Overview: Subclinical TB and its global burden

Emily Kendall, MD PhD
Associate Professor, Johns Hopkins University
School of Medicine
The Union NAR Annual TB Conference
25 Feb 2023, Vancouver
Growing interest and funding around subclinical TB

**Notice of Special Interest (NOSI): Halting Tuberculosis (TB) Transmission**

**Notice Number:** NOT-AI-22-064

**Key Dates**
- **Release Date:** September 20, 2022

**Research Objectives**
Areas of interest include but are not limited to:
- Aerobiology;
- Environmental impacts on transmission;
- Understanding non-traditional spread (e.g., without cough or other symptoms, community spread with limited contact);
- Development or assessment of new methods or tools to measure transmission;
- Understanding how the spectrum of TB disease (including asymptomatic and subclinical disease) determines the risk of transmission;
- Identifying host factors or host/pathogen interactions that encourage transmission;
- Defining characteristics or sub-populations of Mtb strains that impact transmission, including the role of Mtb strain heterogeneity;
- Studies of transmission in high-risk groups (e.g., healthcare workers, congregate settings);
- Understanding the role of asymptomatic, pre-symptomatic and differentially culturable TB in transmission;

**Purpose**
To support travel for researchers from TB-affected countries to a research symposium on the topic of subclinical tuberculosis in Cape Town, January 2023
“Subclinical TB”: What are we talking about?

It’s TB (i.e., a disease).  
* M. Tuberculosis* is causing macroscopic pathology (e.g. visible by imaging)

It lacks clinical signs or symptoms.  
* Usually, symptom negative as judged by “standard” TB symptom screens.*  
- Aligns with data from prevalence surveys  
* Alternative criteria:*  
  - Negative for any symptom (even intermittent, subtle, or misattributed) or physical exam finding,  
  - Or, Not seeking care for symptoms  

It may be sputum culture+ (and potentially infectious).  
* Subclinical TB can even be smear positive.*  
* Aerosol generation doesn’t require cough.*  
* But sputum-negative, x-ray positive disease can also be classified as “subclinical TB”*
Even within sputum-positive subclinical disease, there’s a wide range of symptoms, pathology, and infectiousness. Arrows can move both ways (not necessarily an early stage, nor destined to progress to symptoms). Detection and treatment are possible (though how to approach them is uncertain).

*NB: These names are evolving and categories are being clarified – stay tuned!*
How much (infectious) subclinical TB is there?

*Prevalence surveys and other population-based screening provide estimates*

In prevalence surveys (with symptom or CXR triage), ~50% of sputum+ TB is subclinical

This % would be even greater if everyone got sputum testing

And that’s 50% of a large undiagnosed TB burden!
How long do patients spend with (infectious) subclinical TB?

High P:N ratios + large % subclinical = lots of potentially-infectious time without symptoms

Estimated 4-14 months culture+ before symptom onset

But possibly less for the mildest cases, after accounting for symptom-and smear-dependent trajectories
Summary: The global burden of (infectious) subclinical TB

50% or more of bacteriologically positive TB lacks classic symptoms.

Many patients who develop symptoms had first spent many months with subclinical but potentially infectious TB.

Subclinical TB is a heterogeneous state with variable features and future course.

Key questions
- What does it contribute to transmission?
- What are its clinical and diagnostic features?
- What does it mean for TB care and TB elimination goals in North America?