Subclinical TB: insights from mathematical models

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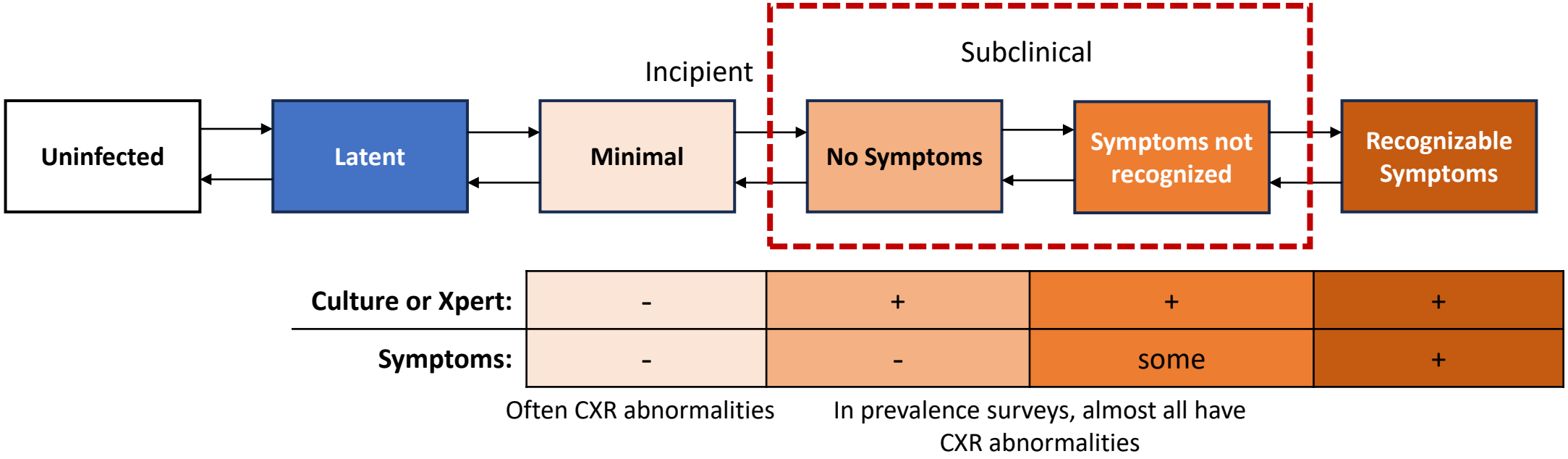
Overview

1. **Introduction and motivation**
2. What can models tell us about subclinical TB? A review of modeling studies.
   A. Duration and clinical course of subclinical TB
   B. Infectiousness of subclinical TB
   C. Importance of finding and treating subclinical TB
3. Summary and outstanding questions

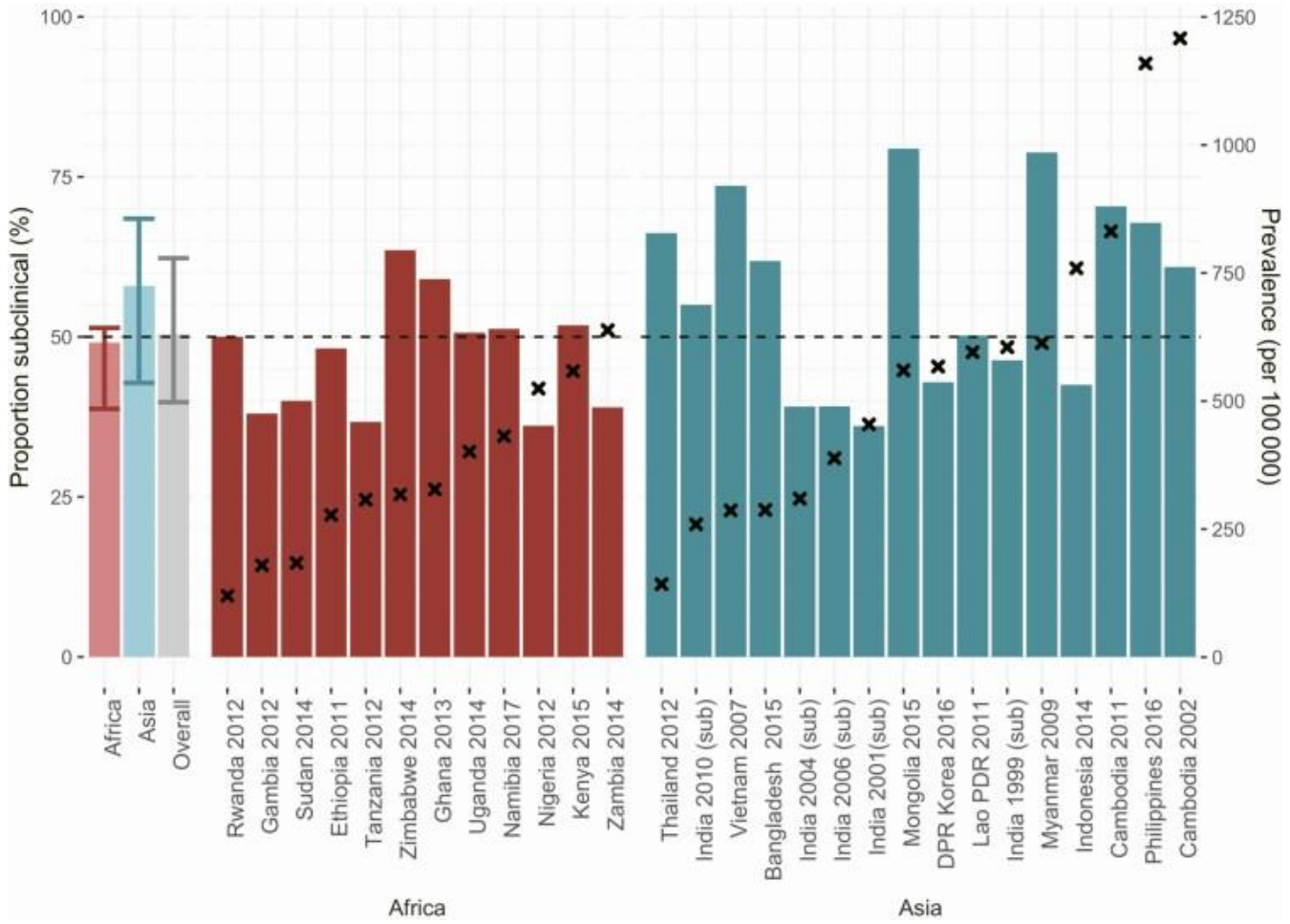
What is subclinical TB?



Adapted from: *Kendall, Shrestha, & Dowdy. The Epidemiological Importance of Subclinical Tuberculosis: A Critical Reappraisal. AJRCCM 2021.*
Frascella et al. Subclinical Tuberculosis Disease—A Review & Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology. CID 2021

What do we know about subclinical TB?

- People w/ subclinical TB make up a large % of all prevalent TB
  - 35-75% of undiagnosed cases



X's indicate overall prevalence.

Frascella et al., Subclinical Tuberculosis Disease-A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology. CID 2021.

What do we know about subclinical TB?

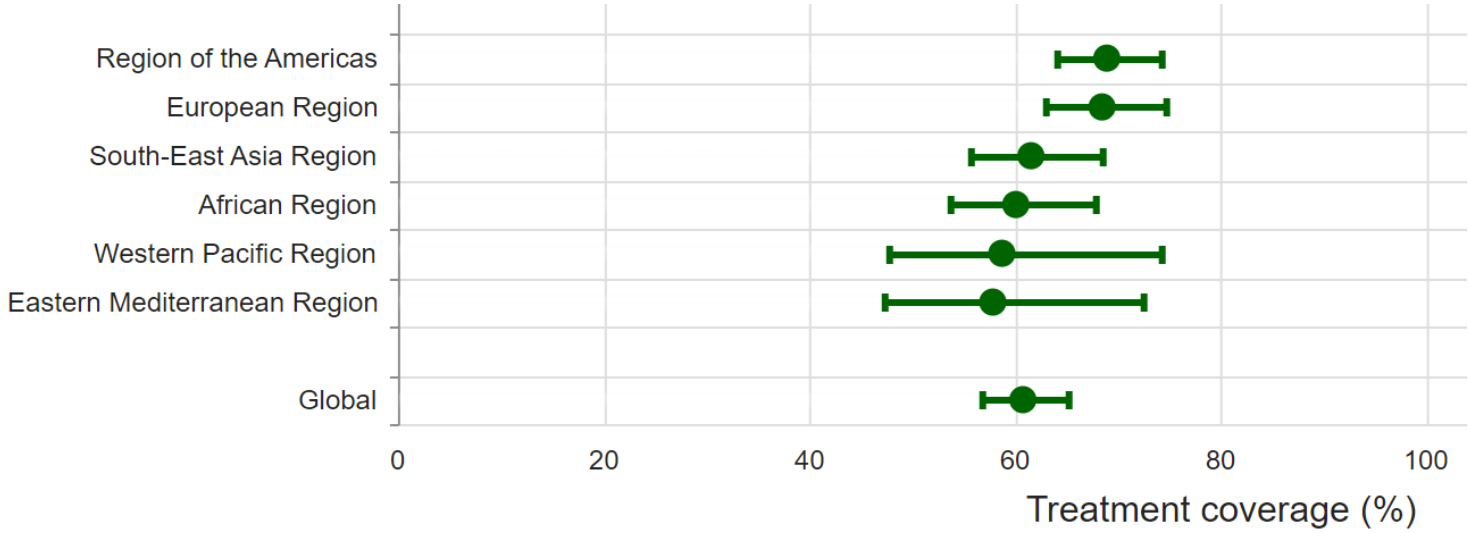
- People w/ subclinical TB make up a large % of all prevalent TB.
- They have the potential to be infectious.

Evidence on the infectiousness of subclinical TB is based on:

- Bacteriologically-positive sputum
  - 25-50% of people w/ subclinical TB are smear-positive
- Face mask sampling & cough aerosol studies
- Household contact studies
- Molecular epidemiology studies

What do we know about subclinical TB?

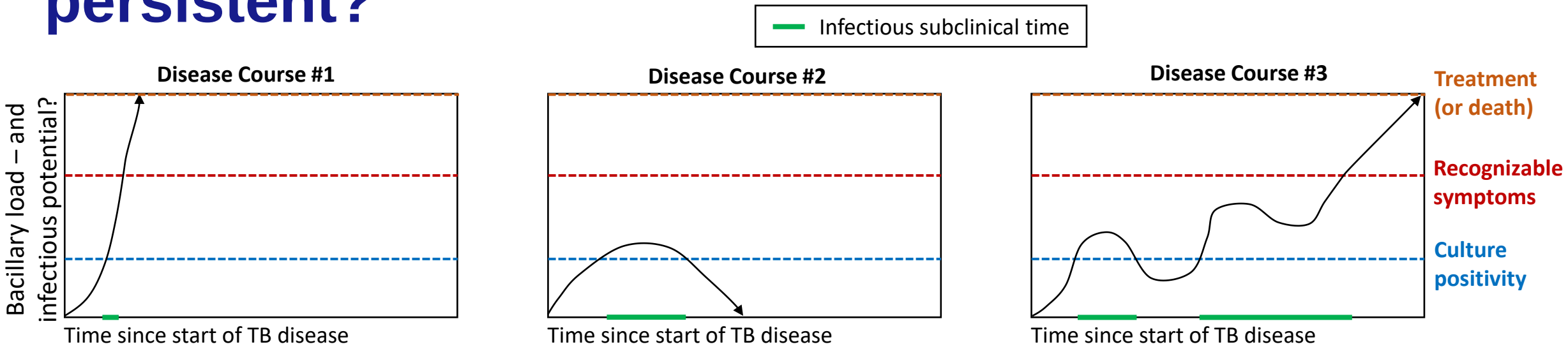
- People w/ subclinical TB make up a large % of all prevalent TB.
- They have the potential to be infectious.
- They are generally not detected by the health system.



WHO. 2022 Global TB Report.

How important is it to find and treat people with subclinical TB?

Can infectious TB be subclinical but persistent?



If most people w/ TB quickly develop symptoms and are treated…

Or quickly resolve without become very infectious…

But if TB can persist, be infectious, and stay largely subclinical for long durations…

…then finding & treating subclinical TB may have little impact.

…then finding & treating subclinical TB may be crucial to reduce transmission.

Adapted from: *Kendall, Shrestha, & Dowdy. The Epidemiological Importance of Subclinical Tuberculosis: A Critical Reappraisal. AJRCCM 2021.*

Modeling methods overview

Develop

Design a model that replicates pop. dynamics or outcomes of interest

- Model the natural history of TB
- Model population-level TB transmission

Calibrate

Find model parameters that yield output consistent w/ empirical data

Longitudinal Data:

- Household contacts
- Outcomes w/ TB infection
- Historical data (outcomes w/ untreated TB)

Cross-Sectional Data:

- Prevalence surveys
- Notifications
- Mortality & incidence estimates

Simulate

Use the calibrated model to simulate outcomes of interest

- Trajectories
- Duration of disease
- Outcomes (deaths, resolutions)
- Impact of interventions

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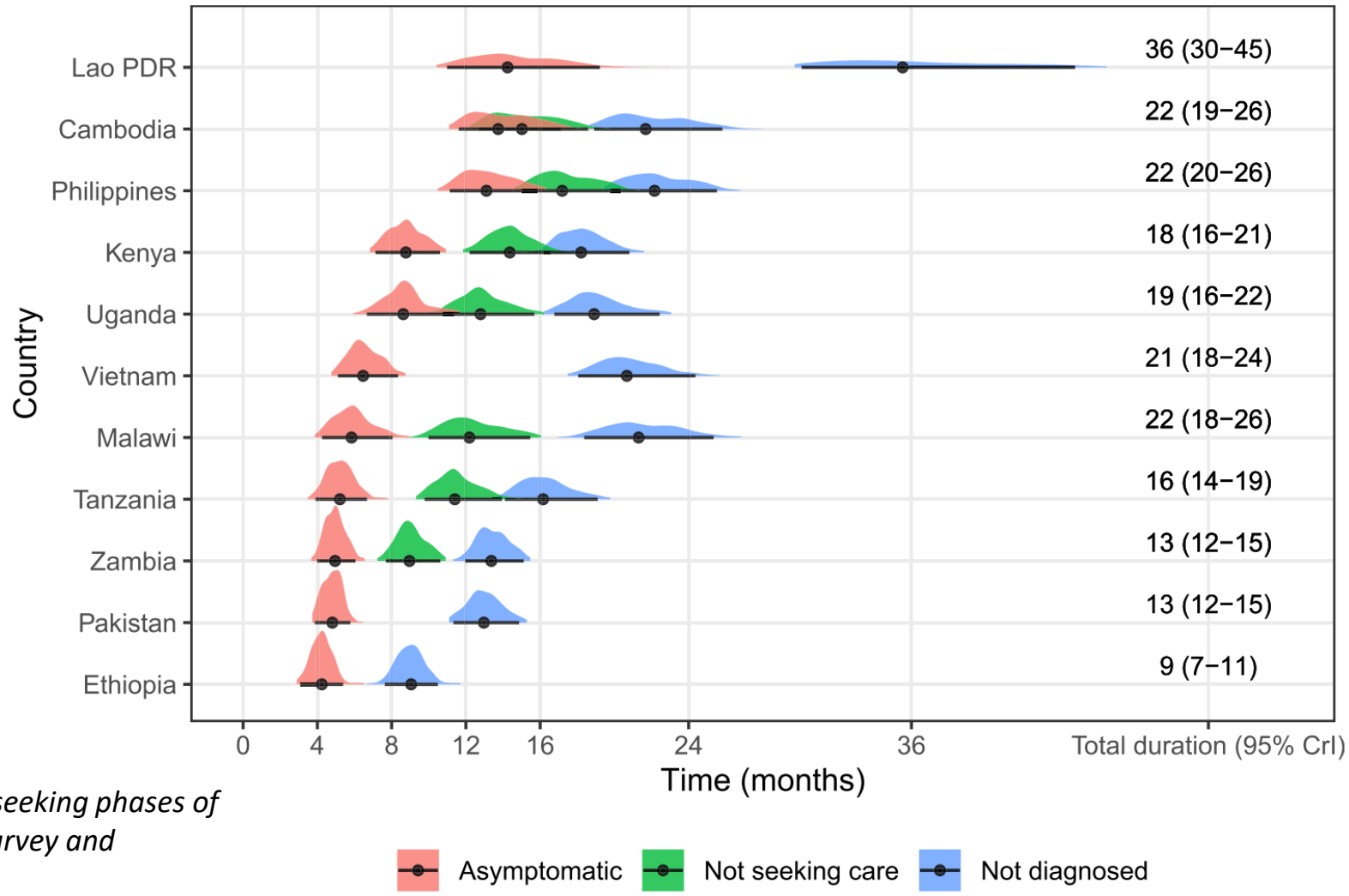
Duration of subclinical TB

Model of symptom progression, care seeking, treatment among incident TB cases:

- Average durations of disease phases:
  - **Subclinical: 6 months**
  - Care-seeking before diagnosis: 1-7 months
  - Total: 1-2 years
- 27-63% of time spent subclinical
- **75-90% of cases eventually develop symptoms.**

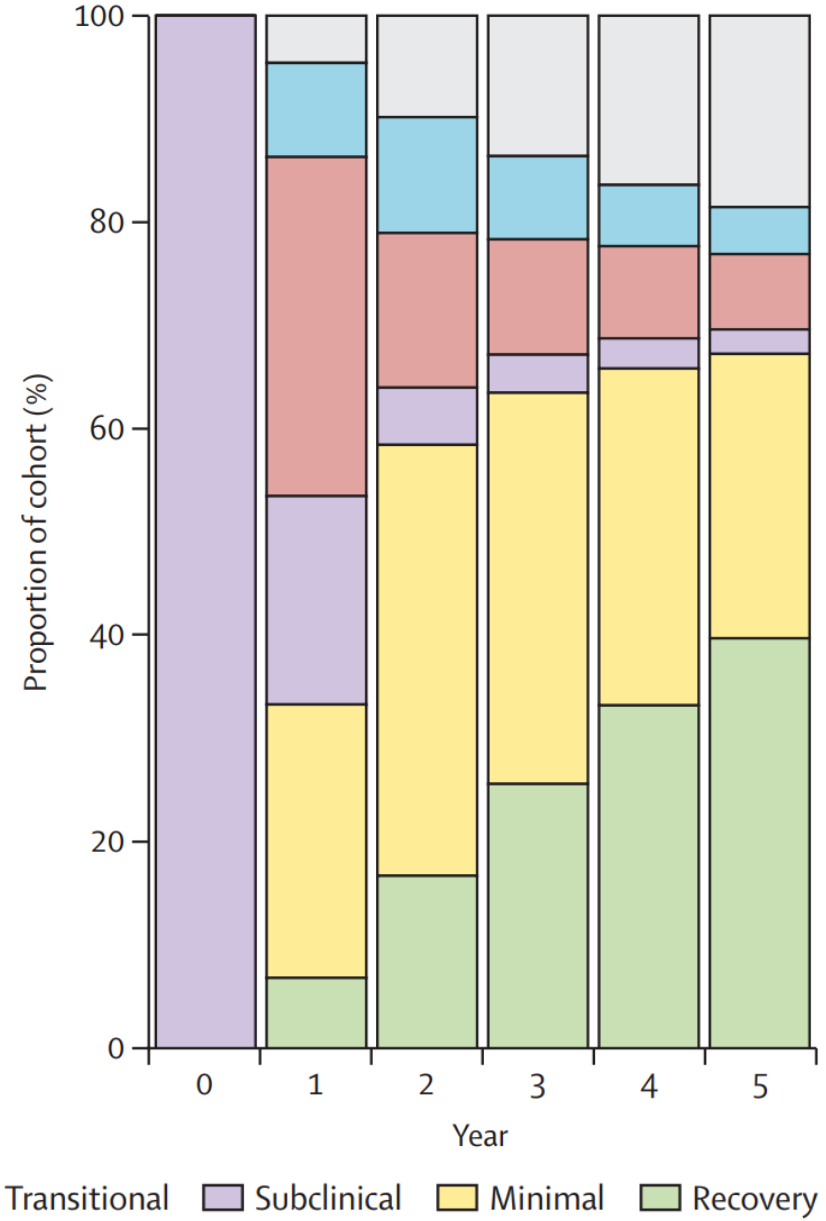


Ku et al. Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data. BMC Medicine 2021.

Duration of subclinical TB

Model of heterogeneity in the clinical course of untreated subclinical TB:

- **Median duration of TB: 7 months**
  - vs. 17 months in those w/ clinical TB
- **50% develop symptoms**
- 18% mortality
- 67% regression (to minimal or recovery)
- Passive detection & treatment do not substantially reduce TB duration (among those w/ subclinical disease).



Richards et al. Quantifying progression and regression across the spectrum of pulmonary tuberculosis: a data synthesis study. Lancet Global Health 2023.

Duration of subclinical TB

Model of heterogeneity in the clinical course of prevalent subclinical TB with passive detection & treatment:

People with each type of TB at a cross-sectional point in time

Average cumulative months spent:	Smear–Negative Subclinical	Smear–Positive Subclinical	Smear–Negative Symptomatic	Smear–Positive Symptomatic	Total Population
Smear–Negative Subclinical	2.5 [1.8–4.7]	0.3 [0.0–0.7]	2.0 [1.1–3.8]	0.2 [0.0–0.5]	1.7 [1.1–3.2]
Smear–Positive Subclinical	0.9 [0.4–1.5]	9.6 [5.9–15.3]	1.2 [0.5–2.0]	4.4 [0.3–8.8]	3.0 [1.4–4.5]
Smear–Negative Symptomatic	0.8 [0.4–1.7]	0.1 [0.0–0.3]	3.1 [2.1–5.1]	0.1 [0.0–0.3]	1.0 [0.5–2.0]
Smear–Positive Symptomatic	0.7 [0.3–1.1]	5.9 [3.7–8.9]	1.3 [0.7–2.0]	6.3 [3.9–9.7]	2.5 [1.4–4.1]
Total with TB (any)	4.8 [3.3–8.4]	15.9 [11.1–23.4]	7.6 [5.3–10.9]	11.0 [6.2–16.0]	8.2 [5.9–10.9]

Months: 12, 8, 4

- **87% resolved**
- 2% mortality

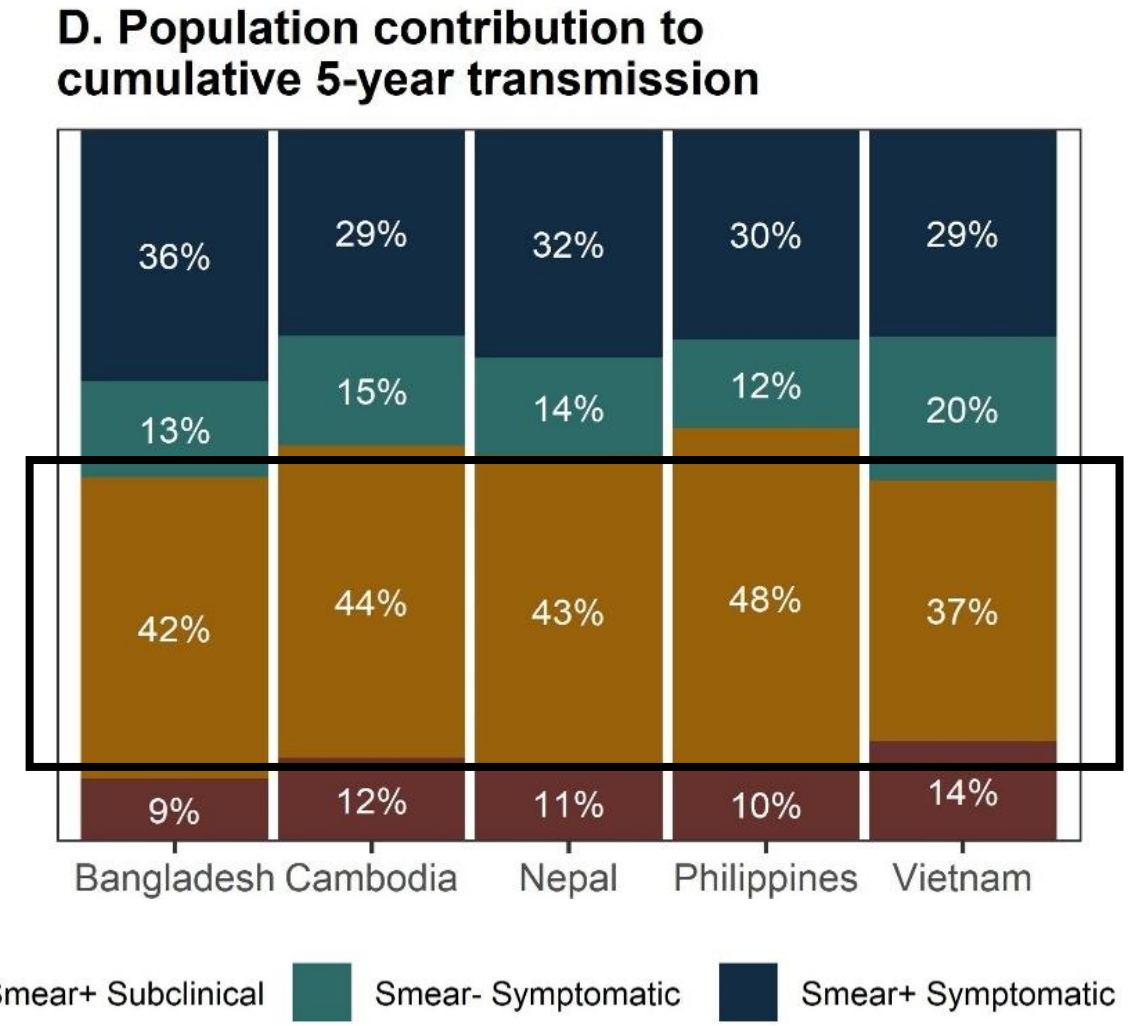
- **96% developed symptoms**.
- 17% mortality.
- Most were eventually treated.

Ryckman, Dowdy, & Kendall. Infectious & clinical tuberculosis trajectories: Bayesian modeling with case finding implications. PNAS 2022.

Infectiousness of subclinical TB

Paired simulated trajectories with evidence on relative infectiousness of different types of TB.

- **Smear-positive subclinical TB:** only 10-20% of prevalent TB but **37-48%** of secondary cases
- **Smear-negative subclinical TB:** 40-55% of prevalent TB but only **9-14%** of secondary cases
- **Symptomatic TB:** 30-45% of prevalent TB and **39-50%** of secondary cases.

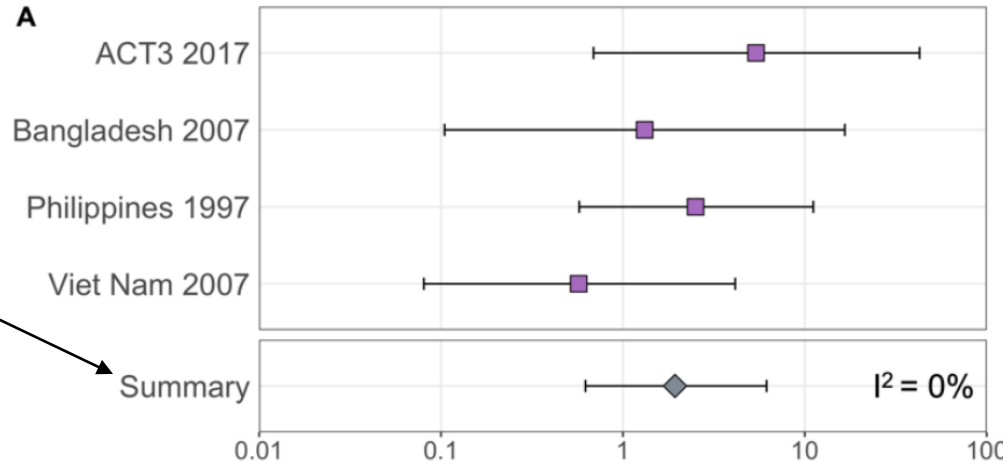


Ryckman, Dowdy, & Kendall. Infectious & clinical tuberculosis trajectories: Bayesian modeling with case finding implications. PNAS 2022.

Infectiousness of subclinical TB

Paired estimates of subclinical TB duration (from *Richards et al.*) with evidence on infectiousness from household contact data:

- Subclinical TB is 1.9 [0.6-6.2] times as infectious as symptomatic TB
- An estimated **68% of global transmission comes from subclinical TB**
  - Range across countries: 45-84%



Infectiousness of subclinical TB vs. symptomatic TB (per unit time)

Preprint by Emery et al. Estimating the contribution of subclinical tuberculosis disease to transmission – an individual patient data analysis from prevalence surveys. medRxiv 2022.

Key findings: duration and infectiousness of subclinical TB

1. Duration of subclinical TB: **~5-7 months**
   - And many (most?) spontaneously resolve.
2. But a small % of subclinical TB may last much longer
   - **Smear-positive subclinical TB: ~16 months**, half without symptoms
3. Subclinical TB may account for around **half of all transmission**.

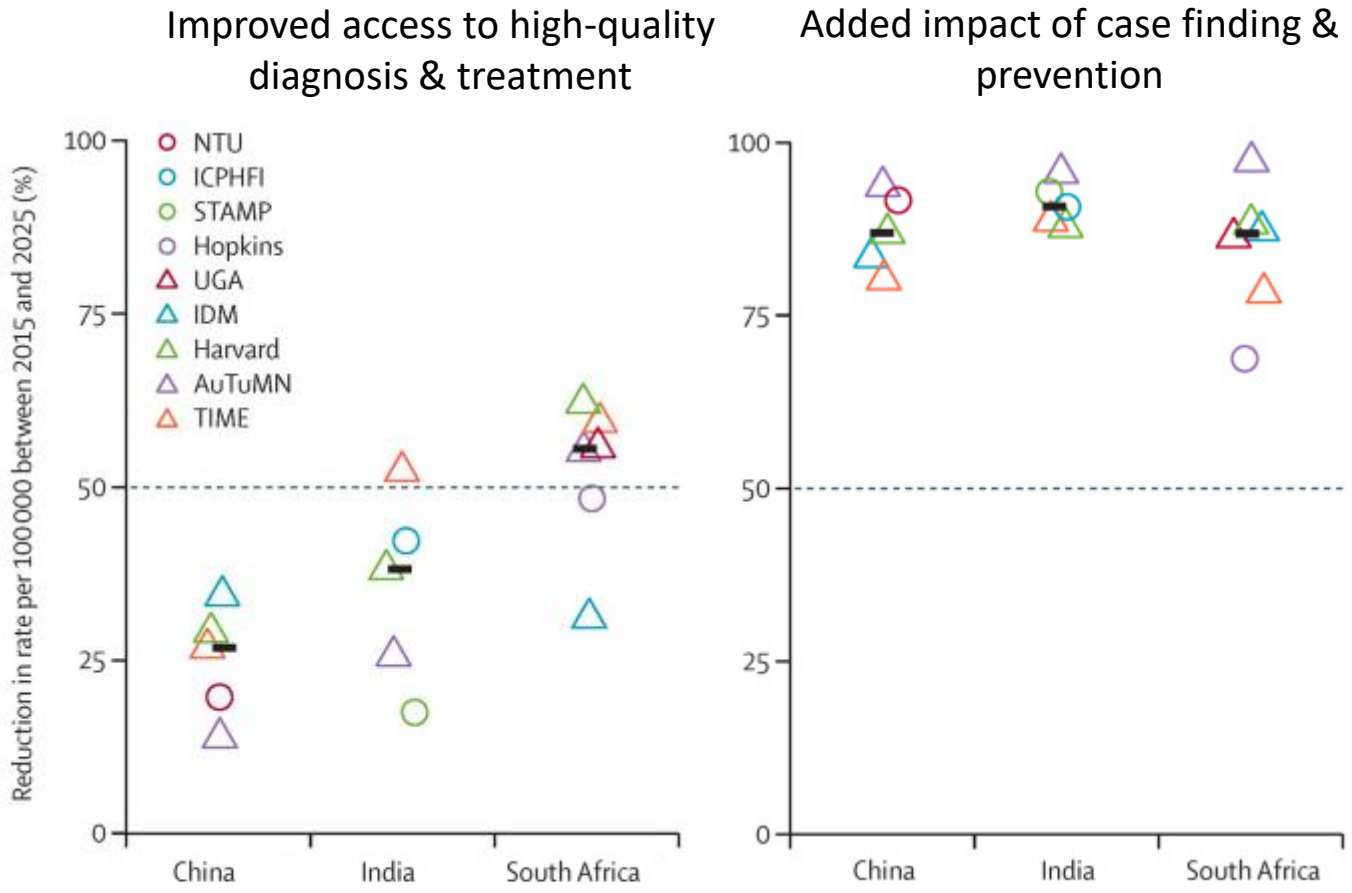
Limitations & knowledge gaps

- **Classification of TB disease in historical studies** used for model calibration
- Dichotomizations in models hide a spectrum of true disease states & **heterogeneity**
- **Simplifying assumptions**
  - 1-way progression, parameters don't vary by smear status, probability of staying in a state is time-independent
- **Generalizability** to specific populations
  - PLHIV, children, EP TB, etc.
  - *Ku et al*: PLHIV have a shorter duration of subclinical TB
- Scant **evidence on the per-unit-time relative infectiousness** of subclinical TB
  - Emery et al: wide uncertainty in estimates (relative infectiousness: 1.9 [0.6-6.2])
  - Other studies are estimates of cumulative relative infectiousness
  - Difficult to account for transitory nature of smear and symptom status in any estimates

Impact of finding subclinical TB

Models of population-level *Mtb* transmission suggest:

- Interventions that address subclinical TB have greater impact.
  - Active case finding
  - Prevention (TPT)

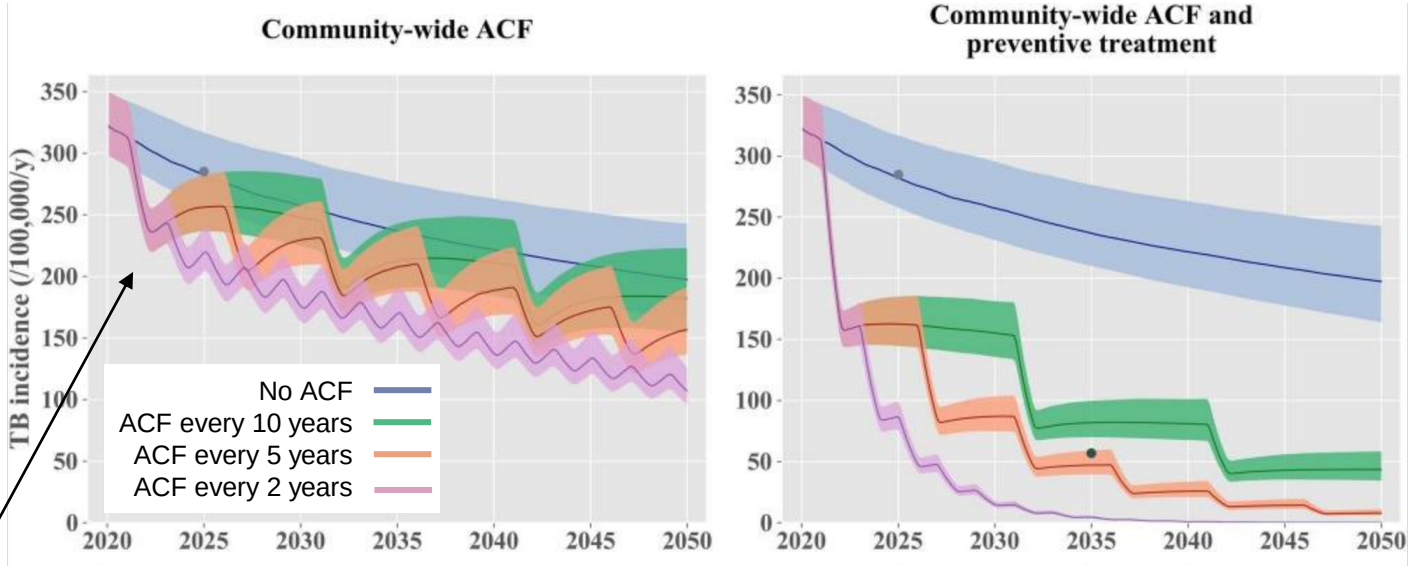


Houben et al. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. Lancet Global Health 2016.

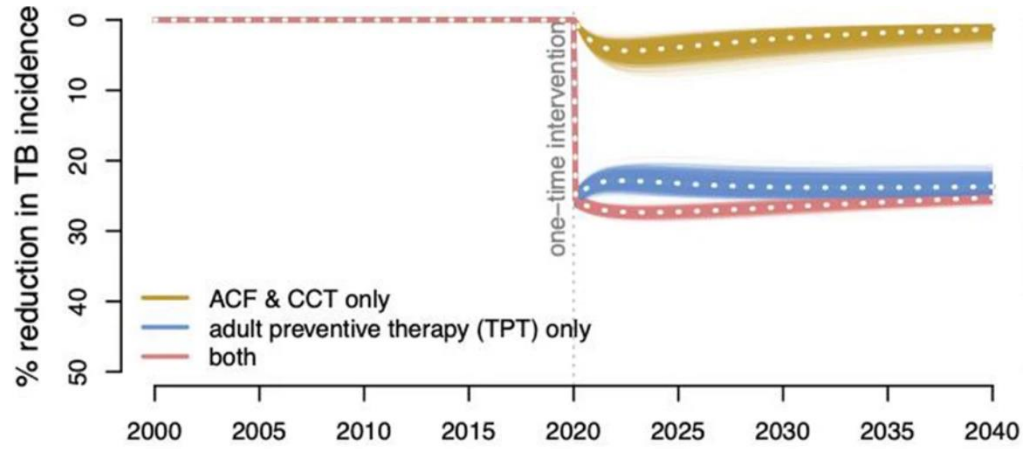
Impact of finding subclinical TB

But models of population-level TB transmission also find:

- One-time active case finding (including subclinical TB) has a modest effect on incidence
- Even repeat case finding will be insufficient to achieve incidence targets (*Ragonnet et al*.)
- Including prevention (TPT) substantially increases impact



Ragonnet et al. Estimating the long-term effects of mass screening for latent and active tuberculosis in the Marshall Islands. Int J Epi 2022.



Shrestha et al. Achieving a "step change" in the tuberculosis epidemic through comprehensive community-wide intervention: a model-based analysis. BMC Medicine 2021.

Why do models predict less impact from subclinical case finding (vs. TPT)?

1. Finding subclinical TB may be necessary, but **not sufficient** to interrupt transmission
2. Transmission models don't adequately capture important **heterogeneities**
   - e.g., in duration and infectiousness
3. Common **simplifying assumptions** in transmission models
   - e.g., about latent TB reactivation and clearance
4. **Insufficient screening tools**
   - Current approaches either find almost all subclinical TB or none of it – may be most important to find subclinical TB w/ high bacillary burden

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Summary of findings & outstanding questions

1. The duration of subclinical TB is highly heterogeneous.
   - Some people spend a lot of time without symptoms (but potentially infectious)

2. Subclinical TB may be responsible for ~50% of transmission.

3. Need to find and treat subclinical TB to reduce transmission.

Better ways to characterize and detect this subset?

Limited by lack of precise estimates of the relative infectiousness of subclinical TB.

- But is case finding sufficient, or is mass prevention needed?
- Optimal treatment of subclinical TB?