DOES SUBCLINICAL TB HAVE A ROLE IN TRANSMISSION?

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Learning objectives

1. Participants will learn about the current knowledge of subclinical TB transmission, how it clarifies and complicates our global understanding of TB transmission.

2. Participants will learn about approaches to measuring transmission potential of subclinical TB, challenges, and opportunities.
Outline

• What is subclinical TB?
• Problem statement(s)
• Minimum requirement for TB transmission
• Do individuals with subclinical TB expel organisms?
• Role of subclinical TB in ongoing transmission?
• Looking ahead
WHAT IS SUBCLINICAL TB?
Definition:
- 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 (Drain et al. CMR 2018)

Practical definition:
- A disease state that is detectable by sputum culture or chest radiography but during which patients would respond “no” if asked whether they are currently experiencing any TB symptom (cough, fever, night sweats, or weight loss) (Kendall et al. AJRCCM 2021).

- Individuals likely unaware of their TB status, unlikely to seek care, and likely missed by health care facility performing symptom-screen only.

Restating Dr. Kendall’s point: these definitions/categories are evolving
Asymptomatic transmission has precedence

- Number of examples of asymptomatic transmission of infection (viral, parasitic as well as bacterial). In fact, likely the norm rather than the exception.

- From not invasive (e.g., MRSA carriage) to infections causing mild symptoms and where disease is not recognized (e.g., SARS-CoV-2).

- Asymptomatic transmission events are often difficult to detect due to recognition and sampling.

- What is asymptomatic or subclinical can (has) been debated; blurry lines do exist. TB a commensal?
Existing data, from large prevalence surveys and active case finding studies, have indicated that subclinical TB comprises a large fraction of prevalent disease at the population level. Evidence indicates that these individuals have meaningful infectious potential, follow a heterogeneous clinical trajectory, and are difficult to diagnose using passive systems. Impeding the reach of End TB goals. Exclusive focus on symptom-driven diagnosis is insufficient to achieve targets for reducing TB incidence.

Investments needed to scale current diagnostics (e.g., Xpert Ultra, digital X-ray), and introduce novel diagnostics (e.g., face mask, tongue swabs, VOC).
Is Passive Diagnosis Enough?
The Impact of Subclinical Disease on Diagnostic Strategies for Tuberculosis

David W. Dowdy\textsuperscript{1,2}, Sanjay Basu\textsuperscript{3,4}, and Jason R. Andrews\textsuperscript{5}

\begin{itemize}
  \item Subclinical Phase
  \item Pre-diagnostic Phase
  \item Diagnostic Phase
\end{itemize}

\begin{itemize}
  \item Symptoms Trigger Care-Seeking
  \item Symptoms Noticeable
\end{itemize}

\begin{itemize}
  \item Onset of Infectiousness
  \item Time
  \item Death or Effective Treatment
\end{itemize}

\textbf{13.5 months} infectiousness prior to seeking care

Dowdy et al AJRCCM 2013
## Community prevalence surveys to determine undiagnosed TB

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Number screened</th>
<th>% with sputum</th>
<th>%HIV</th>
<th>Number Culture +ve</th>
<th>Prev. undiag. TB</th>
<th>Smear+</th>
<th>Asympt</th>
<th>CXR - Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>den Boon et al</td>
<td>S.Africa - 2002</td>
<td>2,608</td>
<td>45 %</td>
<td>NK</td>
<td>27</td>
<td>1.0%</td>
<td>63%</td>
<td>33%</td>
<td>4%</td>
</tr>
<tr>
<td>Wood et al</td>
<td>S.Africa - 2005</td>
<td>762</td>
<td>100 %</td>
<td>23 %</td>
<td>12</td>
<td>1.6%</td>
<td>50%</td>
<td>67%</td>
<td>ND</td>
</tr>
<tr>
<td>Corbett et al</td>
<td>Zimbabwe - 2006</td>
<td>12,426</td>
<td>81 %</td>
<td>21 %</td>
<td>66</td>
<td>0.7%</td>
<td>61%</td>
<td>NK</td>
<td>ND</td>
</tr>
<tr>
<td>Ayles et al</td>
<td>Zambia - 2005</td>
<td>8,325</td>
<td>91 %</td>
<td>29 %</td>
<td>79</td>
<td>1.0%</td>
<td>28%</td>
<td>10%</td>
<td>ND</td>
</tr>
<tr>
<td>van't Hoog et al</td>
<td>Kenya - 2006</td>
<td>20,566</td>
<td>99 %</td>
<td>17 %</td>
<td>119</td>
<td>0.6%</td>
<td>39%</td>
<td>40%</td>
<td>6%</td>
</tr>
<tr>
<td>Shapiro et al</td>
<td>S.Africa - 2009</td>
<td>983</td>
<td>80 %</td>
<td>14 %</td>
<td>4</td>
<td>0.4%</td>
<td>NK</td>
<td>NK</td>
<td>ND</td>
</tr>
</tbody>
</table>

Adapted from Corbett and MacPherson IJTL 2013
Community-wide Screening for Tuberculosis in a High-Prevalence Setting


- Annual house-to-house, community-wide screening (regardless of symptoms) was associated with a 44% lower prevalence of tuberculosis than routine passive case finding after 3 years.

- This result provides important proof-of-principle that community-based active case finding in conjunction with improved diagnostic tools (e.g., the Xpert MTB/RIF assay) can help achieve the case reduction targets set forth in the END TB Strategy by the WHO.
MINIMUM REQUIREMENT FOR TB TRANSMISSION
• Persons need to share airspace (for what duration?)
• Index needs to generate bioaerosols that harbor live/viable *Mtb* and inhaled by contact.
• Productive flight of bioaerosol, highly dependent on host and environment

• Bacillary burden generally impacts relative infectiousness (sputum-positive, Xpert-positive, symptomatic, cavitary disease)
• Cough frequency, talking, singing and more recently tidal breathing

• TiBr is likely to contribute more than 90% of the daily aerosolized Mtb from symptomatic Tb patients irrespective of cough frequency.

• No association seen between the quantity of exhaled Mtb and cough frequency, sputum grade, or severity of X-ray.

• Smear-negative culture-positive tuberculosis appear responsible for about 17% of tuberculosis transmission
DO INDIVIDUALS WITH SUBCLINICAL TB EXPEL ORGANISMS?
YES and often! A few examples

- **CORTIS**: Large biomarker-guided TB preventative therapy RCT study found more than 1% of HIV-uninfected community volunteers had previously undiagnosed, microbiologically confirmed tuberculosis at screening, more than 80% of which was asymptomatic.

- Large simultaneous clinic and community survey based on culture only and culture and Xray (Community): Most participants with Mtb culture-positive sputum were asymptomatic.

- Recurrent subclinical TB among HIV: Follow up identified recurrent TB; 35.4% of these were subclinical, 82.4% were culture positive; 35% resolved TB spontaneously.

- Numerous prevalence surveys...
Subclinical TB is underestimated as a contribution to the TB burden.

57.8% of TB cases did not report any TB symptoms at the time of survey, yet bacteriologically positive for TB (falls within the range of survey in Asia 40-79%).

More common among HIV-negative individuals.

Recent experience from South Africa

- Subclinical TB is underestimated as a contribution to the TB burden.
- 57.8% of TB cases did not report any TB symptoms at the time of survey, yet bacteriologically positive for TB (falls within the range of survey in Asia 40-79%).
- More common among HIV-negative individuals.
• Owing to the robust reporting and surveillance systems, low incidence setting do not conduct population-level prevalence surveys.

• Estimates of subclinical TB among bacteriologically confirmed cases in low incidence settings? Probably data from higher risk groups.
ROLE OF SUBCLINICAL TB IN ONGOING TRANSMISSION? EXAMPLES?

(spoiler alert: not many)
Re-analysis of TB prevalence and tuberculin surveys in Vietnam found significantly elevated risks for TST positivity in children living with patients with subclinical, smear-positive TB, compared with those living with individuals without TB.

A population-based cohort of TB patients in Valencia Region, Spain, systematically sequenced the whole genomes of culture-positive isolates and identified transmission clusters. They found in many cases the index case is likely either not sampled or not the first diagnosed. For several transmitters, transmission likely happened well before diagnosis and symptom onset.
Clustering & transmission inference

SNP-difference based thresholds

- ✓ straightforward interpretation
- ✓ low-transmission settings with robust case-finding

x threshold depends on transmission, sampling, mutation rate

Bayesian inference & transmission trees

\[
P(\theta, N_{eg}, T | P) \propto P(P | N_{eg}, T) P(T | \theta) P(\theta) P(N_{eg})
\]

- ✓ multiple data sources for inference: genomic and case timing
- ✓ incorporates missingness

Walker et al (2014)

Transmission directionality inferred via SNP accumulation

Schürch et al (2010)

Xu et al (2019)
Detection and Quantification of Differentially Culturable Tubercle Bacteria in Sputum from Patients with Tuberculosis

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Designed a study to inform how culture methods affect the ability to study transmission within the household, with important broader implications for studying TB transmission in community settings.

HoTT-DCTB funded NIAID/NIH (R01AI147349)
MPIs: Drs Bavesh Kana and Neil Martinson
Phylogenomic analysis with epidemiologic data can help infer who infected whom.

• Phylogenetic analysis suggest HHC1 likely infected index and secondary household member.

• Index enrolled 5 days prior to household screening.

• Health seeking behavior highly subject to host characteristics (in this example all participants were HIV-uninfected).

• Phylodynamic analysis can help resolve order and directionality.
Looking ahead

• More empirical studies are needed to show and quantify the contribution of the subclinical period to tuberculosis transmission (individuals and population level). Many studies are underway so stay tuned!
• Can Antigen-Specific T-Cell Activation Distinguishes between Recent and Remote Tuberculosis Infection
  Cheleka A. M. Mpande¹, Munyaradzi Musvosvi¹, Virginie Rozot¹, Boitumelo Mosito¹, Timothy D. Reid¹, Constance Schreuder¹, Tessa Lloyd¹, Nicole Bilek¹, Huang Huang², Gerlinde Obermoser², Mark M. Davis², Morten Ruhwald³,⁴, Mark Hatherill¹, Thomas J. Scriba¹*, Elisa Nemes¹*, and the ACS Study Team
  ¹South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, Division of Immunology, Department of Pathology, University of Cape Town, Cape Town, South Africa; ²Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, California; ³Statens Serum Institute, Copenhagen, Denmark; and ⁴Foundation of Innovative New Diagnostics, Geneva, Switzerland
• How diagnostics? Targeted case-finding?
• Once you find them what should you do? How to treat?
• Implications for low incidence settings….is the effort “worth” it?
Thank you

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