# Need for high-resolution observational cohort studies to understand the natural history of tuberculosis

*Lancet Microbe* 2024
Published Online
https://doi.org/10.1016/S2666-5247(24)00140-X

Data challenging the simplistic binary model of non-pathogenic infection with *Mycobacterium tuberculosis* (latent tuberculosis) versus active tuberculosis have resulted in renewed interest in better understanding and defining the natural history of tuberculosis.[1] In the past, latent tuberculosis was viewed as a state of bacterial containment in some inactive form because of the immune response to *M tuberculosis*. However, in recent times, people with latent tuberculosis have been recognised to include a wide spectrum of individuals, ranging from those who previously had, and spontaneously cleared, *M tuberculosis* infection to those with actively replicating bacilli.[2] As a result, instead of a clear distinction between latent infection and active disease, tuberculosis is now recognised as a spectrum with varying levels of immunological, pathological, and infectious activities.[1,3,4] Establishing clear, well understood, and accepted definitions of disease states goes beyond mere semantics. The absence of state-specific diagnostics and therapeutics stems from the lack of definitions and reference standards, indicating that the current tuberculosis spectrum model is not useful in clinical or programmatic settings. Hence, the establishment of definitions is important for directing research efforts, including the development of novel diagnostics and therapeutics, while also broadening our understanding of the natural history of tuberculosis. This approach will ensure comparability of diagnostic accuracy estimates across studies and enable evaluation of novel therapeutics for individualised treatment regimens. Focus on the middle of the spectrum, namely people with actively replicating *M tuberculosis* that will result in pathology and transmission but has not yet done so, is crucial.

One of the frameworks that aimed to capture the tuberculosis spectrum was proposed by Drain and colleagues (appendix p 1).[1] However, a limitation arises in the interpretation of incipient tuberculosis, which was defined as infection with viable *M tuberculosis* bacteria that has not yet caused clinical symptoms, radiographic abnormalities, or microbiological evidence consistent with active tuberculosis, but which might be more likely to progress to active disease.[1] Furthermore, the term incipient has been used in a contradictory manner. Some studies defined incipient tuberculosis as an inevitable progression to tuberculosis,[1,5] others referred to an undulating period during which inflammation and pathology could progress but also regress,[6] and some considered incipient tuberculosis to be the transitional phase between *M tuberculosis* infection and subclinical tuberculosis.[7] These contradictory definitions are partly explained by the fact that diagnosing people with incipient tuberculosis on the basis of the provided definition and current tools is currently impossible, circling back to the lack of reference standards hampering progress in research and policy development.

A recently published review collated different tuberculosis states from the literature to identify commonly used and agreed-upon concepts.[8] In parallel, the International Symposium on New Concepts in Early TB Disease (ICE-TB) aimed to reach consensus on a conceptual framework for the tuberculosis spectrum and consequently proposed five states: *M tuberculosis* infection, subclinical tuberculosis non-infectious, subclinical tuberculosis infectious, clinical tuberculosis non-infectious, and clinical tuberculosis infectious.[8,9] The ICE-TB framework aims to be more clinically relevant through definitions based on clinically measurable parameters (symptomology, radiology, and microbiology); however, the ICE-TB framework, which replaces the incipient terminology with subclinical non-infectious state, does not offer greater clarity on incipient tuberculosis than the Drain framework. A clear definition and associated reference standard to compare new diagnostics remain to be proposed.

Conceptual states and the ICE-TB framework should not only be applied in modelling studies,[10] which have primarily assessed progression and pathways, but also in diagnostic accuracy studies, prevalence surveys, programmatic interventions, and longitudinal cohort studies. Longitudinal cohort studies conducted during the pre-chemotherapy era with longer follow-up and detailed clinical description have enhanced our understanding of the natural history of tuberculosis (appendix p 2).[3] In fact, the existence of radiological evidence of tuberculosis without symptoms and microbiological confirmation (subclinical tuberculosis non-infectious) was acknowledged in the pre-chemotherapy era. Since then, imaging technology, assessments, and understanding of inflammation and host response have greatly advanced and enabled the detection

See Online for appendix

of more subtle changes. Despite these advancements, our understanding of how to treat subclinical tuberculosis states has not correspondingly progressed.

Detailed cohort studies have immeasurable value in characterising individual clinical, radiological, and immunological trajectories, which are crucial for understanding disease progression. The proposed conceptual frameworks described herein were all developed on the basis of data from cross-sectional assessments. Incipient TB, by definition, requires a time dimension. Given the cross-sectional nature of the ICE-TB framework, the incipient TB state is not reflected, and has been characterised as the subclinical non-infectious state. The speed of disease progression and regression and the duration of pathological and inflammatory activation across the tuberculosis spectrum are not only poorly characterised but also do not inform about one's belonging to a tuberculosis state or likelihood of progression. Descriptive detailed cohort studies using novel technologies and longer follow-up might provide insight in the trajectories of markers used to characterise tuberculosis and might shed light on progression and regression within and between tuberculosis states. The time dimension is fundamental because currently, without new tools, characterisation of tuberculosis states such as subclinical non-infectious (or incipient tuberculosis) is only possible when reviewing the history of cases before diagnosing microbiologically confirmed tuberculosis. By examining the trajectory of people who are later identified to have microbiologically confirmed tuberculosis, we will be able to identify when and if they had subclinical non-infectious tuberculosis at an earlier time. This approach is important for establishing a reference standard against which diagnostics for promptly identifying people with intermediate tuberculosis states can be evaluated.

Additional insights can be gained by incorporating easily measured clinical markers such as BMI; inflammatory markers, including C-reactive protein or white blood cell count; T-cell immune response to *M tuberculosis* antigens; RNA signatures; and advanced imaging modalities repeatedly. Importantly, rather than considering only the absolute value of a measurement, changes between timepoints, whether positive or negative, are likely to be important for understanding transition between states and trajectories.

The frequency, intensity, and duration of follow-up are crucial for cohort studies. More frequent data collection (ie, weekly or monthly) could provide more granular insights. However, intensive sampling and data collection over longer periods of time pose financial and resource challenges and might not be acceptable among participants. For follow-up studies after a discrete *M tuberculosis* exposure (ie, household contacts), more frequent data collection in the first few months of the study followed by longer intervals at later stages of follow-up might prove to be the best trade-off between granularity and cost. Furthermore, the low incidence of tuberculosis, for example among household contacts, requires recruitment and follow-up of a large number of individuals over a considerable period of time to obtain detailed insights into the few individuals who experience pathological changes. This approach requires substantial funding over a long period, which are conditions rarely fulfilled by current research funders. Nonetheless, a plethora of longitudinal studies of people at high risk of tuberculosis have already been concluded and could be combined to form an individual participant dataset. An individual-level analysis of parameters measured across studies (eg, BMI or C-reactive protein) might be a good starting point to understand progression and regression of immune response and disease activity. A list of promising markers, reached by consensus, could be generated to be measured in each cohort study. Future studies with longitudinal follow-up, particularly concerning vaccines designed to halt progression from *M tuberculosis* infection to disease, offers opportunities to conduct detailed observational analysis of early states.

Innovative analytical methods might also be of value. Despite differences in pathology, many diseases present as a spectrum with undulating activity (such as rheumatoid arthritis),[11] and methods used to characterise diseases with a broad spectrum could be applied to tuberculosis. For example, multi-state models, a statistical approach commonly used to characterise the transitions of individuals through different disease states, have been used to identify progression through intermediate states of chronic conditions or evaluate the natural history of cancer.[12] Longitudinal observational studies also present an opportunity to use more complex statistical and modelling methods such as growth mixture modelling or longitudinal latent class analysis.[13] These approaches can identify longitudinal changes and patterns within sub-populations, offering a promising approach for analysing the tuberculosis spectrum.[13] Although appealing, these novel-to-tuberculosis techniques can only be applied when conducting large well characterised longitudinal cohort studies.

In conclusion, the paradigm shift towards tuberculosis as a spectrum of disease and the creation of the ICE-TB

framework has important implications for tuberculosis research, clinical decision making, and programmatic interventions. Comprehensive longitudinal observational studies involving people at risk for tuberculosis offer the best approach to gain a clear understanding of disease trajectories and the transition of individuals between states. Notably, this approach relies on conducting longitudinal cohort studies with frequent and sustained follow-up, including among clinically vulnerable populations and people with comorbidities. Such studies should integrate novel tools and routinely collected clinical and inflammatory data. Efforts to understand the progression from infection to disease will enhance our understanding of tuberculosis and also pave the way for more effective prevention, detection, and treatment strategies, ultimately reducing the global burden of tuberculosis.

We declare no competing interests. This study was produced in the framework of the ERASE-TB project, which is part of the EDCTP2 programme supported by the European Union (grant number RIA2018D-2508 ERASE-TB). The views and opinions of the authors expressed herein do not necessarily state or reflect those of the European & Developing Countries Clinical Trials Partnership (EDCTP). Further funding was provided by the German Center for Infection Research (DZIF). CJC is funded by Wellcome Trust (203905/Z/16/Z). The funders of the study had no role in the conceptualisation and execution of the manuscript. KK, LL, and RKG developed the concept of the manuscript. LL conducted the literature review. KK, LL, CJC, CK, and RKG critically appraised the literature and developed the main message for the manuscript. LL and KK wrote the first draft of the manuscript. All authors contributed to subsequent drafts and approved the final manuscript.



*Leyla Larsson, Claire J Calderwood, Rishi K Gupta, Celso Khosa, Katharina Kranzer*
**leyla.larsson@med.uni-muenchen.de**

Institute of Infectious Diseases and Tropical Medicine, Klinikum der Ludwig-Maximilians-Universität, Munich 80802, Germany (LL, KK); The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe (CJC, KK); Faculty of Infectious and Tropical Diseases (CJC) and Department of Clinical Research (KK), London School of Hygiene & Tropical Medicine, London, UK; Institute of Health Informatics, University College London, London, UK (RKG); Instituto Nacional de Saúde (INS), Maputo, Mozambique (CK); Departments of Clinical Science and International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK (CK)

1 Drain PK, Bajema KL, Dowdy D, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clin Microbiol Rev* 2018; **31:** e00021-18.
2 Barry CE 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat Rev Microbiol* 2009; **7:** 845–55.
3 Sossen B, Richards AS, Heinsohn T, et al. The natural history of untreated pulmonary tuberculosis in adults: a systematic review and meta-analysis. *Lancet Respir Med* 2023; **11:** 367–79.
4 Richards AS, Sossen B, Emery JC, et al. Quantifying progression and regression across the spectrum of pulmonary tuberculosis: a data synthesis study. *Lancet Glob Health* 2023; **11:** e684–92.
5 Dheda K, Davids M. Latent tuberculosis infection-associated immunodiagnostic test responses as biomarkers of incipient tuberculosis: fruitful or futile? *Am J Respir Crit Care Med* 2020; **201:** 895–98.
6 Kik SV, Schumacher S, Cirillo DM, et al. An evaluation framework for new tests that predict progression from tuberculosis infection to clinical disease. *Eur Respir J* 2018; **52:** 1800946.
7 Frascella B, Richards AS, Sossen B, et al. Subclinical tuberculosis disease-a review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. *Clin Infect Dis* 2021; **73:** e830–41.
8 Zaidi SM, Coussens A, Kredo T, et al. Beyond latent and active – a scoping review of conceptual frameworks and diagnostic criteria for tuberculosis. *medRxiv* 2023: 2023.07.05.23292171.
9 Seddon JA. Inside or outside the lung: where do EPTB and paediatric TB fit in? The Union World Conference on Lung Health; Nov 17, 2023.
10 Horton KC, Richards AS, Emery JC, Esmail H, Houben RMGJ. Reevaluating progression and pathways following Mycobacterium tuberculosis infection within the spectrum of tuberculosis. *Proc Natl Acad Sci U S A* 2023; **120:** e2221186120.
11 Weyand CM, Goronzy JJ. The immunology of rheumatoid arthritis. *Nat Immunol* 2021; **22:** 10–18.
12 Meira-Machado L, de Uña-Alvarez J, Cadarso-Suárez C, Andersen PK. Multi-state models for the analysis of time-to-event data. *Stat Methods Med Res* 2009; **18:** 195–222.
13 Herle M, Micali N, Abdulkadir M, et al. Identifying typical trajectories in longitudinal data: modelling strategies and interpretations. *Eur J Epidemiol* 2020; **35:** 205–22.