Overview: Subclinical TB and its global burden

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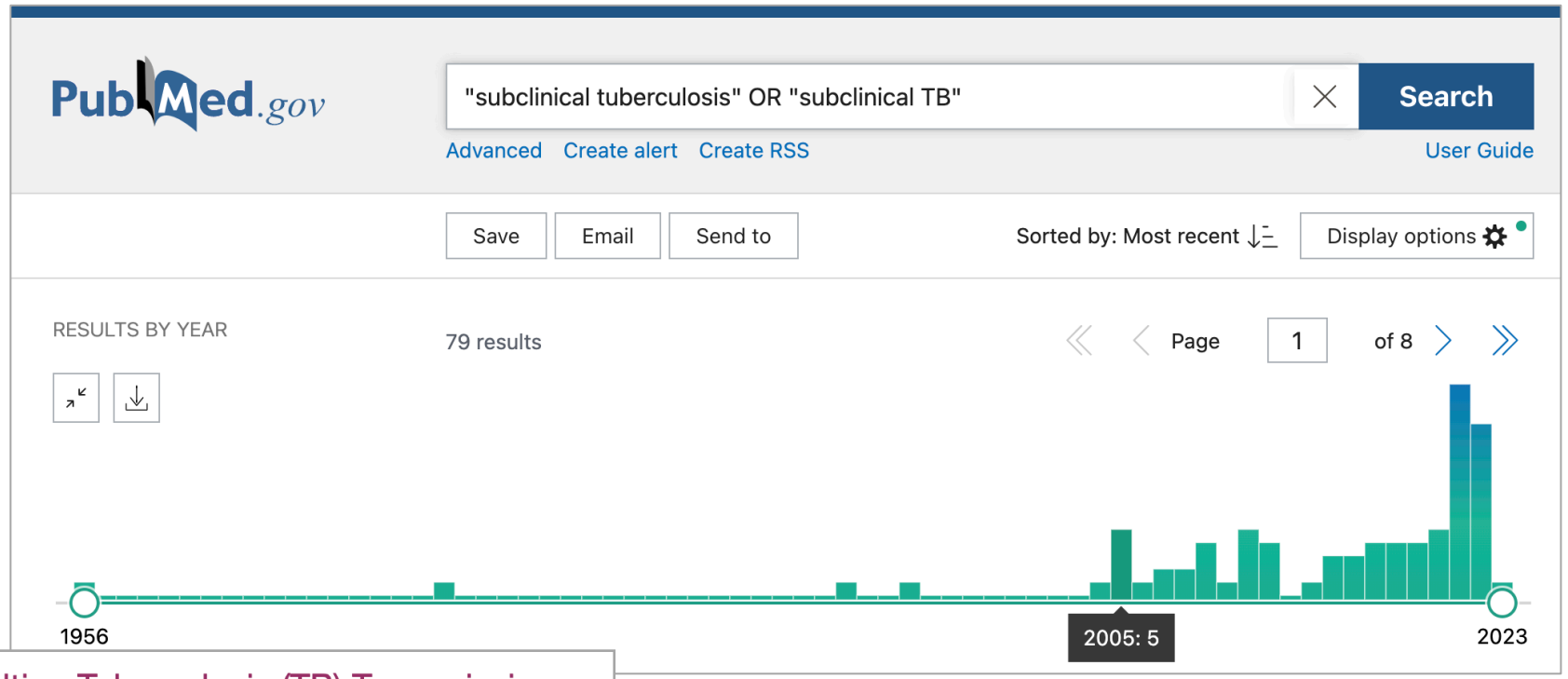
The Union NAR Annual TB Conference

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 sub-clinical 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;

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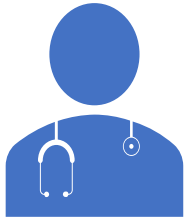
Purpose

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)

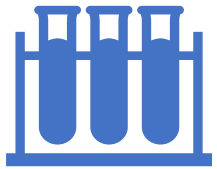


It lacks clinical signs or symptoms.

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



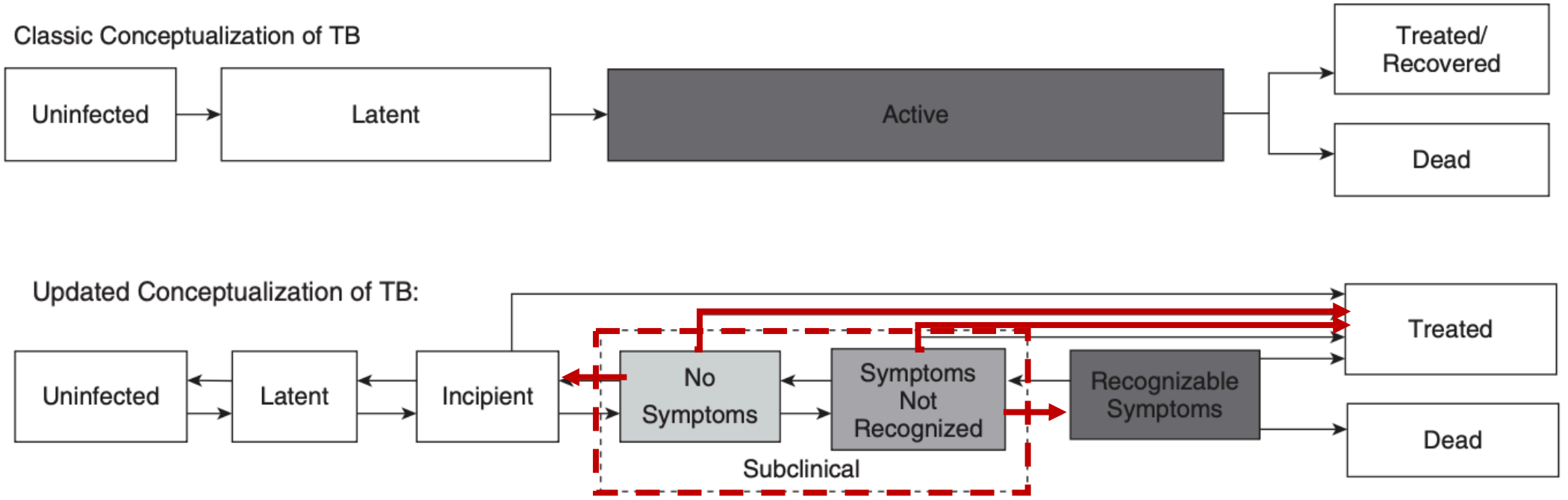
It may be sputum culture+ (and potentially infectious).

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”

Where does it fit on the TB spectrum?



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

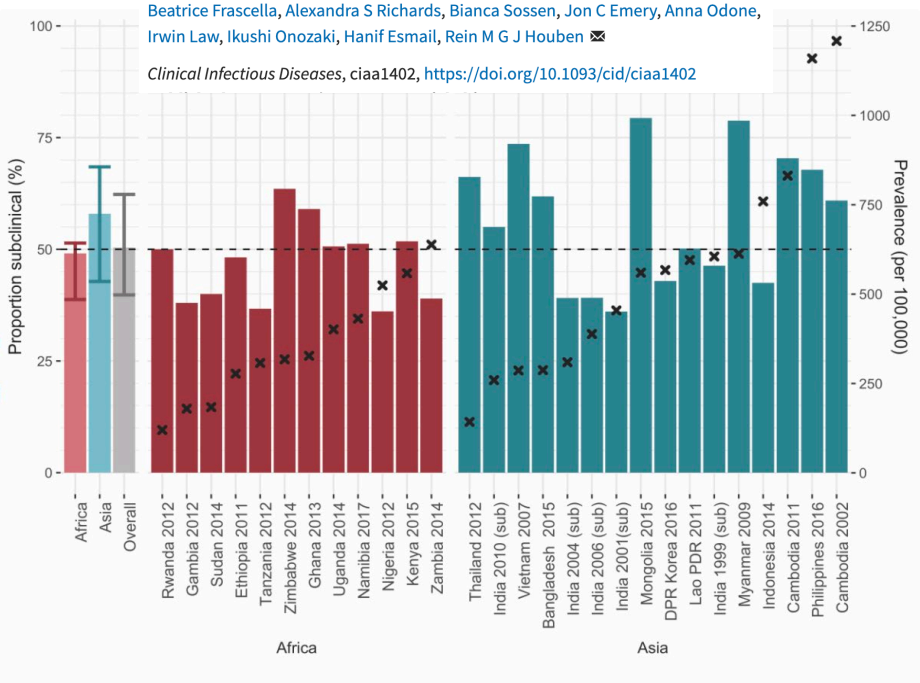
And that's 50% of a large undiagnosed TB burden!

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

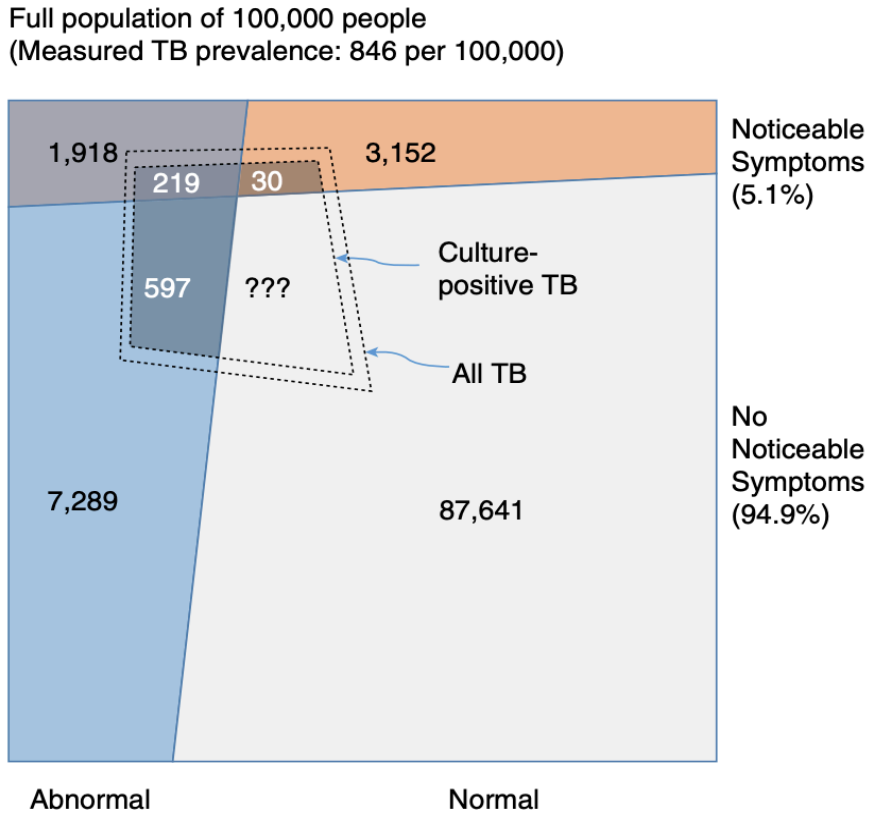
Subclinical tuberculosis disease – a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology

Beatrice Frascella, Alexandra S Richards, Bianca Sossen, Jon C Emery, Anna Odone, Irwin Law, Ikushi Onozaki, Hanif Esmail, Rein M G J Houben

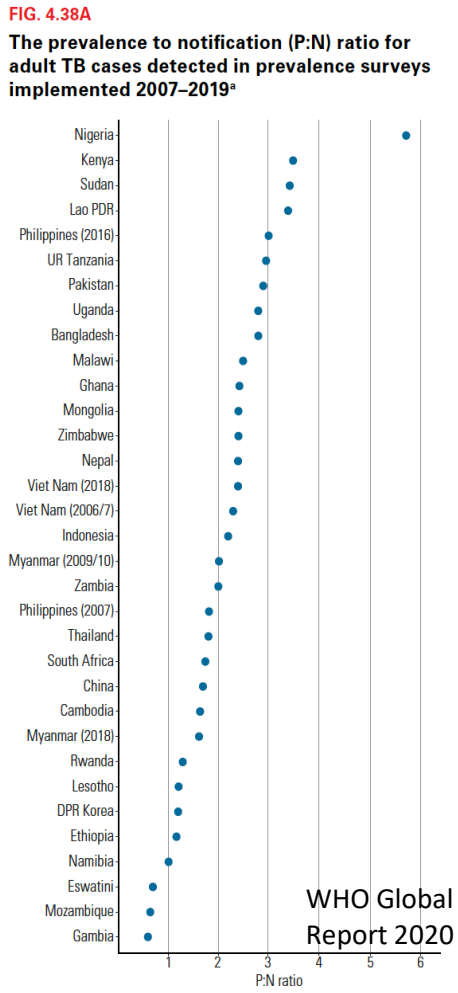
Clinical Infectious Diseases, ciaa1402, https://doi.org/10.1093/cid/ciaa1402



This % would be even greater if everyone got sputum testing



Illustrative data from Cambodian prevalence survey; Figure from Kendall et al AJRCCM 2021



How long do patients spend with (infectious) subclinical TB?

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

Ku et al. BMC Medicine (2021) 19:298
https://doi.org/10.1186/s12916-021-02128-9

BMC Medicine

Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data

Chu-Chang Ku[1*], Peter MacPherson[2,3,4], McEwen Khundi[2,4], Rebecca H. Nzawa Soko[2], Helena R. A. Feasey[2,4], Marriott Nliwasa[5], Katherine C. Horton[6], Elizabeth L. Corbett[2,4] and Peter J. Dodd[7]

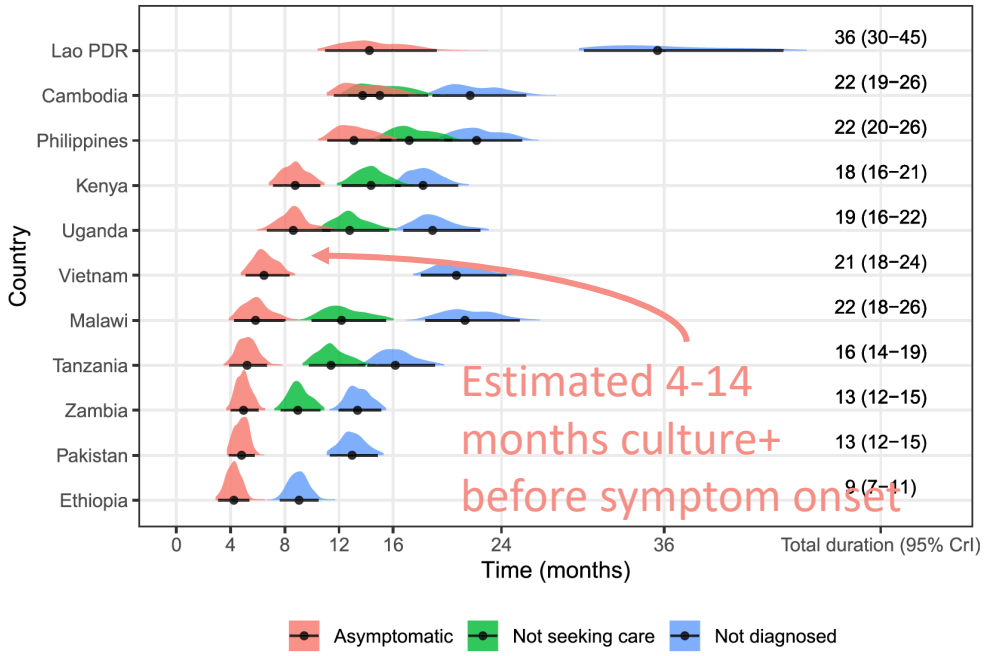


Fig. 2 Total time in months spent in each state during bacteriologically-positive TB disease. 'Not diagnosed' includes all states (white boxes) in Fig. 1. Median and 95% quantiles are shown as points and error bars, respectively. Posterior distributions are shown by coloured kernel density estimates

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES

Infectious and clinical tuberculosis trajectories: Bayesian modeling with case finding implications

Theresa S. Ryckman[a,1], David W. Dowdy[a], and Emily A. Kendall[b]

A **Durations**

Average cumulative months spent:	States at time 0: 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

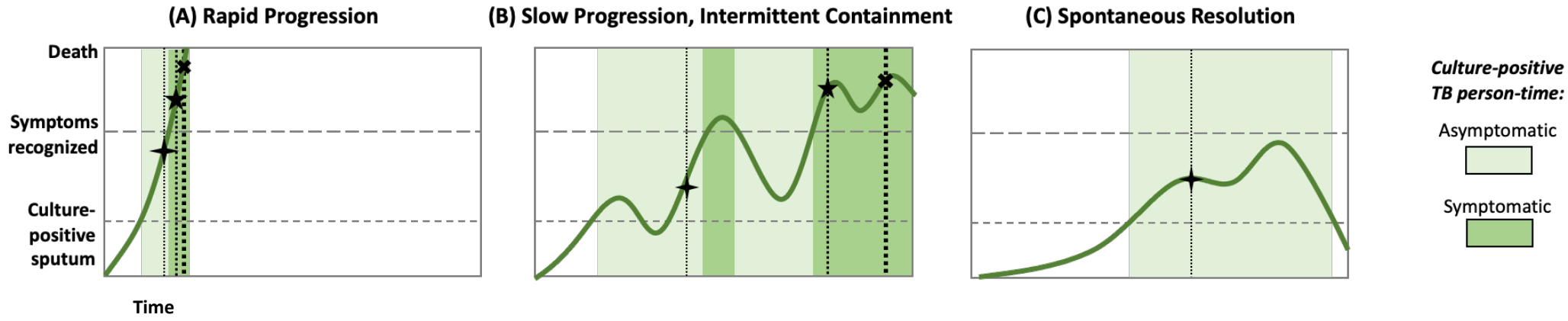
But possibly less for the mildest cases, after accounting for symptom-and smear-dependent trajectories

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 it does it mean for TB care and TB elimination goals in North America?