

## Title

### **TB transmission in the “subclinical” period. Could unrelated cough play a role?**

## Authors

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## Body (886 words 12 ref)

*Mycobacterium tuberculosis* (Mtb) is the leading cause of death from an infectious disease globally and is estimated to have infected approximately 25% of the world's population.<sup>1</sup> To achieve the dramatic reductions in tuberculosis (TB) incidence required to meet consensus targets, interventions that minimise Mtb transmission will be critical.

The long infectious period of TB is becoming increasingly apparent and is likely a major factor in the pathogen's success. If granulomatous control fails, pulmonary TB typically progresses into a bronchogenic pneumonia (sometimes visible radiographically), resulting in bacilli in respiratory secretions (the basis of diagnosis via sputum examination).<sup>2</sup> The development of cough facilitates transmission and, along with other symptoms, increases subjective awareness of illness, encouraging healthcare-seeking behaviour.

Prevalence/notification ratios suggest the duration of culture-positive disease prior to passive case detection may be as long as 18 months, which corresponds with recent evidence that the emergence of a TB transcriptional profile in blood is detectable over a similar period.<sup>3-5</sup> However, patients often report symptoms only in the 2-3 months before diagnosis.<sup>6</sup>

The premise of active case finding (ACF) for TB is to identify individuals with infectious TB who have not yet sought care, thus treating disease earlier, reducing risk of death for individuals and, critically, the period of transmission in the population. Active case finding often uses symptom screening (e.g. cough, fever, night sweats and weight loss) to decide who to test for TB. However, in recent TB prevalence surveys in Asia, TB symptoms were not reported by a majority (up to 80%) of individuals with bacteriologically confirmed infectious

TB.<sup>5</sup> It is perhaps not surprising that a systematic review of ACF studies found limited evidence for benefit to individual or population outcomes.<sup>7</sup> One explanation for this may be that TB symptom screening, misses individuals who either don't report or have alternative explanations for their symptoms, but nevertheless contribute to transmission. Their contribution may be particularly important if they cycle through periods of higher infectiousness, or have significant social contact. Conceptual frameworks that only link TB transmission to symptoms caused by TB, omitting the possibility of transmission by those with no or unrelated respiratory symptoms, may lack utility in understanding TB epidemiology and designing interventions.

Transmission of TB occurs via aerosolisation of infectious droplet nuclei, which are most efficiently produced by coughing. Infectiousness depends on both droplet nuclei production rates and concentration of bacilli in respiratory secretions. Frequency of spontaneous coughing in those without respiratory pathology is low and therefore individuals with subclinical TB (with less advanced disease) have traditionally been considered uninfected.

However, TB transmission during the subclinical phase may be enhanced by either acute or chronic coughing resulting from conditions unrelated to TB pathology. The prevalence of chronic productive cough (present for at least three months of the year for at least two consecutive years) is 10-15% in European countries.<sup>8</sup> This prevalence may be greater in populations with high levels of indoor, outdoor or occupational air pollution (e.g. 50% of miners without silicosis report chronic cough), which are commoner in high-burden TB countries. Individuals with chronic cough may cough 50 times per hour in contrast to twice per hour in those without respiratory pathology.<sup>9</sup> A systematic review of TB diagnostic delay identified chronic cough as a major contributor to delay, potentially due to patient normalization to this symptom.<sup>6</sup> No studies have directly explored the contribution of chronic cough to TB transmission, however household contacts of smokers with TB have consistently been shown to be at increased risk of latent TB infection.<sup>10</sup> Although this may reflect the effect of smoke exposure on the innate immune system, it could also be accounted for by increased chronic cough in smokers. Bouts of acute cough may also contribute to transmission. The average TB case might be expected to have two or three episodes of upper respiratory tract infection (URTI) during their period of subclinical disease (higher if co-habiting with young children).<sup>11</sup> After some viral URIs, as many as 16% of people with no prior respiratory pathology cough for more than two weeks.<sup>12</sup> TB might piggyback transmission with viral URIs, which could be a contributing factor to the seasonality of TB.

The potential for the long period of subclinical TB to contribute to transmission (four to six times as long as the recognised 'symptomatic' period) and be amplified by chronic cough and acute cough is illustrated in the Figure. This has implications for TB epidemiology and control. Screening approaches for ACF in certain populations may need to rely more on radiography or utilize screening questionnaires focussing on chronic respiratory symptoms, regardless of cause. Common causes of chronic cough, both infectious and non-infectious, may provide additional targets for intervention in TB endemic communities and control measures for viral URIs may also benefit TB control.

We need to develop a better understanding of the importance of these factors. Mathematical modelling provides tools to explore the implications of pre-clinical natural history for epidemiology and control. However, further empirical studies are needed to demonstrate and quantify the contribution of the subclinical period to TB transmission, which may be facilitated by the increasing use of whole genome sequencing.

We live an era where accelerated progress towards ending TB is demanded, but old approaches repeatedly fail to deliver. Fresh thinking is required, and a better understanding of TB transmission during the subclinical phase could open new avenues of attack.

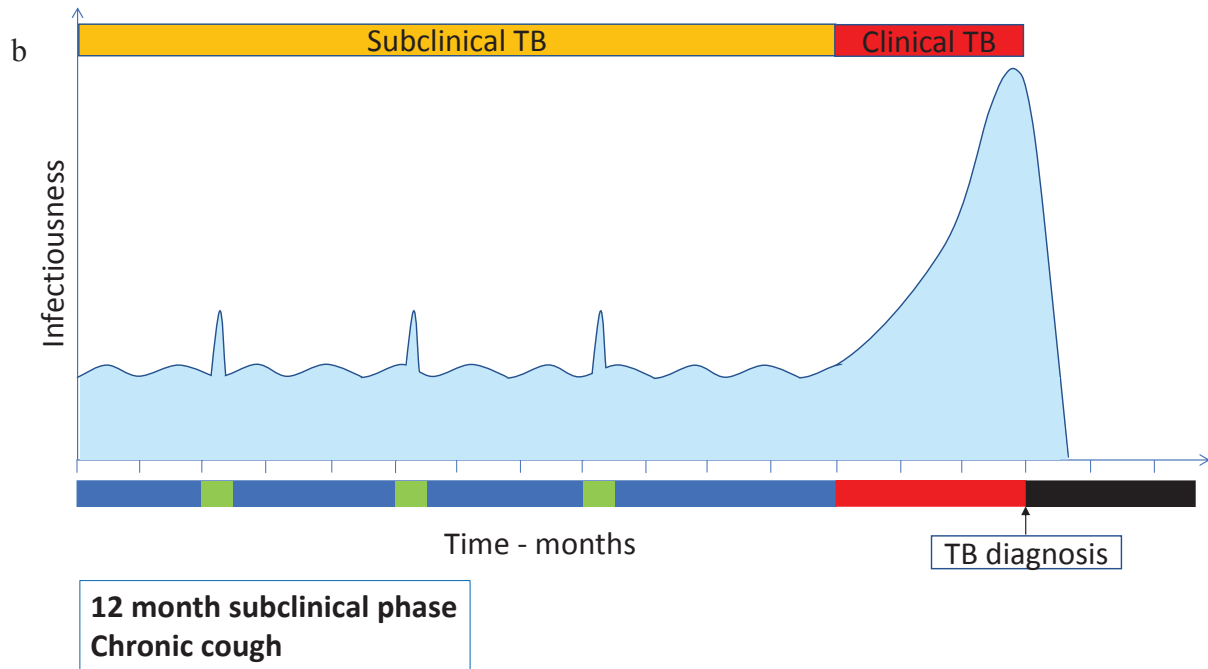
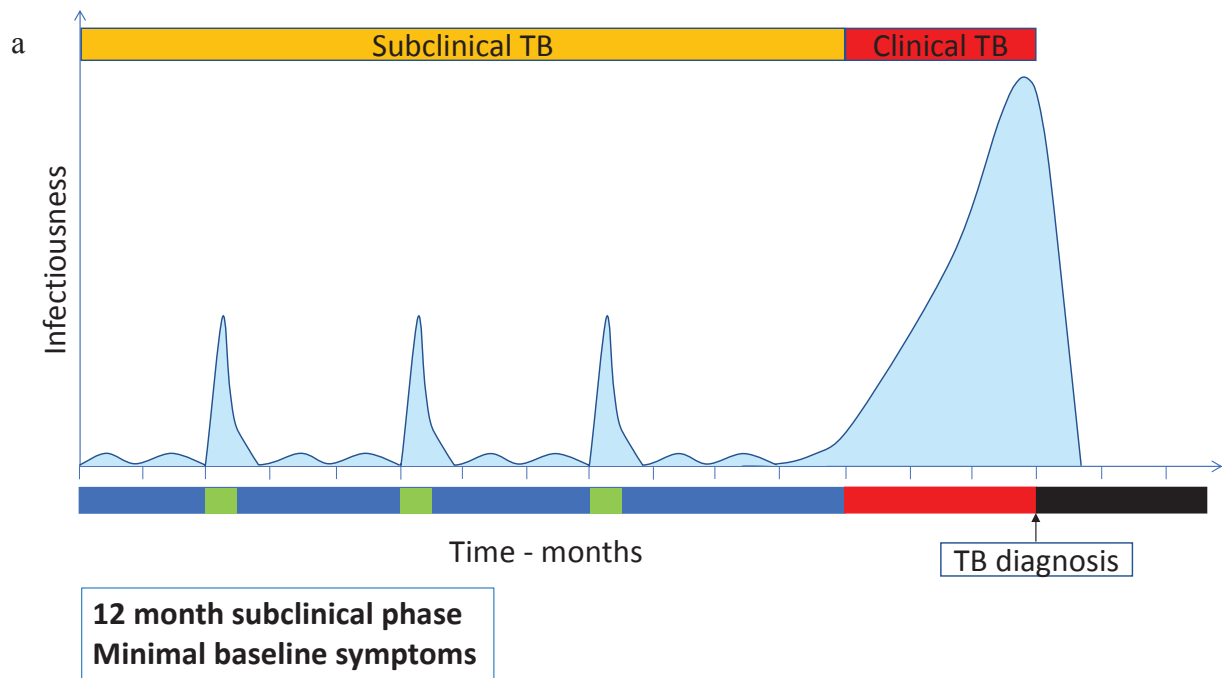
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**Figure**



- |   |                        |   |                          |
|---|------------------------|---|--------------------------|
|  | Baseline symptoms      |  | Symptoms related to URTI |
|  | Symptoms related to TB |  | Period of TB treatment   |

### **Figure: Transmission potential in subclinical and clinical TB**

Cartoons show how infectiousness may change over time in two scenarios. Infectiousness on the  $y$ -axis is considered to be a function of the rate of droplet nuclei production (through coughing) and the concentration of bacilli in respiratory secretions. The duration of subclinical disease (culture positive with baseline symptoms) is 12 months and clinical disease with symptoms related to TB is three months. Area under curve represents transmission potential. Identifying individuals as early as possible in clinical phase of TB may still miss transmission in the subclinical phase.

- a) Shows a scenario in which baseline symptoms are minimal with 3 episodes of upper respiratory tract infection (URTI).
- b) Shows a scenario in which a chronic cough unrelated to TB is present with 3 episodes of URTI.