HEARTLAND
NATIONAL TB CENTER
THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT TYLER

Medical Consultants Meeting

Is Subclinical TB Disease Important?

San Antonio, Texas

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Marcos Burgos, MD

Professor of Medicine UNM SOM

Medical Director Tuberculosis Program

New Mexico Department of Health

Chief Infectious Diseases

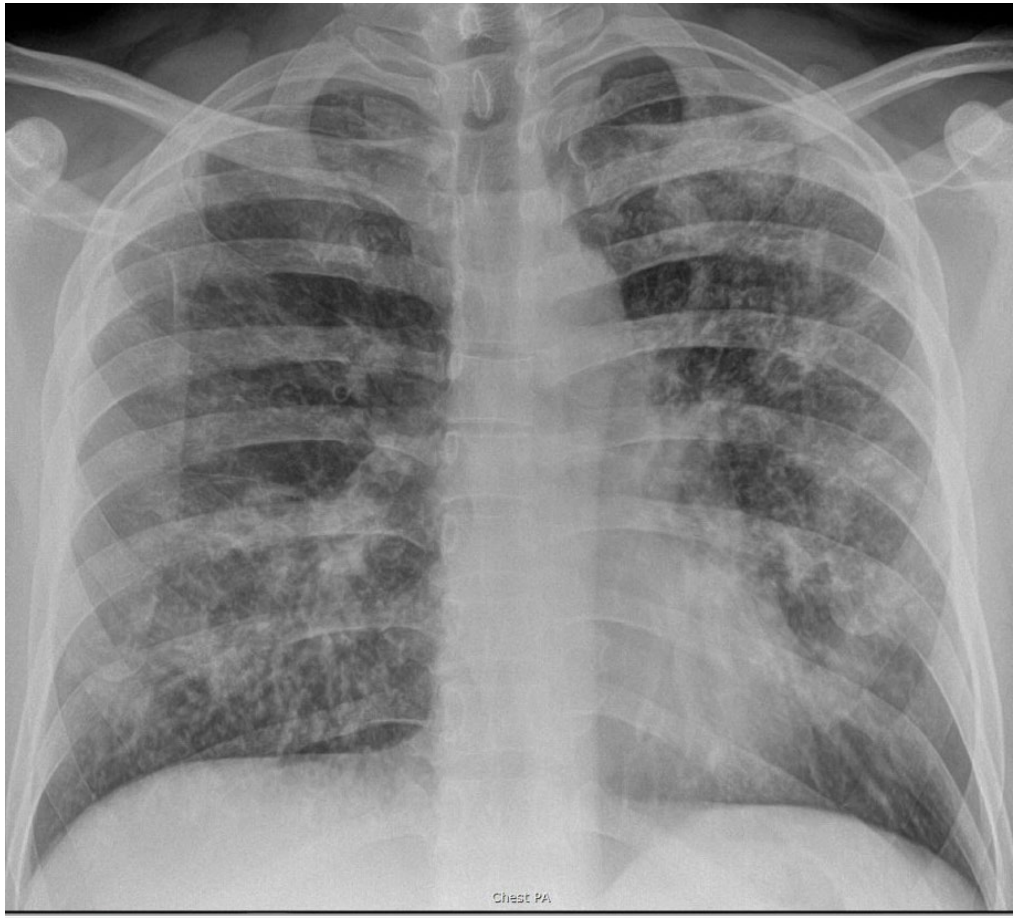
New Mexico VA Health Care System

Introduction

- In some infectious diseases patients without symptoms play an important role in the transmission of infectious pathogens, i.e., STDs, malaria, HIV, COVID-19
- Some persons with active tuberculosis disease do not experience symptoms
  - Can their undetected disease have an impact on morbidity, mortality, transmission and incidence?
- Millions of active TB disease cases goes undiagnosed in the world
  - How much of undetected TB is subclinical?

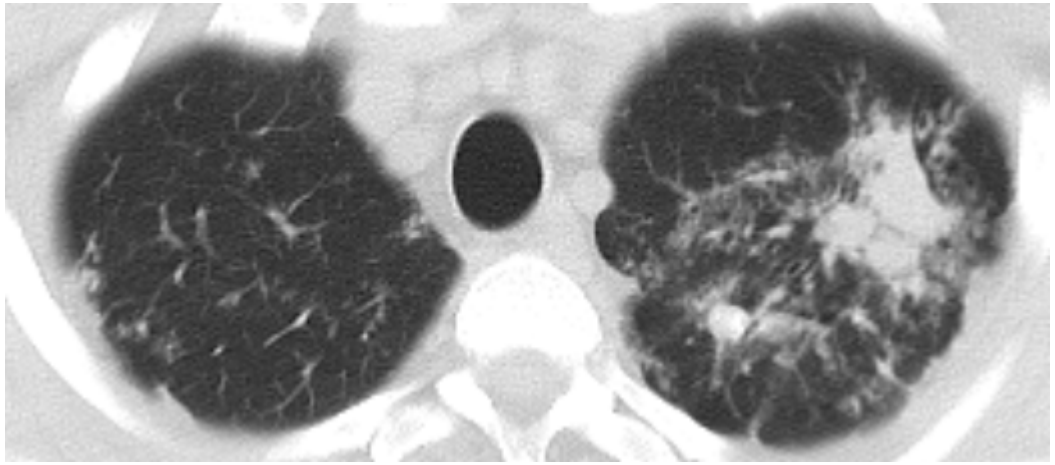
37-year-old male from Peru

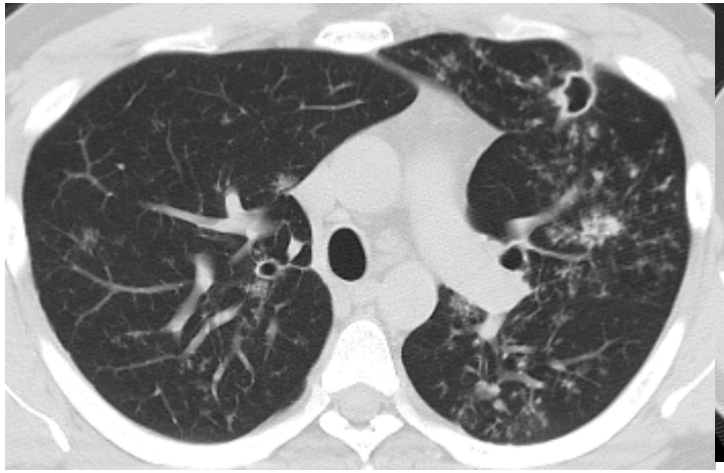
- Detained in an ICE facility
  - Abnormal CXR – Bilateral infiltrates
  - Denies symptoms
- 3 Sputum were collected
  - 4+ AFB, Gene-X-Pert
  - MTB, Rif resistant
  - Mutations resistance INH + Rif

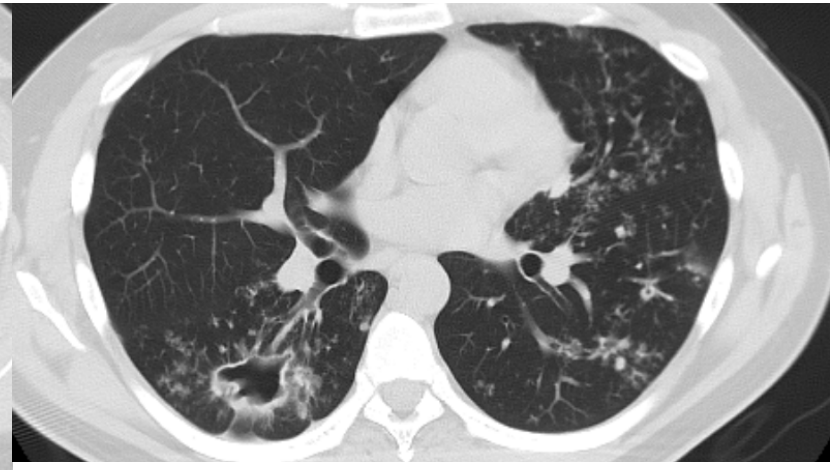


37-year-old male from Peru

- Positive IGRA
- HIV neg
- Started on BPaL treatment
- Tolerating treatment well
- Denies any changes in symptoms after 4 weeks of treatment







Incipient Tuberculosis

- An infection with viable MTB that is likely to progress to active TB disease
- It cannot currently be diagnosed by standard methods
  - No symptoms, CXR normal, negative microbiology testing
- Can be identified with research-based methods
  - Measurement of immune biomarkers, such as RNA, proteins, antigens
  - Blood based genome-wide transcriptional profiles have identified gene signature at risk
- Can assume incipient TB in some immunosuppressed persons
  - Transplanted organ with TB
  - Untreated advanced HIV and LTBI
  - Biologicals in those with untreated LTBI

Definition of Subclinical TB

- Bacteriological, positive cultures for MTB
- Denies symptoms
  - Respond NO to a list of current symptoms
- Symptoms usually in line with TB prevalence surveys (no cough, or cough of a certain duration)
- May have abnormalities or atypical radiological changes on CXR

- For 45 years WHO recommended, 2 weeks of cough or longer as main selection criteria for further work up for tuberculosis
  - 65% of active cases could be detected based on symptoms

Diagnosing and treating TB disease

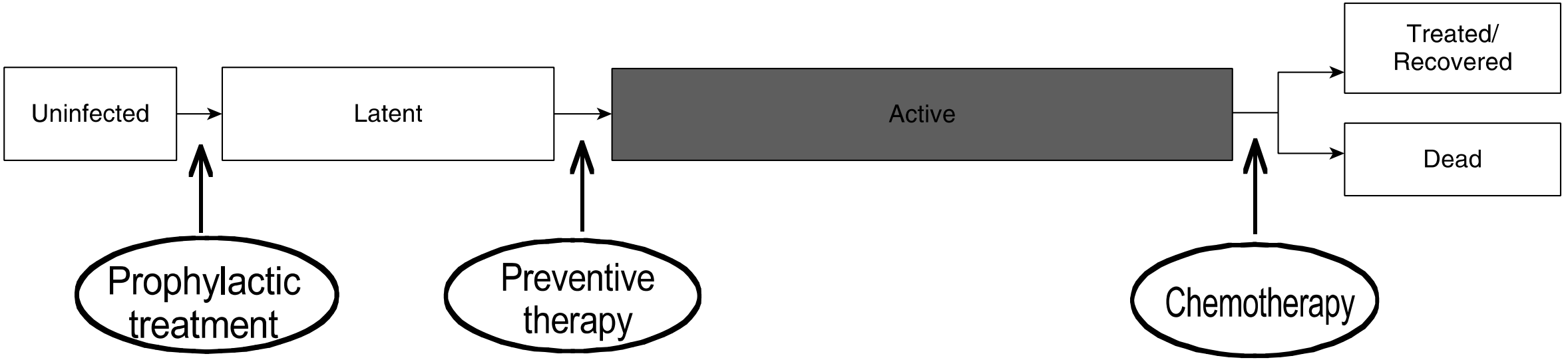
Passive Case Finding (PCF)

- Defined as detecting TB at health facilities among persons that seek medical care on their own
- Usually based on symptoms
- Detects more advance disease

Active Case Finding (ACF)

- Defined as systematic screening for TB, including outside health facilities
- May be symptom-based agnostic
- Usually based on CXR, AFB, culture and/or Gene-X-Pert
- Detects diagnosis early, less advance

Classic Conceptualization of TB

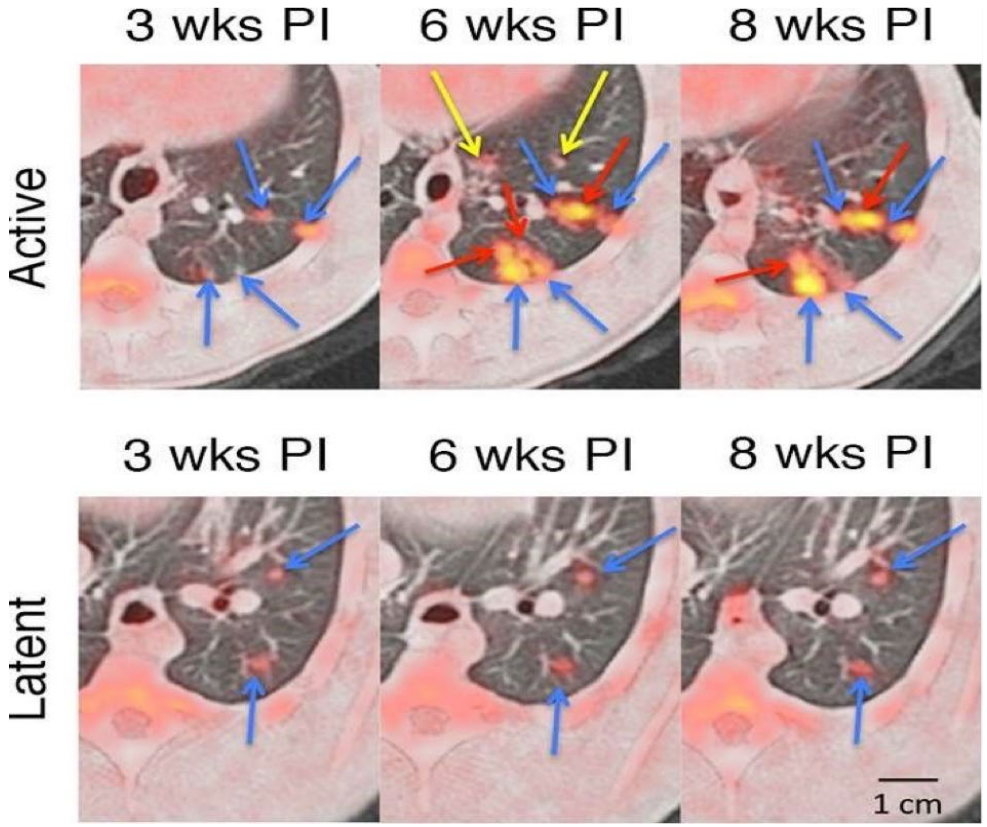


The main aim of the interventions is to reduce the incidence of tuberculosis or this approach is what we called “tuberculosis control”

- Kendall EA, et al., Epidemiological importance of Subclinical TB; 2021 AJRCCM
- Rieder H, Interventions for Tuberculosis Control and Elimination, 2002

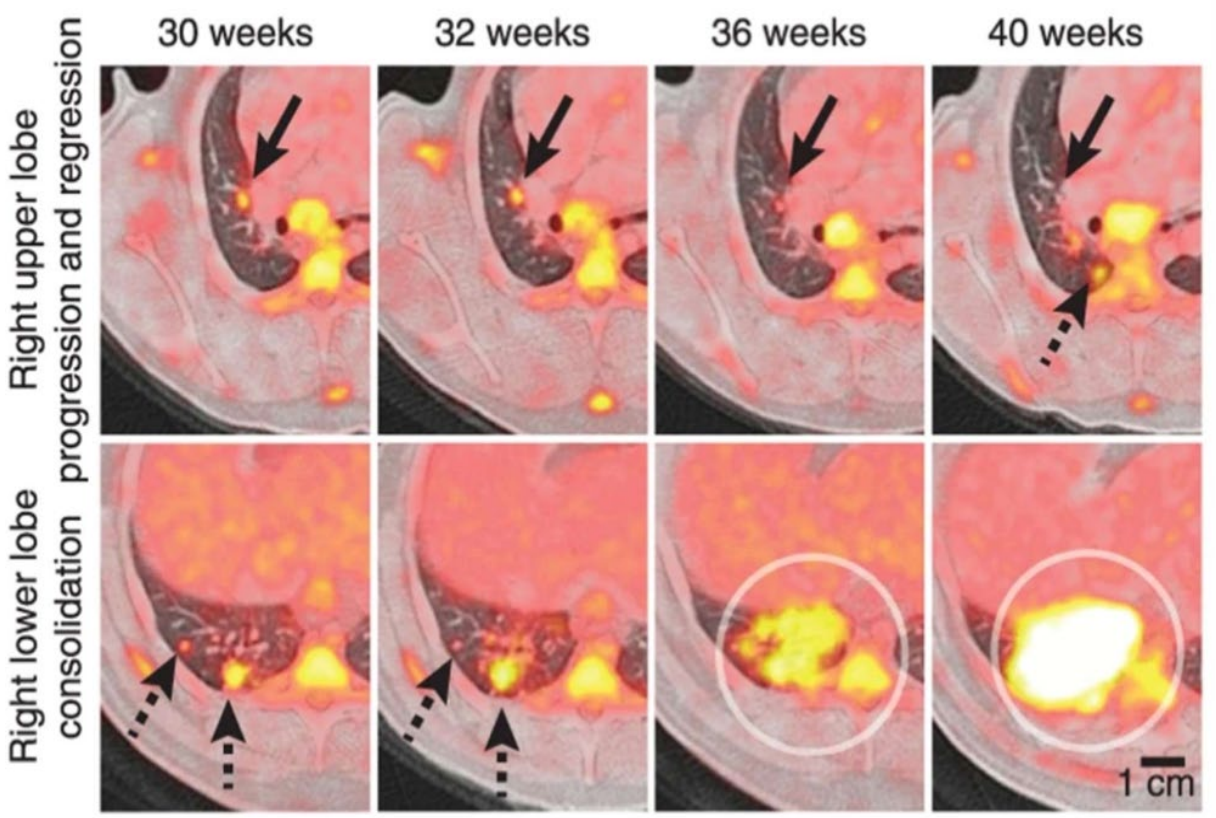
PET CT following active lesions Primate Model

Active vs. Latent TB



Coleman. Infect Immun. 2014.

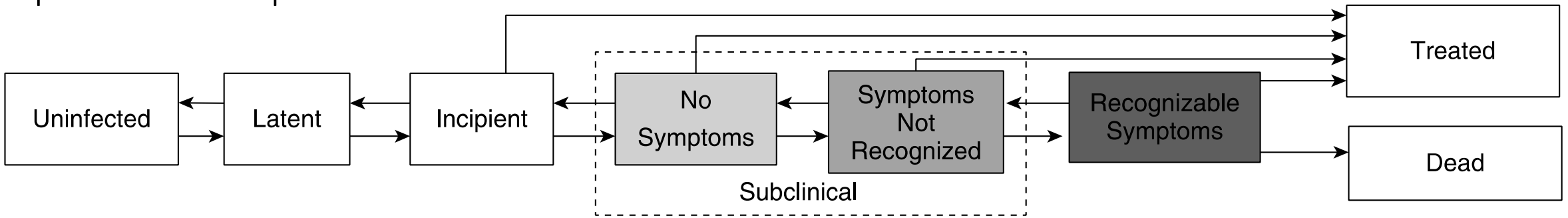
Growth/Regress



Lin PL et al (JL Flynn) Nature Medicine 2013

Classic Conceptualization of TB

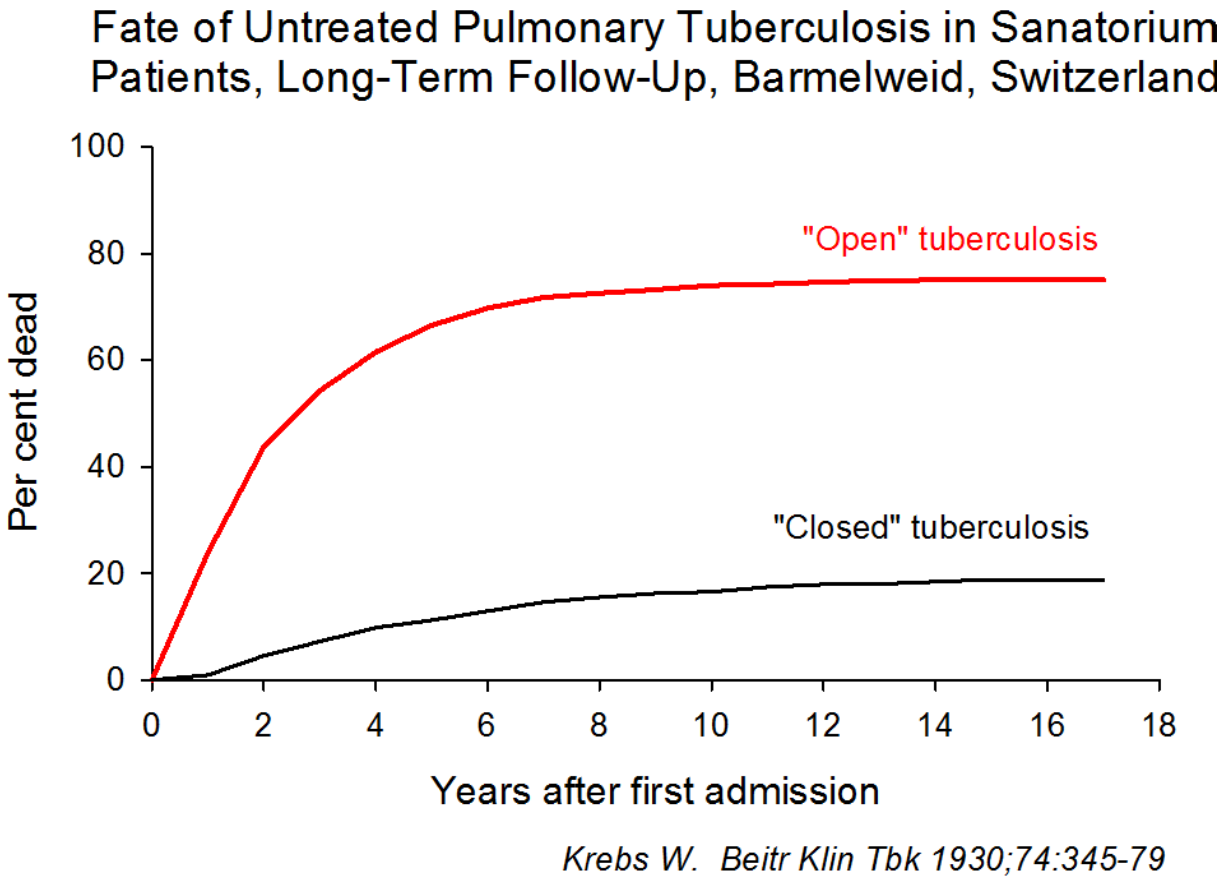
Updated Conceptualization of TB



- Subclinical stages from which transmission may occur
- Regression/Resolution
- The potential for diagnosis and treatment

Kendall EA, et al., Epidemiological importance of Subclinical TB; 2021 AJRCCM

Fate of Untreated Pulmonary Tuberculosis in Sanatorium



- Large difference between case fatality from **sputum smear-positive** ("open" tuberculosis) and **sputum smear-negative** ("closed" tuberculosis).
- Fatality from sputum smear-positive tuberculosis approximates 80%, while that of sputum smear-negative tuberculosis does not exceed 20%.
- Similar Findings Metanalysis by Ragonnet R, et al., Revisiting the Natural History of Pulmonary Tuberculosis; CID 2020.

INCIDENCE OF BACILLARY PULMONARY TUBERCULOSIS IN KOLIN DISTRICT IN 1961-64, BY MODE OF DETECTION [a]

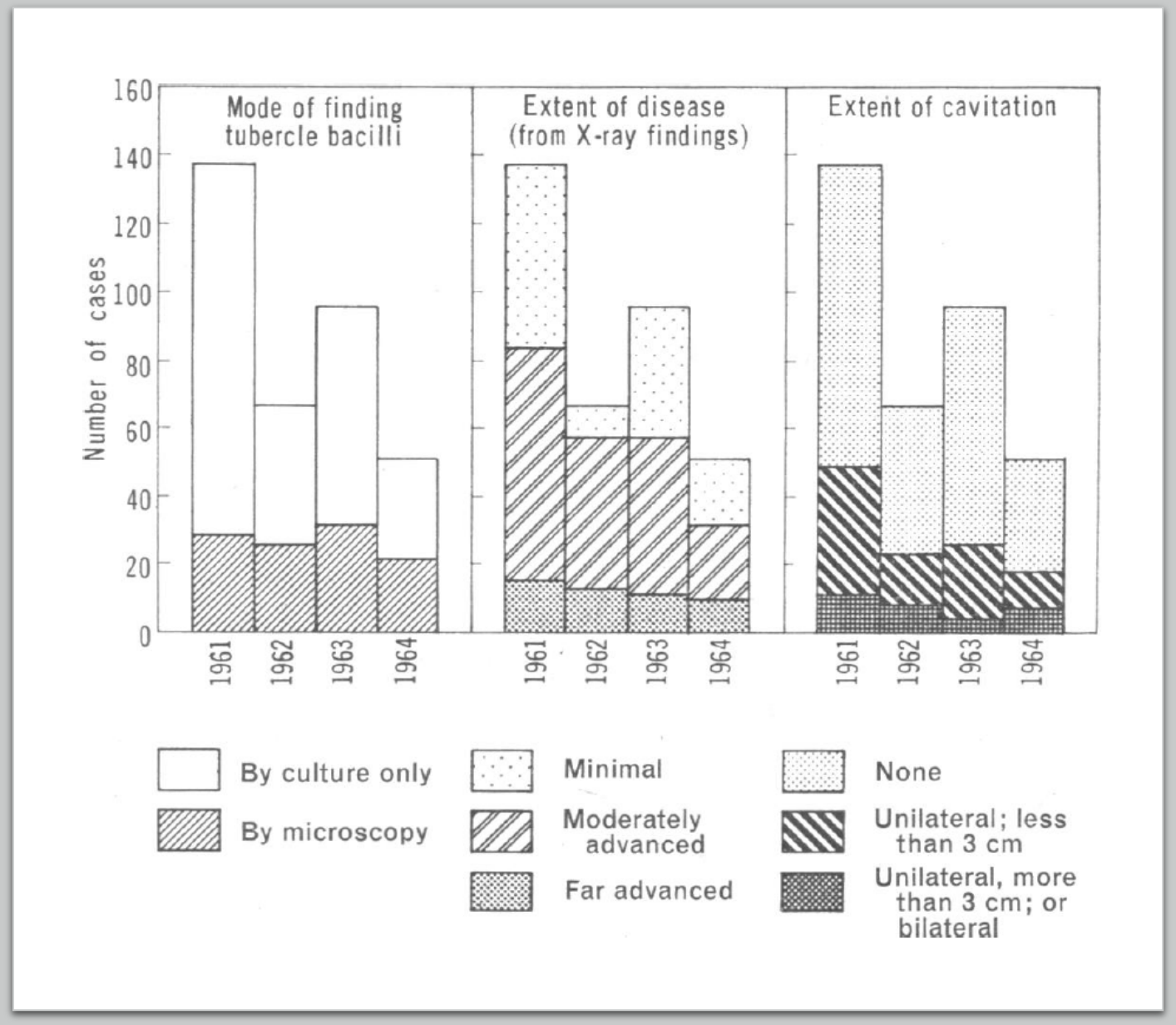
Mode of detection	Incidence				Total	
	1961	1962	1963	1964	No.	Percentage of microscopically positive cases
Previously normal chest X-rays						
On account of symptoms	17 (8)			7 (7)	66 (25)	38
By mass photofluorography	97 (11)			—	148 (23)	16
By other preventive examination	5 (1)	11 (7)	4 (1)	7 (4)	27 (13)	(48)
Total	119 (20)	37 (17)	61 (13)	24 (11)	241 (61)	25
Previous fibrotic lung lesions						
All methods	19 (7)	29 (9)	34 (16)	25 (9)	107 (41)	38
Grand Total	138 (27)	66 (26)	95 (29)	49 (20)	348 (102)	29

75% Asymptomatic

[a] The number of persons found to be excreting mycobacteria by direct smear microscopy is given in parentheses.

New Cases of Bacillary pulmonary Tuberculosis in Kolin District, 1961-1964

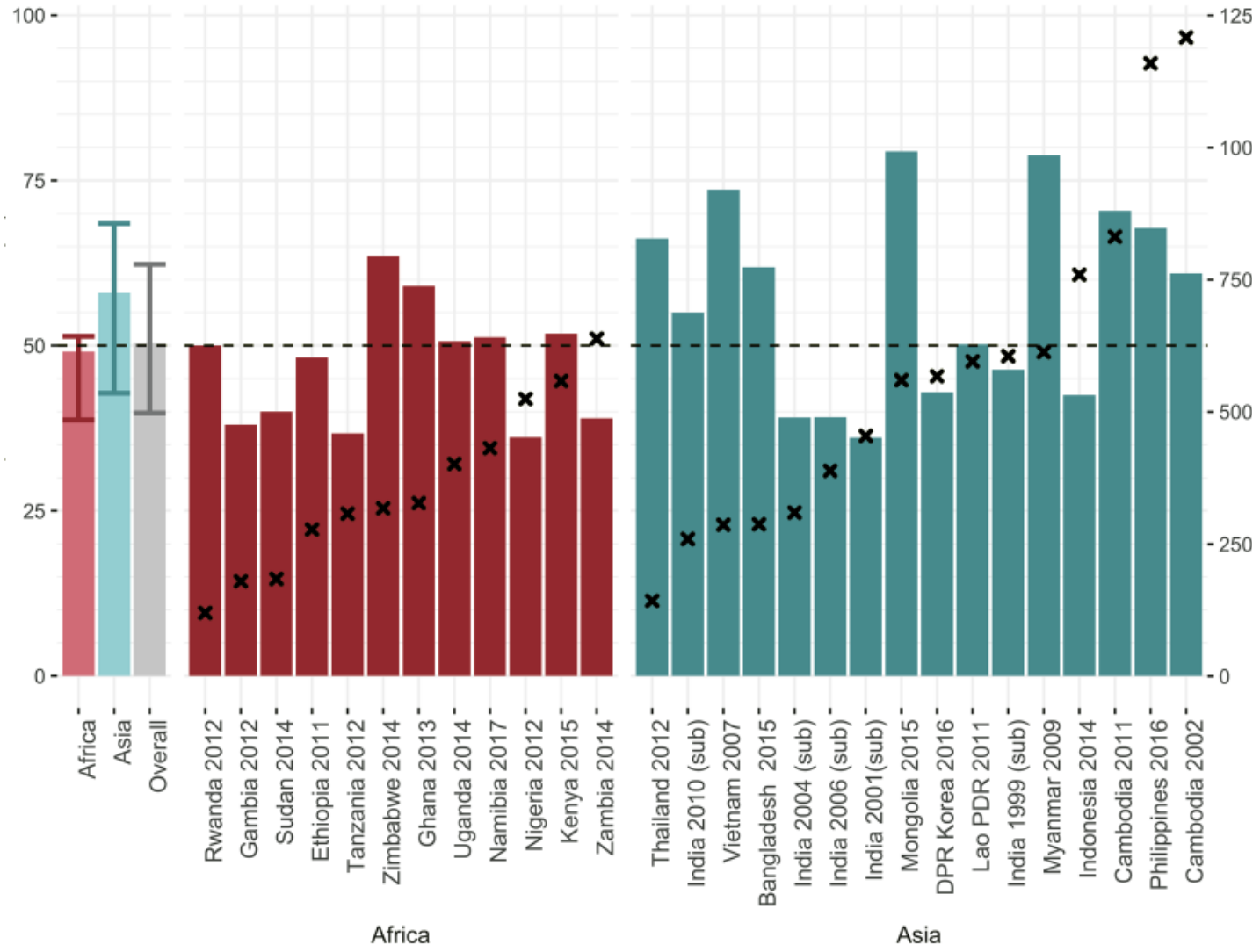
- Detecting active tuberculosis early:
- Decrease morbidity and mortality
- Decrease incidence of disease



WHO Bulletin 1967 Epidemiological and Clinical Study of Tuberculosis in the District of Kolin, Czechoslovakia

Is the Burden of Subclinical TB disease significant?

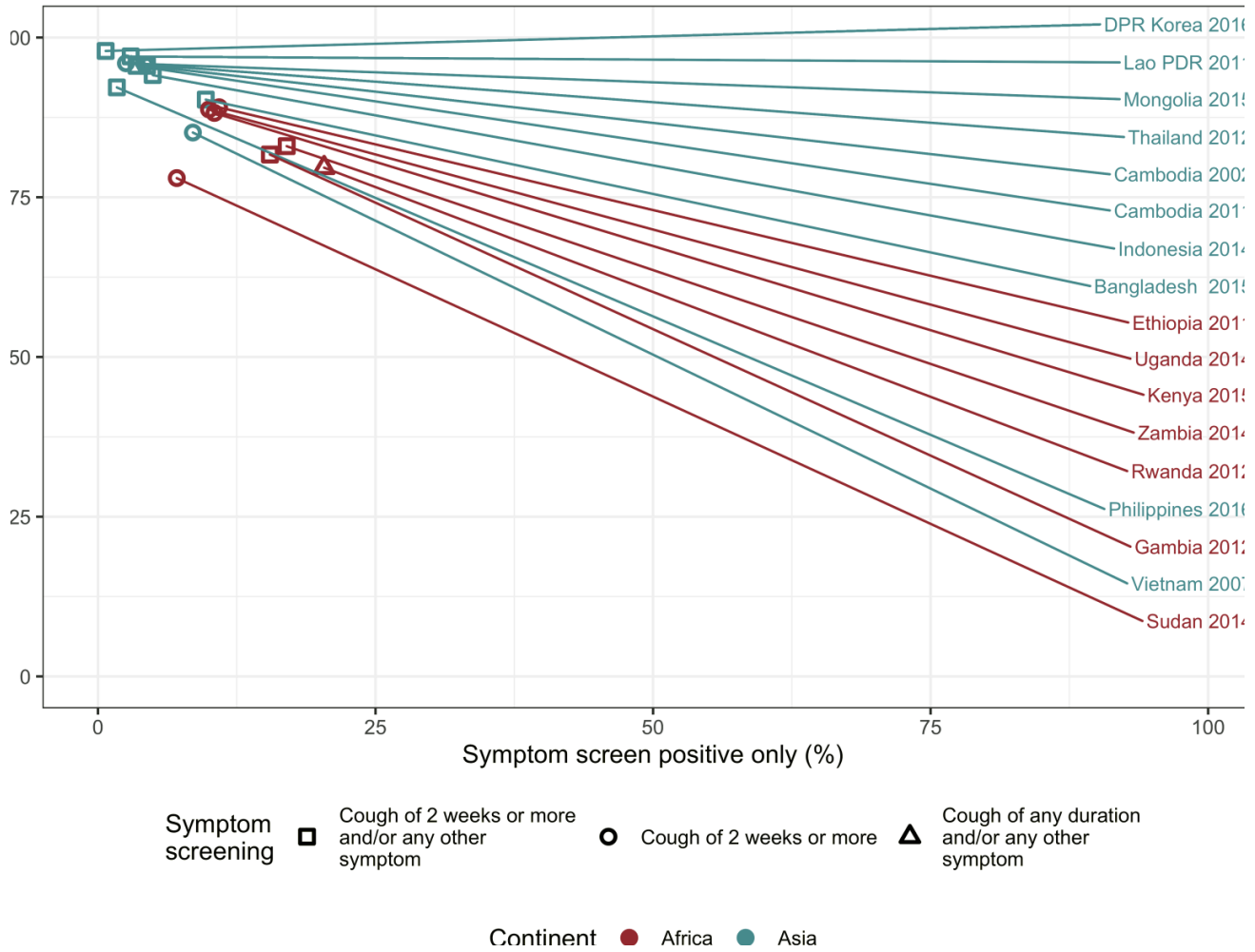
- 28 TB prevalence population surveys
- The median percentage of subclinical TB cases was 50.4%



Frascella et al. CID 2021:73

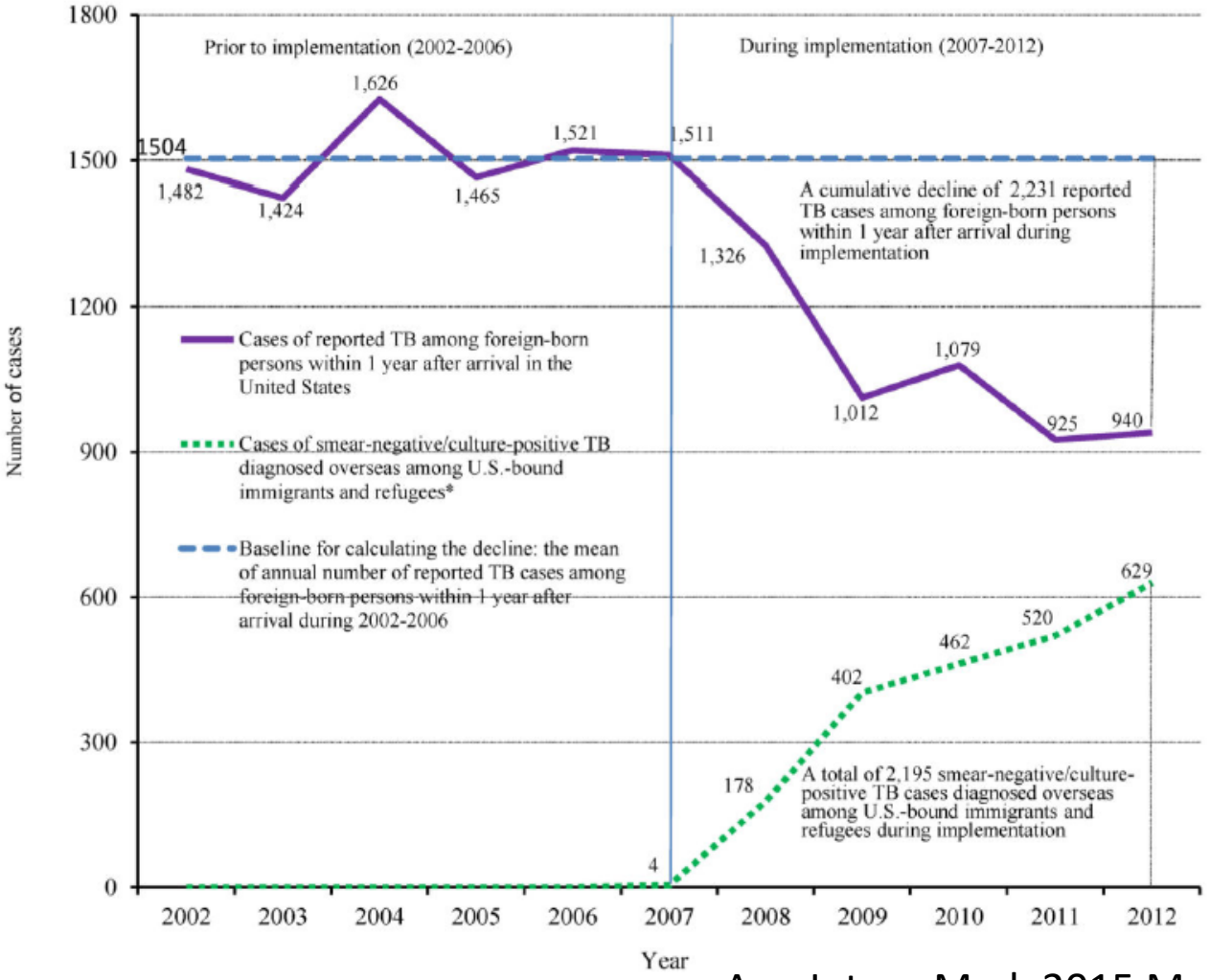
Screening Modality for Bacteriologically Confirmed TB cases

- Proportion of bacteriologically confirmed cases in prevalence surveys that screened positive on CXR or on symptom screen
  - Chest Xray detected a median of 89% of bacteriologically confirmed TB
  - Cough, was reported by around half of bacteriologically confirmed cases



Frascella et al. cid 2021:73

Effect of a Culture-Based Screening Algorithm on Tuberculosis Incidence in Immigrants and Refugees Bound for the United States



One study, 18% with any symptoms

Implementation of the culture-based algorithm substantially reduced the incidence of TB among newly arrived, foreign-born persons

Ann Intern Med. 2015 March 17; 162(6): 420–428; Maloney SA, Arch Int Med Jan 23 2006

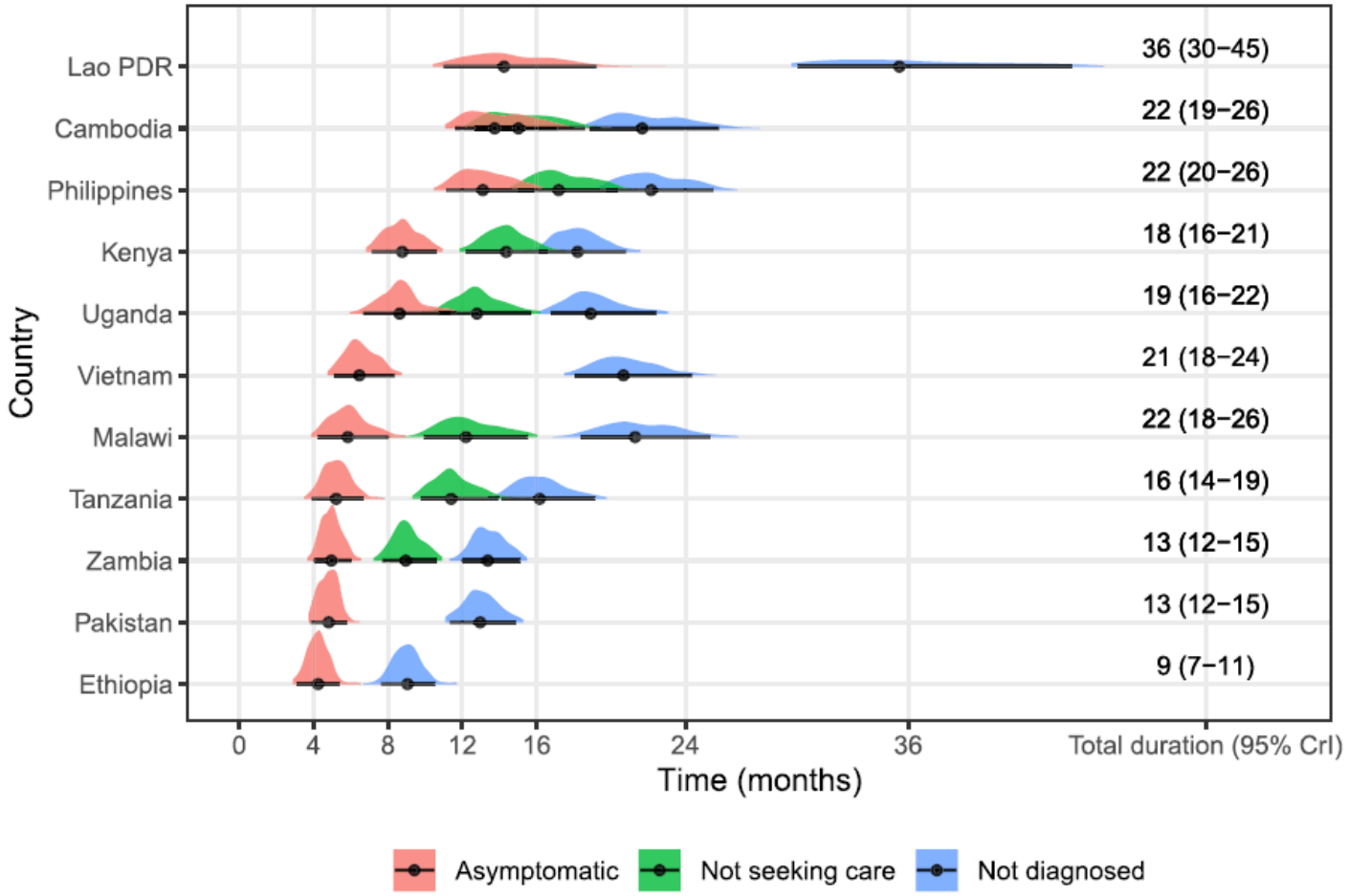
Corbett et al (2010)[11]	Zimbabwe, general population (urban)	Before-after comparison within a cluster RCT	Door to door and mobile clinics (vans)	Sputum smear if symptoms for ACF; culture for all for prevalence survey	0·56 (0·38–0·83)‡	0·59 (0·40–0·89)§
Ayles et al (2010)[36]	Zambia and South Africa, general population (high tuberculosis prevalence districts)	Cluster RCT	Community mobilisation and mobile clinics	Sputum smear if symptoms for ACF; culture for all for prevalence survey	1·29 (0·88–1·87)	1·09 (0·86–1·40)¶
Marks et al (2019)[37]	Vietnam, general population	Cluster RCT	Door to door	Sputum Xpert regardless of symptoms (ACF and prevalence survey)	0·56 (0·40–0·78)††	0·55 (0·39–0·77)‡‡

Burke RM, Community-bases ACF interventions for TB: Review The Lancet, public Health, 2021

- ACF in Vietnam of reduced adult TB disease prevalence
- Two trials showed lower frequencies of TB infection among children where TB screening was done
- Active case-finding, may positively affect the community epidemiology of tuberculosis

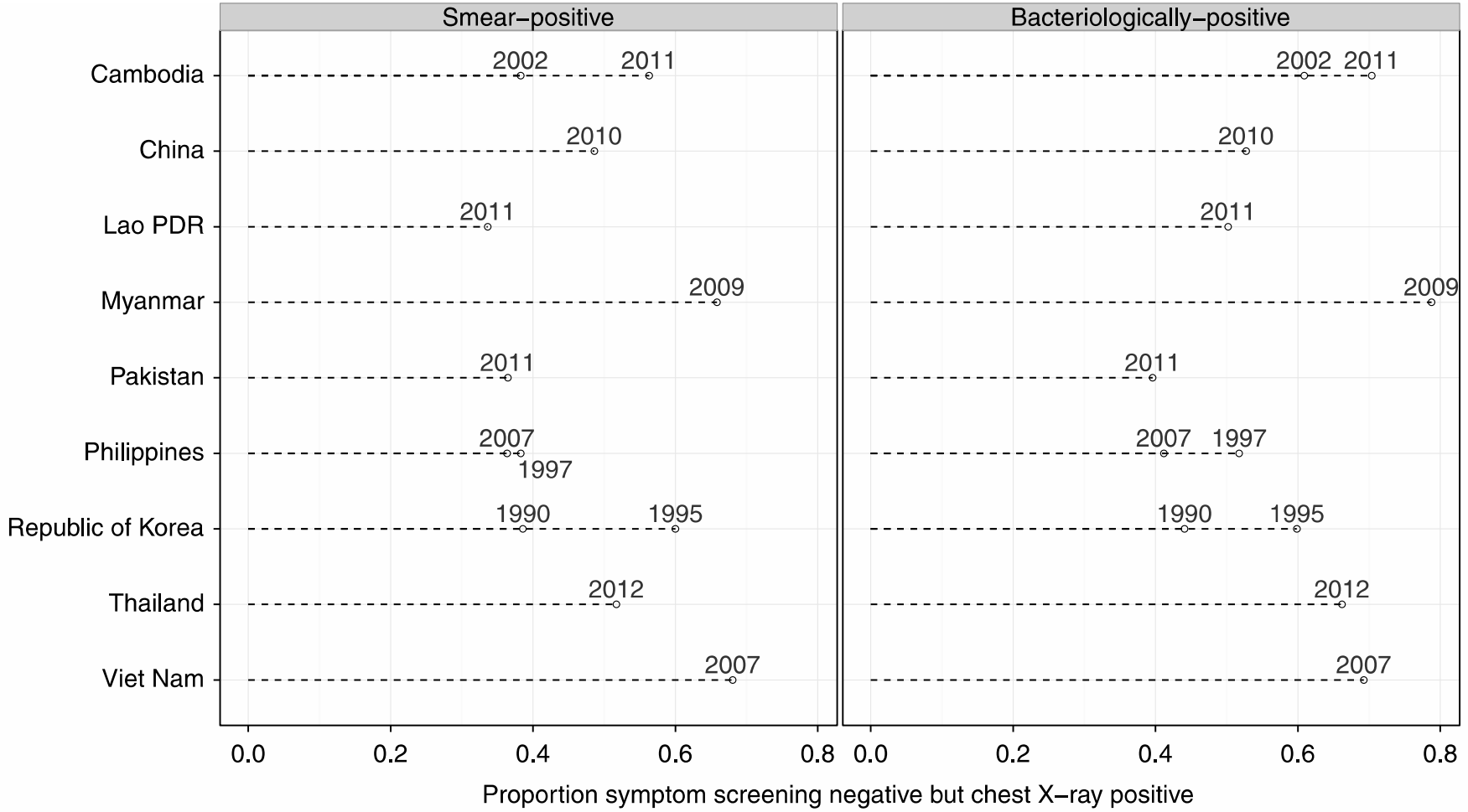
Durations of asymptomatic, symptomatic and care-seeking phases of tuberculosis disease

- Total time in months spent in each state during bacteriologically-positive TB disease from 11 National TB data sets
- Asymptomatic TB disease typically lasts around 4-14 months, average 6 months.
- Asymptomatic phase could be 2 to 6 times greater than symptomatic disease phase



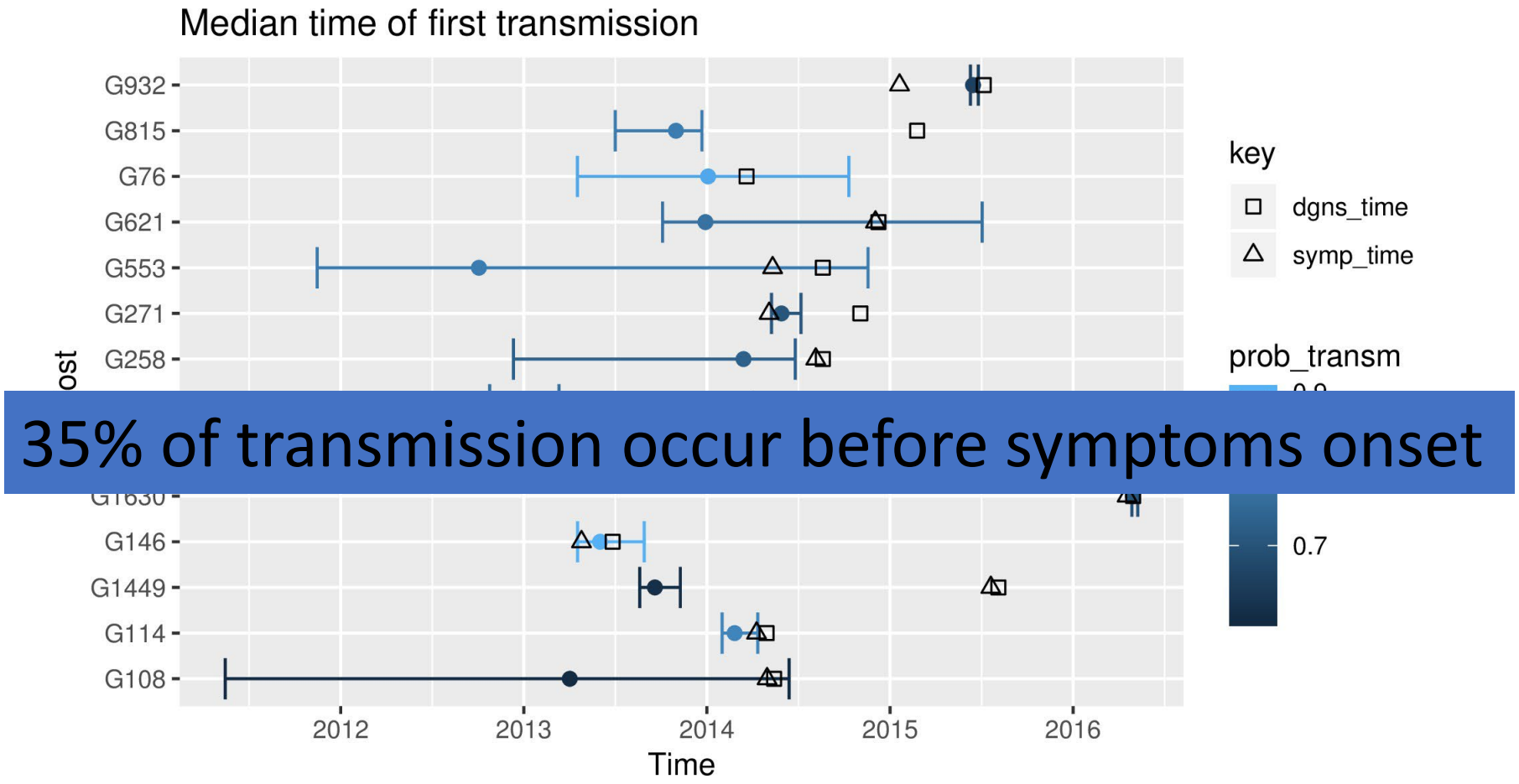
Ku et al. BMC Medicine (2021) 19:298

Is Subclinical TB infectious?



Ikushi Onozaki, National TB prevalence in Asia, 2015 Trop Med International Health

Can Subclinical TB transmit?



35% of transmission occur before symptoms onset

Xu, Y et al. PLOS Medicine, October 31, 2019

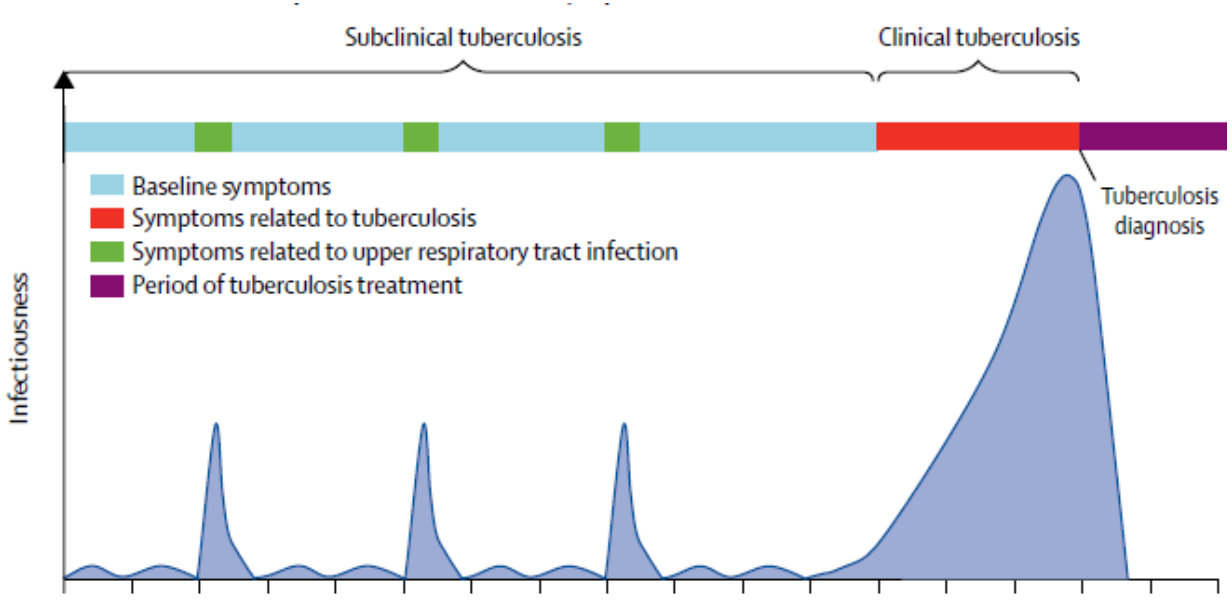
Coughing is not the only prerequisite for generating aerosols

- Aerosols can be generated without recognizable symptoms
  - Normal cough, speaking, breathing, singing, other respiratory illness
- All respiratory activities potentially release aerosol
- A single cough has an increased likelihood to carry *Mtb* aerosols compared with a single tidal breath
  - But, breathing is typically at least 30 times more frequent than coughing in TB disease
  - *Thus, cough Mtb* aerosols may be rarer than *breath Mtb* aerosols

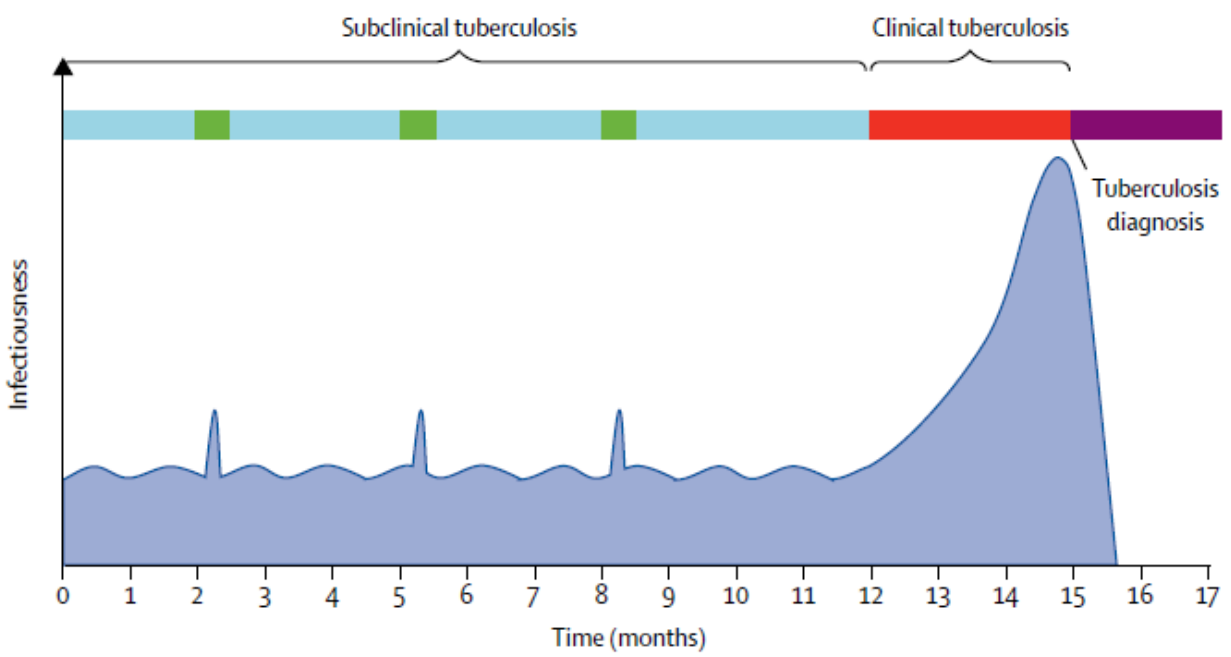
Esmain et al lancet respir med 2018; Williams et al lancet ID 2020;
B. Patterson et el, Tuberculosis 117 (2019) 31–3532

Transmission Potential of Subclinical and Clinical Tuberculosis

Minimal baseline symptoms



Chronic cough



Esmail Hanif, et al. Tuberculosis transmission during the subclinical period: could unrelated cough play a part? The lancet Resp Med, 2021.

Diagnostic Accuracy of Screening Methods for Tuberculosis disease

Screening test	No. of studies (no. of participants)	Sensitivity	No. of studies (no. of participants)	Specificity
WHO target product profile	NA	> 0.90	NA	> 0.70
Prolonged cough (≥ 2 weeks)	40 (6 737)	0.42	40 (1 284 181)	0.94
Any cough	21 (2 734)	0.51	21 (768 291)	0.88
Any TB symptom (cough, haemoptysis, fever, night sweats, weight loss)	28 (3 915)	0.71	28 (460 878)	0.64
Chest radiography (any abnormality)	22 (4 243)	0.94	22 (1 012 752)	0.89
Chest radiography (suggestive abnormality)	19 (2 152)	0.85	19 (464 818)	0.96
Molecular WHO-recommended rapid diagnostic test	5 (337)	0.69	5 (8 619)	0.99

WHO consolidated guidelines on tuberculosis: systematic screening for tuberculosis disease.

Main changes to the WHO guidance for Screening for M. tuberculosis

- Less emphasis on symptoms screening
- Community-wide systematic screening
- CXRs and Computer-aided detection (CAD) as an alternative to human interpretation of digital chest X-ray (CXR) for screening and triage for TB
- Molecular rapid diagnostic test
- C-reactive protein

WHO consolidated guidelines on tuberculosis: systematic screening for tuberculosis disease.

Conclusions- Subclinical TB

- A large part of the prevalent TB disease
- Follows varied clinical trajectory
- Has meaningful infectious potential
- Miss by using passive screening tools
- ACF improves subclinical TB detection
- May account for a large fractions of TB transmission