical TB is particularly interesting due to its asymptomatic or minimally symptomatic nature, yet it has the ability to transmit TB.[3] Recent studies analyzing data from African and Asian countries found that about two-thirds of global TB transmission may stem from subclinical TB.[3,5] Despite its significant role in the global burden of TB, subclinical TB often goes undiagnosed without active case-finding strategies, as it does not present symptoms.[6] This issue needs to be addressed further in order to effectively control TB infection and ultimately eliminate TB in the near future.[3]

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Definition and Classification of Subclinical TB

Subclinical TB, or asymptomatic TB, is a recently introduced concept with several suggested definitions. Drain et al.[4] defined subclinical TB as "disease due to viable M. tuberculosis bacteria that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays." Kendall et al.[7] described subclinical TB as a disease state in which chest radiography or sputum culture can test positive for TB, but the patient does not exhibit TB symptoms, such as prolonged cough, fever, or weight loss, and will deny having these symptoms during screening history taking. Subclinical TB patients may be asymptomatic or exhibit mild or intermittent symptoms that are not recognized as TB-related.[7] Furthermore, following a recent consultation in October 2024, the WHO has provided a definition for asymptomatic TB (or subclinical TB), describing an asymptomatic TB patient as "a person with TB disease who did not report symptoms suggestive of TB during screening."[3]

Regarding the stage of the disease, subclinical TB is considered an early stage that occurs before the disease progresses to active TB. This concept is supported by evidence that subclinical pulmonary TB cases tend to have lower rates of multiple pulmonary lesions and less extensive radiographic abnormalities compared to active TB cases.[4,8,9] Subclinical TB also has higher treatment success rates and lower mortality, further supporting the idea that it is less severe, being an earlier stage prior to active TB.[10]

The WHO's recent consultation also resulted in the classification of asymptomatic/subclinical TB, dividing it into bacteriologically confirmed and unconfirmed types, as illustrated in Figure 1. This distinction is based on the results of bacteriological tests, such as the WHO-recommended rapid diagnostic test, culture, or smear microscopy. For subclinical TB that is bacteriologically unconfirmed, diagnosis relies on chest radiography, other imaging techniques (like computed tomography), and histopathological examination, along with a history suggesting exposure to or a prior occurrence of TB.[3]

Additionally, recent research by Coussens et al.[11] introduced a novel concept of TB classification, using three pathophysiological components to categorize different states of TB. The distinct disease dimensions are macroscopic TB pathology, infectiousness, and TB symptoms or signs. For the first component, macroscopic TB pathology, advanced imaging techniques such as PET-CT, CT, MRI, and histopathology are used as reference standards, while chest X-ray can be applied for operational use. This component helps differentiate individuals with TB infection without disease from those with active disease. The next step is to use the other two components to distinguish different states of TB disease. For the second component, infectiousness, sputum culture can be used for examination. This component classifies cases into infectious and non-infectious types. TB symptoms or signs, the last component, will be evaluated using the WHO four-symptom screen (cough, fever, night sweats, or weight loss),[11,12] symptom severity scores, or prolonged cough lasting more than two weeks. This component divides TB disease into clinical and subclinical disease. Thus, the infectiousness and symptoms or signs components together will categorize TB disease into four states, as shown in Table 1. Thus, subclinical TB will be classified into subclinical TB, non-infectious, and subclinical TB, infectious.[11]

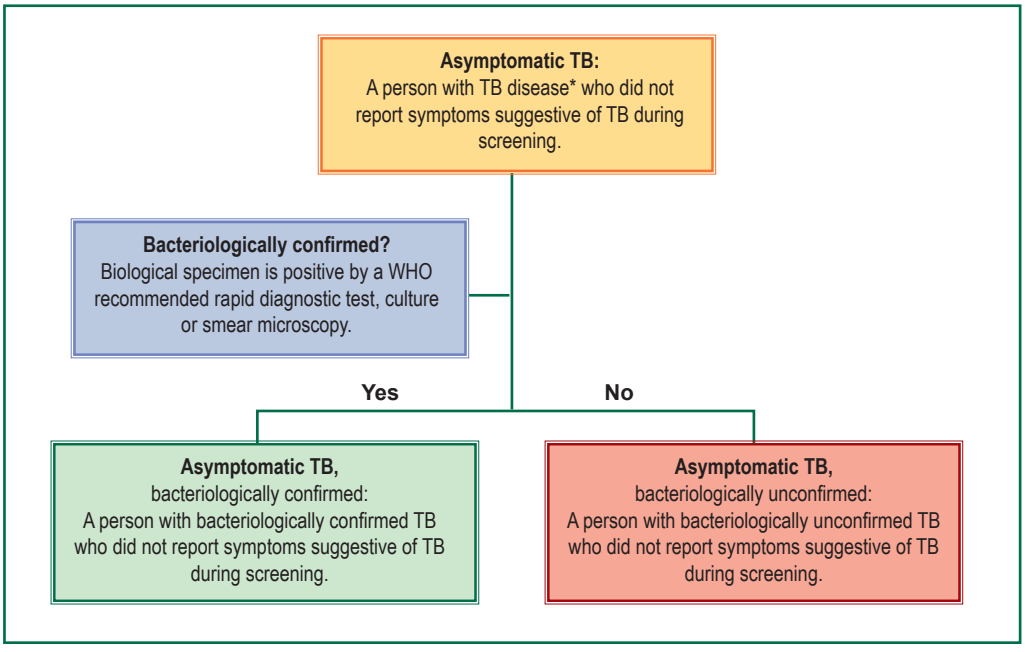


Figure 1: Definitions and classification of asymptomatic TB following a WHO consultation.[3]
* Case detection for non-infectious asymptomatic TB relies on imaging modalities. In cases of infectious subclinical TB, imaging remains a critical diagnostic tool, while microbiological testing is also essential for case identification. Please refer to the *Diagnosis and Disease Control of Subclinical Tuberculosis section.*

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Table 1: Distinct disease dimensions define different states of TB according to research by Coussens et al.[11]

	Disease dimensions		
	Macroscopic pathology	Infectiousness	Symptoms and signs
TB infection			
Subclinical TB (Non-infectious)	✓		
Subclinical TB (Infectious)	✓	✓	
Clinical TB (Non-infectious)	✓		✓
Clinical TB (Infectious)	✓	✓	✓

To conclude, according to the WHO and research conducted by Coussens et al.,[11] subclinical TB can be classified, based on its infectious nature, into bacteriologically confirmed/infectious subclinical TB and bacteriologically unconfirmed/non-infectious subclinical TB.[3,11] Both types hold clinical significance not only on an individual scale but also at the community level, which will be discussed in the following section of this article.

Prevalence and Clinical Significance of Subclinical TB

Several studies have examined the prevalence of subclinical TB, showing varying percentages of subclinical disease among all TB cases. A study in China found that 18.2% of TB cases were subclinical,[8] while another study in South Korea reported a similar prevalence of 19.3%.[9] Studies in Thailand, however, have shown a much higher proportion of subclinical cases. A recent 2024 study on pulmonary tuberculosis among healthcare workers at a university hospital over a five-year period (2018-2022) found that nearly 7 out of 10 TB cases were subclinical.[13] Another study at a different university hospital found a lower proportion of 43.53%.[14] Additionally, a study of the general population undergoing check-ups at a university hospital in Bangkok, based on data collected from 2014 to 2019, revealed that 84.8% of all TB cases were subclinical.[15] A study of COVID-19 patients also found that nearly half of the patients diagnosed with TB did not have symptoms suggestive of TB.[16] These findings from Thailand align with a systematic review and meta-analysis by Mahmoudi et al.[17] in 2024, which analyzed studies published from 2000 to 2022 and found that the prevalence of subclinical TB in Asian countries was over 60% of all TB cases. This is also consistent with a meta-analysis by Hamada et al. that found the prevalence of subclinical TB ranged from 15% to 57%.[18]

From the studies above, it is clear that subclinical TB cases constitute a substantial proportion of all TB cases. However, the issue is not just the number of cases; subclinical TB holds clinical significance at both individual and community levels. Both infectious and non-infectious types of subclinical TB can progress to a clinical stage, where patients begin to suffer from TB symptoms. If left undetected and untreated, subclinical TB can advance to a more severe form, leading to extensive lung damage and long-term post-tuberculosis sequelae.[11] Subclinical TB also plays a significant role in TB transmission, particularly in the infectious type. Patients are capable of transmitting the disease because they may have high TB pathogen loads despite exhibiting no symptoms.[11,19] Therefore, the potential for TB transmission in subclinical cases is associated with sputum positivity.[13] A meta-analysis conducted by Stuck et al.[20] found that 29% of TB patients without a persistent cough and 23% of those without any cough had positive sputum smear results. A study in China revealed that 23% of all subclinical TB cases were culture-positive,[8] while a study in South Korea reported 46%.[9] According to a cohort study with 1,720 subclinical TB patients in South Korea, half of the subclinical patients were culture-positive.[21] Furthermore, a modeling study based on genomic-epidemiological analysis suggested that approximately 35% of TB transmission occurred before the appearance of symptoms, during which patients were mostly sputum-negative.[22] These study results provide supportive evidence of the role subclinical TB plays in disease transmission.

In Thailand, several studies have analyzed the proportion of subclinical TB cases that have smear and/or culture evidence of TB. Studies of healthcare workers at a university hospital found that 22.2% to 29.8% of asymptomatic individuals had a positive sputum culture for TB, categorizing them as subclinical cases with transmission potential.[13] In another study of healthcare workers at a different university hospital, 59.45% of subclinical cases were culture-positive, and 56.76% were PCR-positive.[14] The culture positivity proportion in these studies suggests that a substantial number of subclinical TB patients are highly contagious and that subclinical cases have contributed significantly to TB transmission in Thailand.

Subclinical TB patients may spread the disease through unrecognized respiratory symptoms, such as a mild or unrelated cough.[23] Moreover, although classic TB symptoms, especially coughing, are the main mechanism for spreading the disease, researchers have found that all respiratory activities, including breathing, can release aerosols containing TB pathogens. This means that patients without a cough can still

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transmit TB to others.[24] This is supported by a study in Vietnam, which revealed that subclinical pulmonary TB patients could spread the disease to household contacts.[25] Additionally, a study analyzing data from fourteen countries across Asia and Africa suggested that nearly 70% of global transmission comes from subclinical TB. This leads to the conclusion that subclinical TB contributes significantly to TB transmission at the population level, similarly to active TB.[5]

Diagnosis and Disease Control of Subclinical TB

Subclinical TB patients are either asymptomatic or exhibit symptoms or signs that go unrecognized or unacknowledged by the individual, preventing them from seeking medical attention. This can lead to disease progression, resulting in adverse consequences of tissue damage and chronic inflammation of lungs.[11] For the same reason, subclinical TB plays a significant role in spreading disease within the population. This is explained by the high prevalence and long duration of subclinical TB, as patients in this group can transmit the infection to the community for years without developing symptoms that would lead to diagnosis and treatment.[7]

To prevent such negative consequences, subclinical TB cases should be early diagnosed and treated. Thus, promoting early detection of subclinical TB would be the key solution for addressing TB disease control.[7] However, owing to the lack of noticeable symptoms, symptom-based or passive case-finding methods would fail to detect and diagnose subclinical TB.[7] A 2025 study in Singapore found that, among all sputum culture-positive TB patients, 41.6% had no cough or had a cough lasting less than 2 weeks.[26] Frascella et al.[27] found that the median percentage of subclinical TB cases in Asian countries was 56.4% of microbiologically confirmed cases. Similarly, research conducted at a university hospital in Bangkok found that nearly half of patients with both COVID-19 and TB co-infection, who were bacteriologically confirmed to have TB, did not exhibit symptoms consistent with TB.[16] This proportion indicates cases with transmission potential that would be missed if a symptom-based diagnostic approach were used. Therefore, it can be predicted that if healthcare providers continue relying solely on passive case-finding, the TB burden, both in Thailand and globally, will not be alleviated.[7]

Active case-finding through vigilant screening for subclinical TB should be implemented, as this approach will target not only symptomatic patients but also the asymptomatic population.[28] For non-infectious subclinical TB, which is negative on sputum microbiology, case identification relies on screening methods using imaging techniques, such as chest X-rays (CXR) or CT scans.[3,11] For infectious subclinical TB, in addition to imaging, microbiological testing using culture-based or PCR-based sputum testing plays a role in case-finding. It is anticipated that improved sampling techniques for respiratory aerosols could further enhance detection. Imaging still plays a role in identifying this type, as, although there are a few cases with positive sputum microbiology and normal CXR results, higher-resolution imaging can detect these cases.[11] Therefore, performing CXR, typically as part of routine health checks, is potentially useful in detecting subclinical TB.[13,29] In the case of equivocal radiographic findings, performing low-dose CT (LDCT) on the same day is recommended to reduce diagnostic delays. This recommendation is based on the fact that, despite lower radiation exposure compared to conventional-dose CT, LDCT can improve diagnostic accuracy and facilitate the diagnosis of subclinical TB. However, further studies on the application of LDCT in TB screening are needed.[30]

In conclusion, early diagnosis through proactive approaches that enable prompt treatment initiation would benefit the individual by preventing symptoms, limiting further lung damage, and addressing chronic inflammation early. This would help prevent additional illness, reduce long-term complications, and lower morbidity and mortality. Furthermore, it would also prevent potential future TB transmission within the community, ultimately leading to a decrease in the incidence and burden of TB.[11]

Conclusion

Subclinical tuberculosis (TB) represents a significant, yet often overlooked, contributor to the global TB burden.[7] Due to its asymptomatic nature and potential to spread pathogens, most subclinical TB patients experience diagnostic delays and can serve as silent sources of infection.[6] As a result, subclinical TB is as significant as active TB in contributing to both individual health deterioration and social TB transmission.[5] Early detection and treatment of subclinical TB cases is crucial for TB control and must be prioritized to make meaningful progress toward TB elimination, particularly in high-burden countries like Thailand.[7,28,30] Passive diagnostic methods, which rely solely on symptom identification, are insufficient for detecting subclinical TB. It is recommended that, in addition to passive diagnostic systems, active case-finding strategies be proactively implemented in the population. Such proactive approaches would enable early diagnosis and prompt treatment, promoting secondary prevention by limiting further pathological damage to patients. Additionally, they would encourage primary prevention of TB infection by preventing its spread, ultimately lowering incidence and the overall burden of the disease.[7,11,30] In conclusion, prioritizing the detection and treatment of subclinical TB is essential for achieving both global and Thailand's TB elimination goals.[1,2]

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