



Evoluzione della LTBI: approccio diagnostico-terapeutico

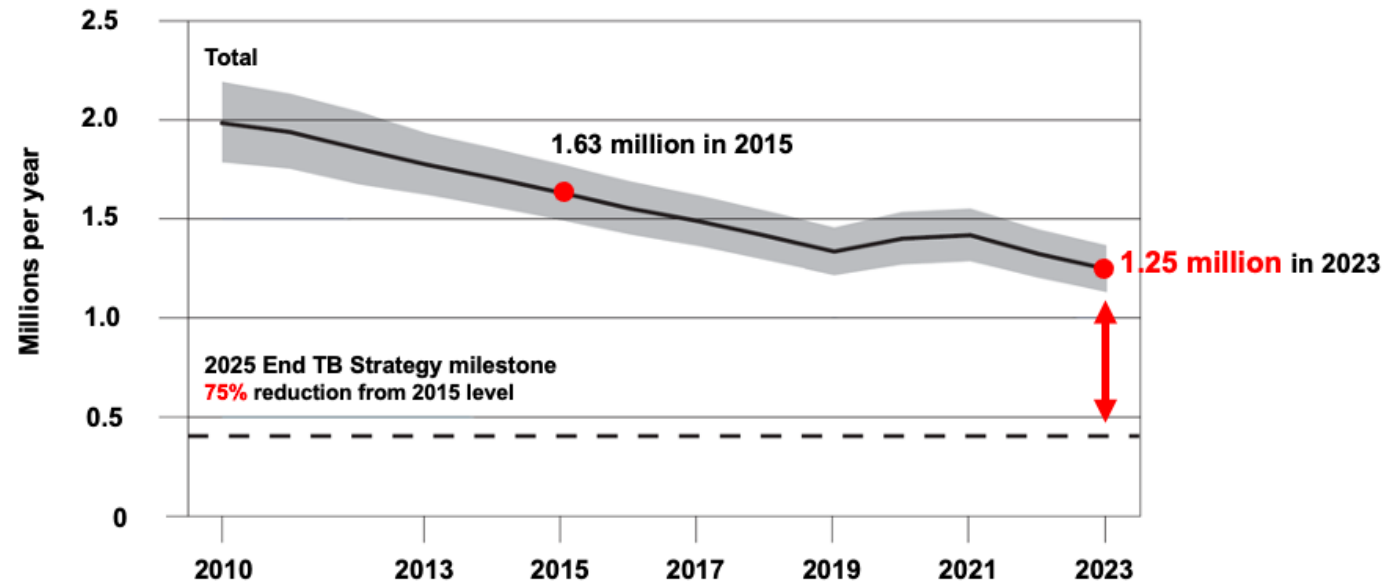
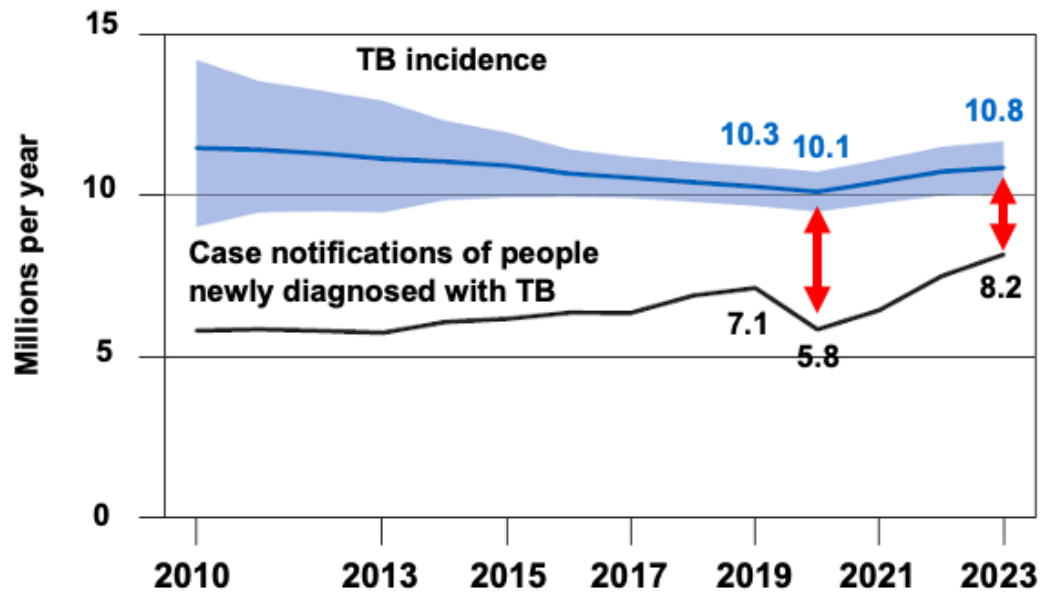
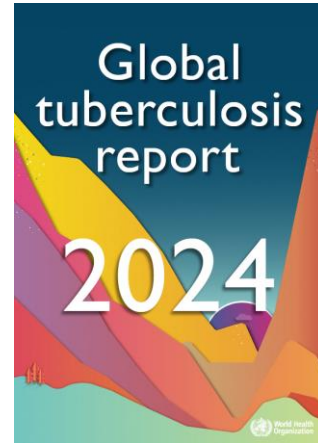
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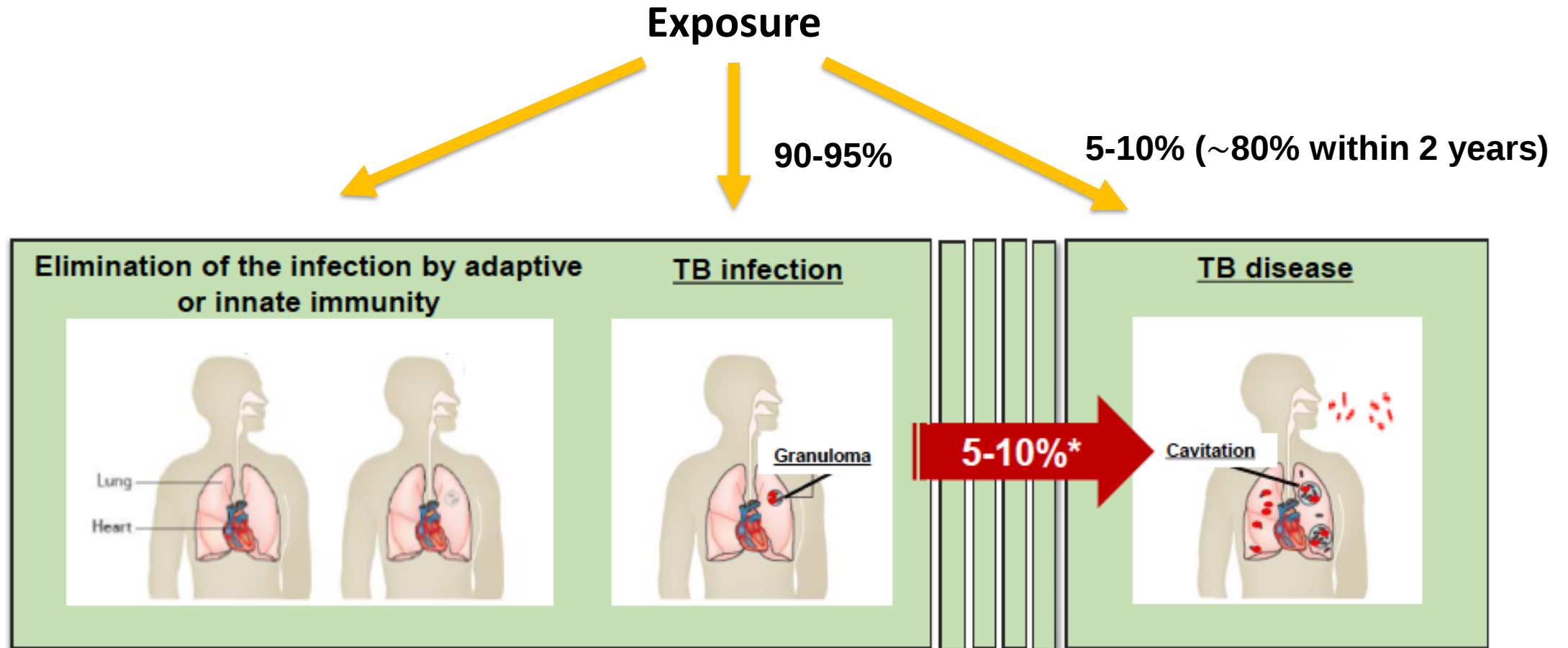
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Current TB burden estimates

- 10.8 million (95% UI: 10.1-11.7 million) incident TB cases estimated in 2023
- 8.2 million people with TB notified in 2023 – more than ever
- Cased detection gap is reducing but still over 2.6 million people last year!
- 1.25 million estimated deaths from TB in 2023

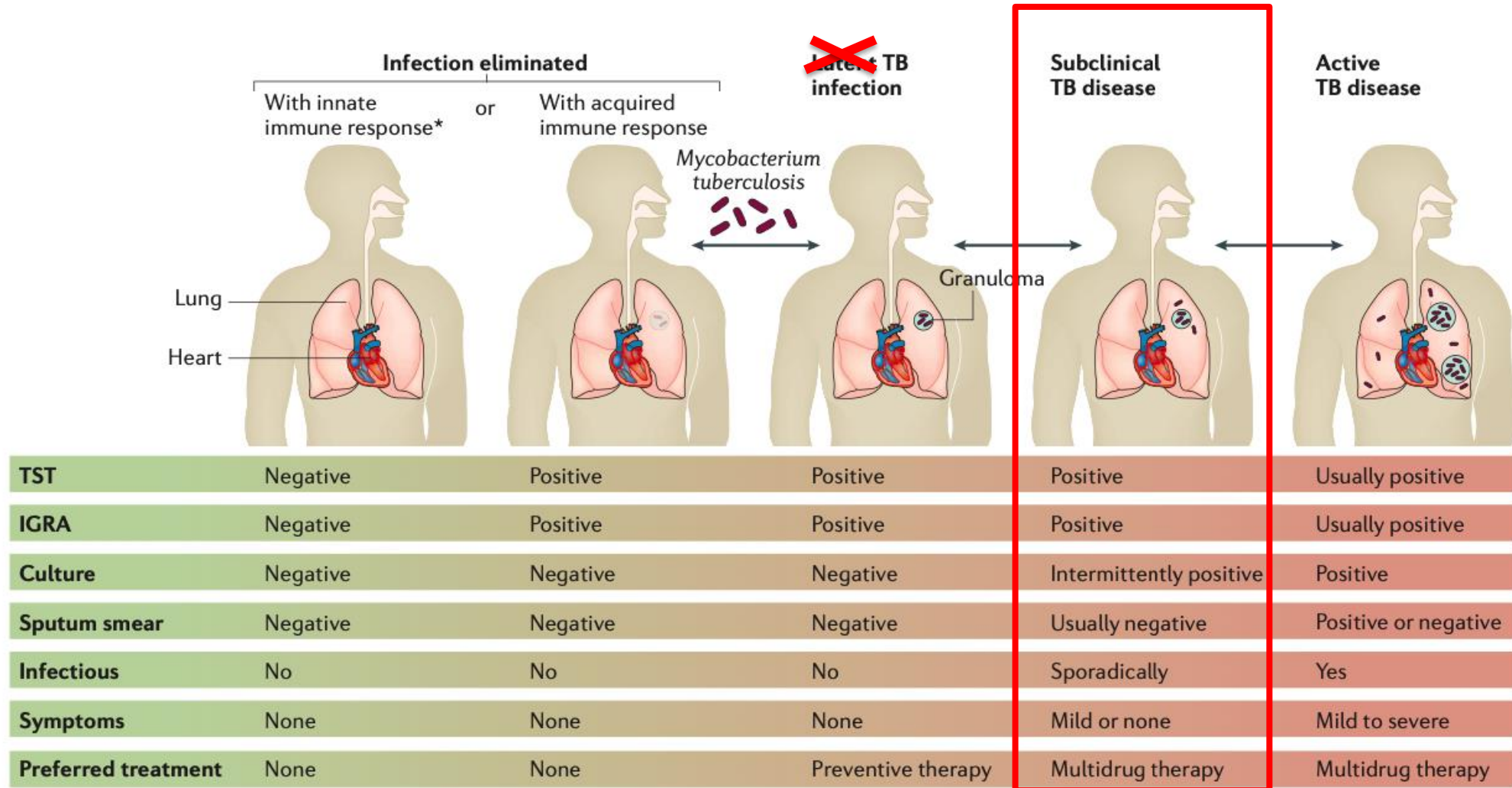


Natural history of TB

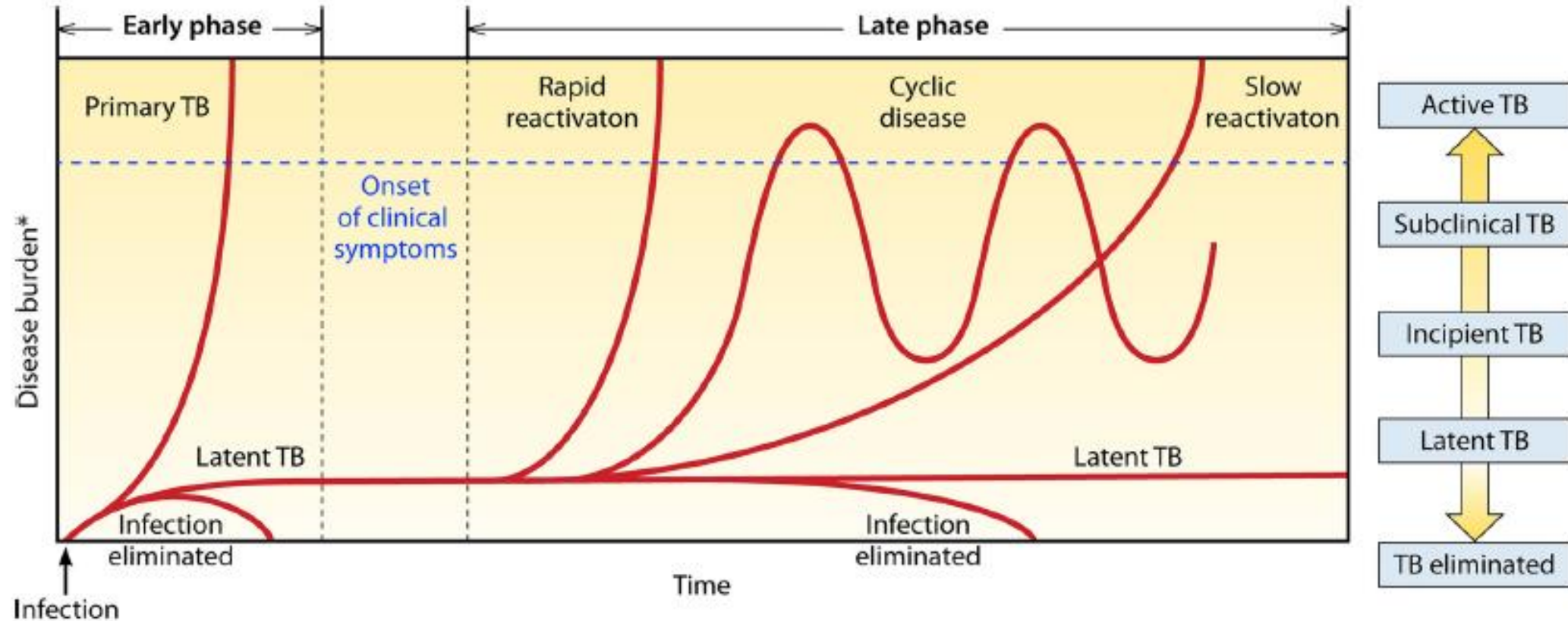


* In the lifetime

Tuberculosis

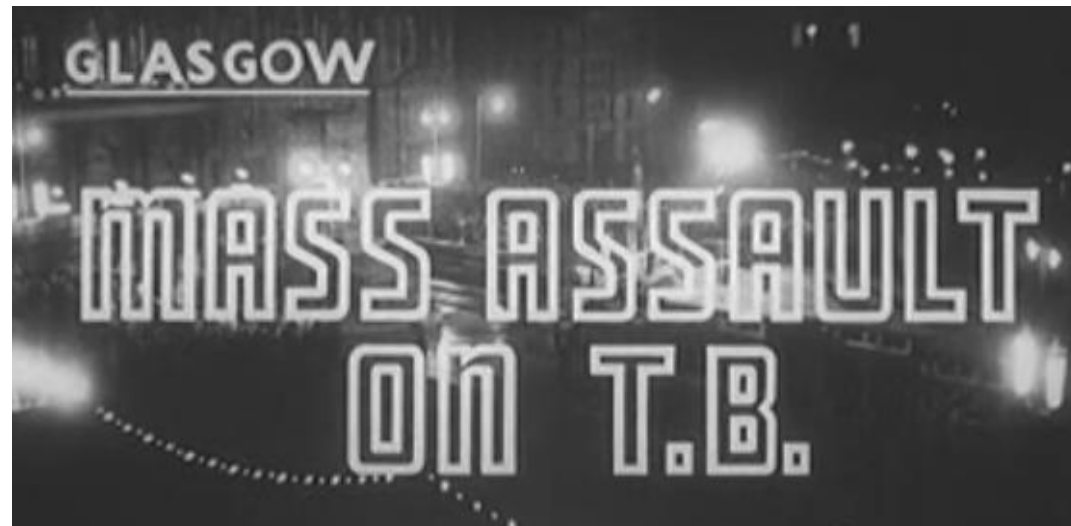


Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection



Early popularity of mass TB screening

- Mass TB screening by chest radiography commonplace in 1930's-1960's in several countries, with 3 main objectives:
 1. Detect patients earlier to reduce mortality
 2. Isolate TB patients to reduce transmission
 3. Identify people at high risk to progress for follow up
- Follow-up surveys often found substantial reductions in prevalence of TB in communities



Community-wide Screening for Tuberculosis in a High-Prevalence Setting

Guy B. Marks, M.B., B.S., Ph.D., Nhung V. Nguyen, M.D., Ph.D.,
Phuong T.B. Nguyen, Ph.D., Thu-Anh Nguyen, M.D., Ph.D.,
Hoa B. Nguyen, M.D., Ph.D., Khoa H. Tran, M.D., Son V. Nguyen, M.D.,
Khanh B. Luu, B.P.H., Duc T.T. Tran, M.P.H., Qui T.N. Vo, B.A.,
Oanh T.T. Le, B.P.H., Yen H. Nguyen, B.P.H., Vu Q. Do, Ph.D.,
Paul H. Mason, Ph.D., Van-Anh T. Nguyen, Ph.D., Jennifer Ho, M.B., B.S., Ph.D.,
Vitali Sintchenko, M.D., Ph.D., Linh N. Nguyen, M.D., Ph.D.,
Warwick J. Britton, M.B., B.S., Ph.D., and Greg J. Fox, M.B., B.S., Ph.D.

N ENGL J MED 381;14 NEJM.ORG OCTOBER 3, 2019

Community-based active case-finding interventions for tuberculosis: a systematic review

Rachael M Burke, Marriott Nliwasa, Helena R A Feasey, Lelia H Chaisson, Jonathan E Golub, Fahd Naufal, Adrienne E Shapiro, Maria Ruperez, Lily Telisinghe, Helen Ayles, Elizabeth L Corbett, Peter MacPherson

Clinical Infectious Diseases

REVIEW ARTICLE



Subclinical Tuberculosis Disease—A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology

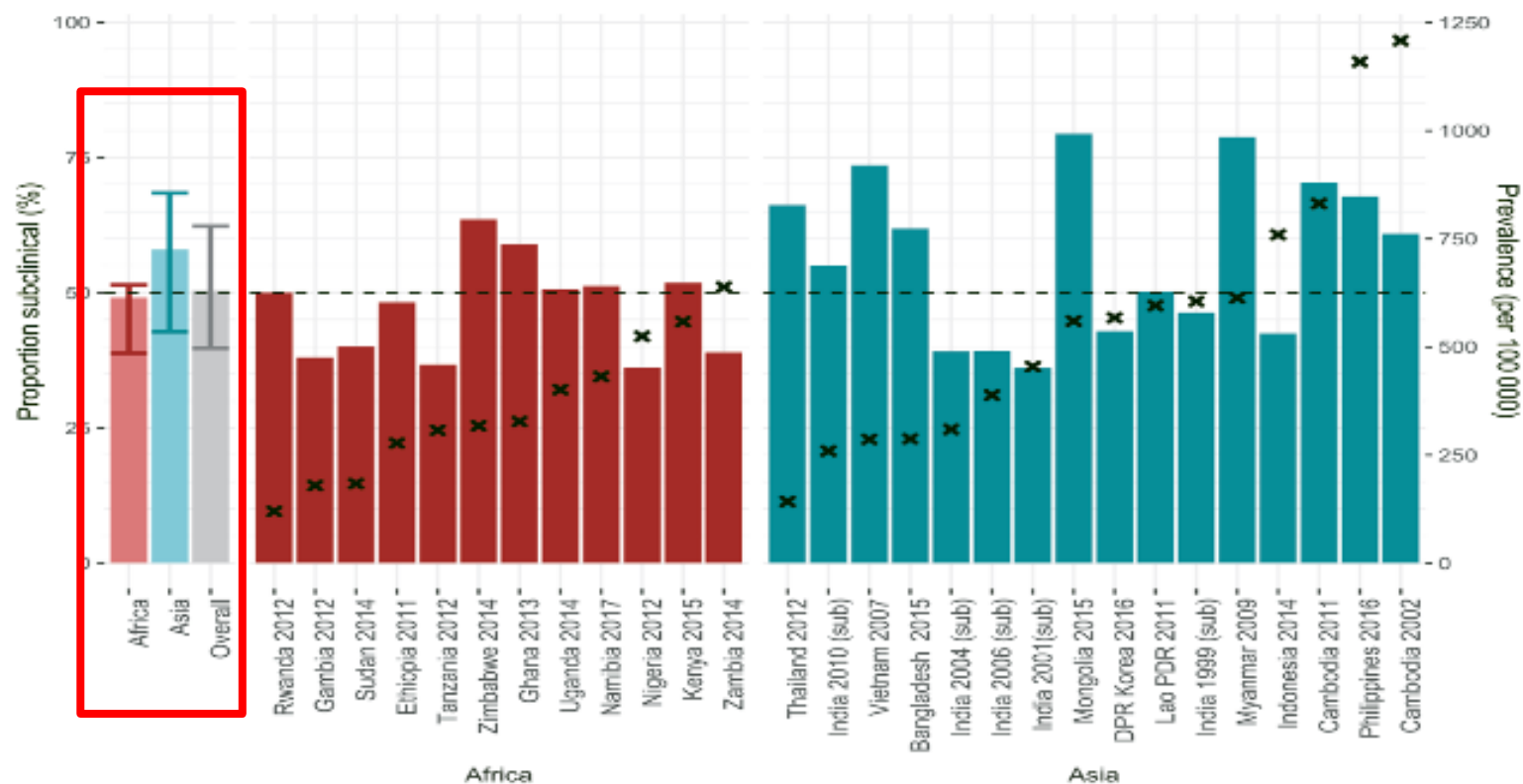
Beatrice Frascella,¹ Alexandra S. Richards,^{2,3} Bianca Sossen,^{4,5,6} Jon C. Emery,² Anna Odone,¹ Irwin Law,⁷ Ikushi Onozaki,⁸ Hanif Esmail,^{4,5,9} and Rein M. G. J. Houben^{2,3}

¹School of Public Health, Vita-Salute San Raffaele University, Milan, Italy, ²TB Modelling Group, TB Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom, ³Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine, London, United Kingdom, ⁴Institute for Global Health, University College London, London, United Kingdom, ⁵Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa, ⁶Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa, ⁷Global Tuberculosis Programme, World Health Organization, Geneva, Switzerland, ⁸World Health Organization, Yangon, Myanmar, and ⁹Medical Research Council Clinical Trials Unit at University College London, London, United Kingdom

Estimating the contribution of subclinical tuberculosis disease to transmission: An individual patient data analysis from prevalence surveys

Jon C Emery^{1*}, Peter J Dodd², Sayera Banu³, Beatrice Frascella⁴, Frances L Garden^{5,6}, Katherine C Horton¹, Shahed Hossain⁷, Irwin Law⁸, Frank van Leth^{9,10}, Guy B Marks^{5,11}, Hoa Binh Nguyen¹², Hai Viet Nguyen¹², Ikushi Onozaki¹³, Maria Imelda D Quelapio¹⁴, Alexandra S Richards¹, Nabila Shaikh^{1,15}, Edine W Tiemersma¹⁶, Richard G White¹, Khalequ Zaman³, Frank Cobelens¹⁷, Rein MGJ Houben¹

How much of TB is Subclinical?

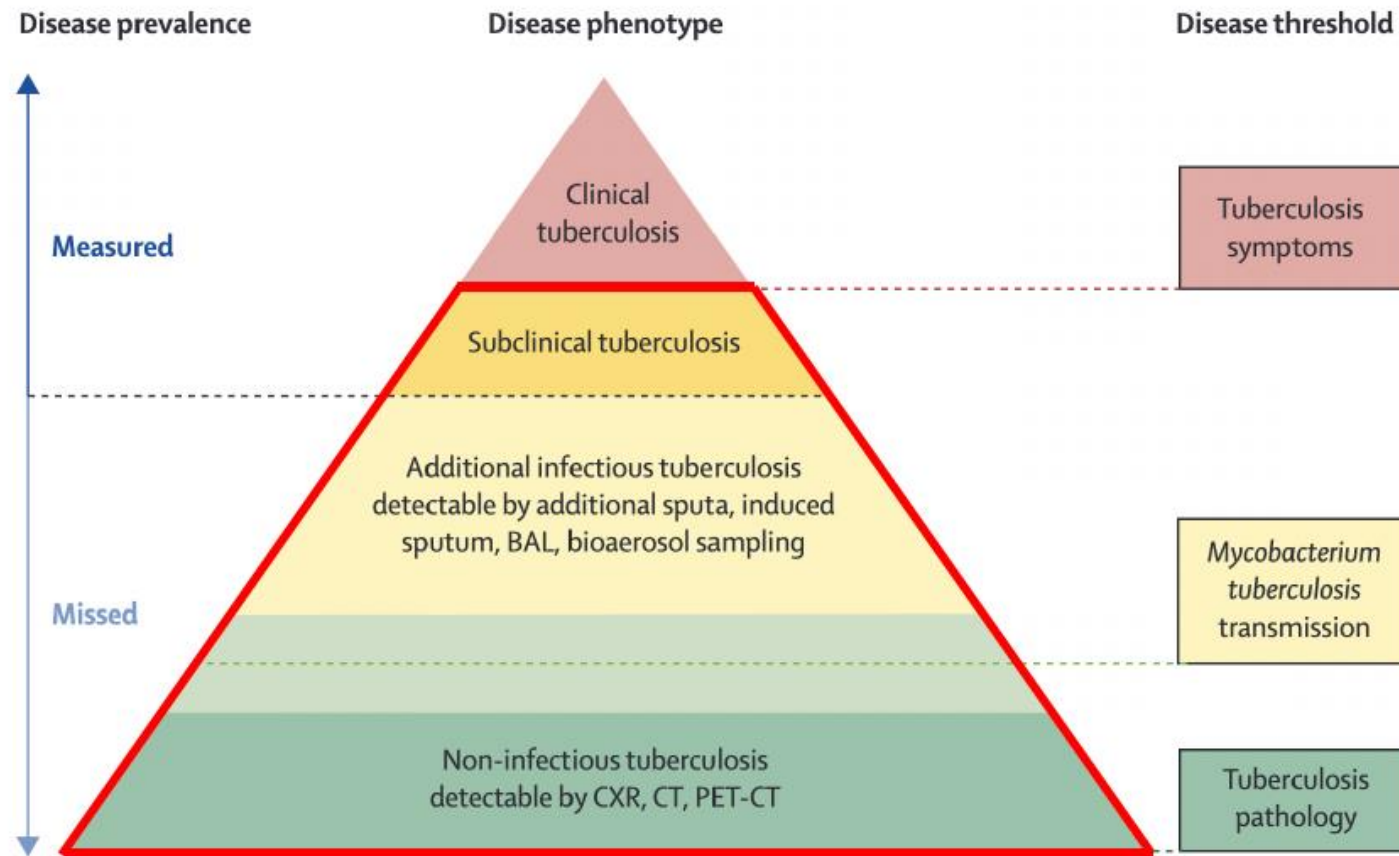


50.4% of TB detected from 28 prevalence surveys subclinical

Different definitions for subclinical used by surveys

*Frascella et al, 2021

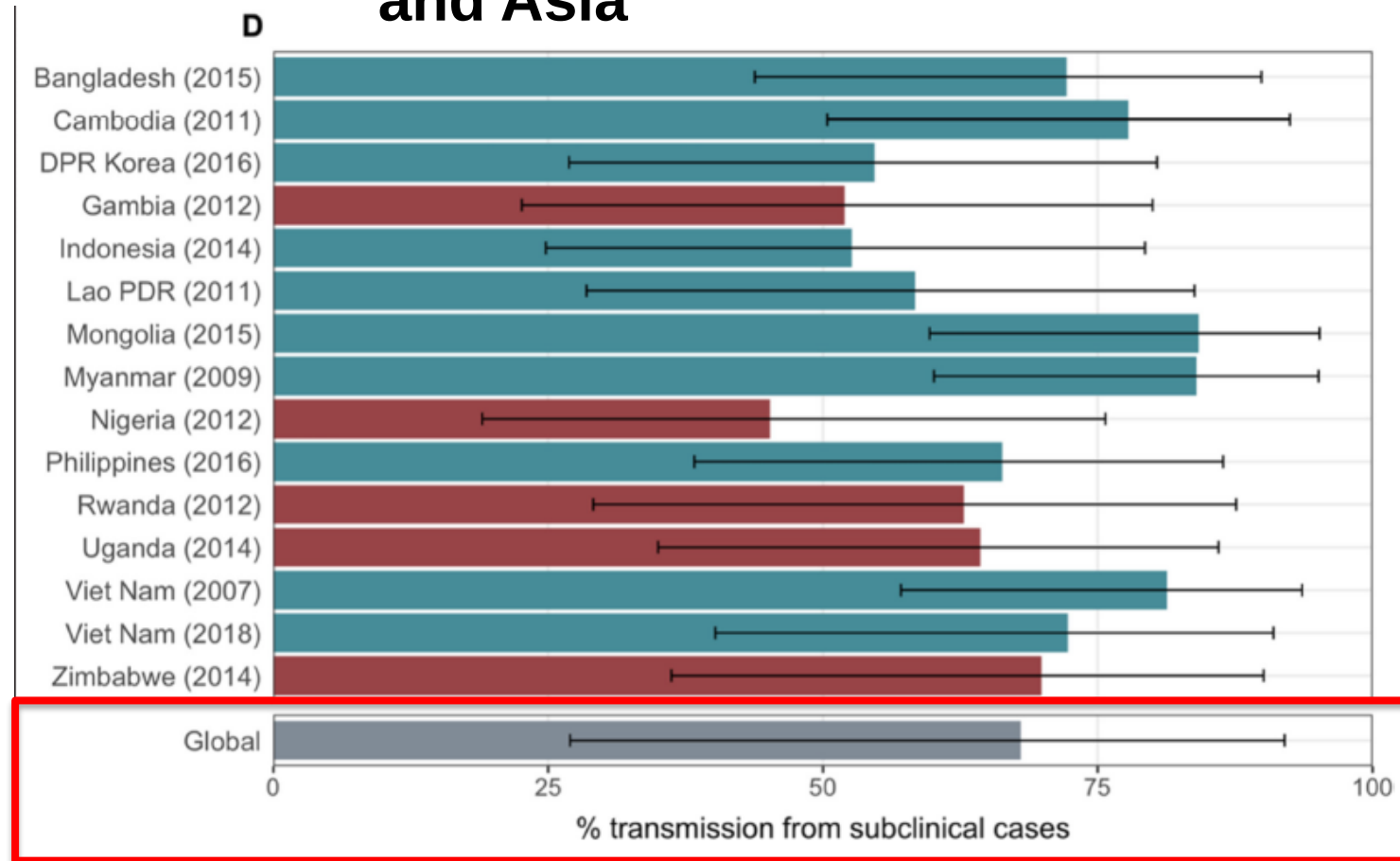
Tuberculosis prevalence: beyond the tip of the iceberg



Houben et al. Lancet RM 2022

Growing recognition of the role of
subclinical TB
in perpetuating the TB epidemic

Estimated proportion of transmission from subclinical TB at the time of and in the location of each of the prevalence surveys in Africa and Asia



68%!!

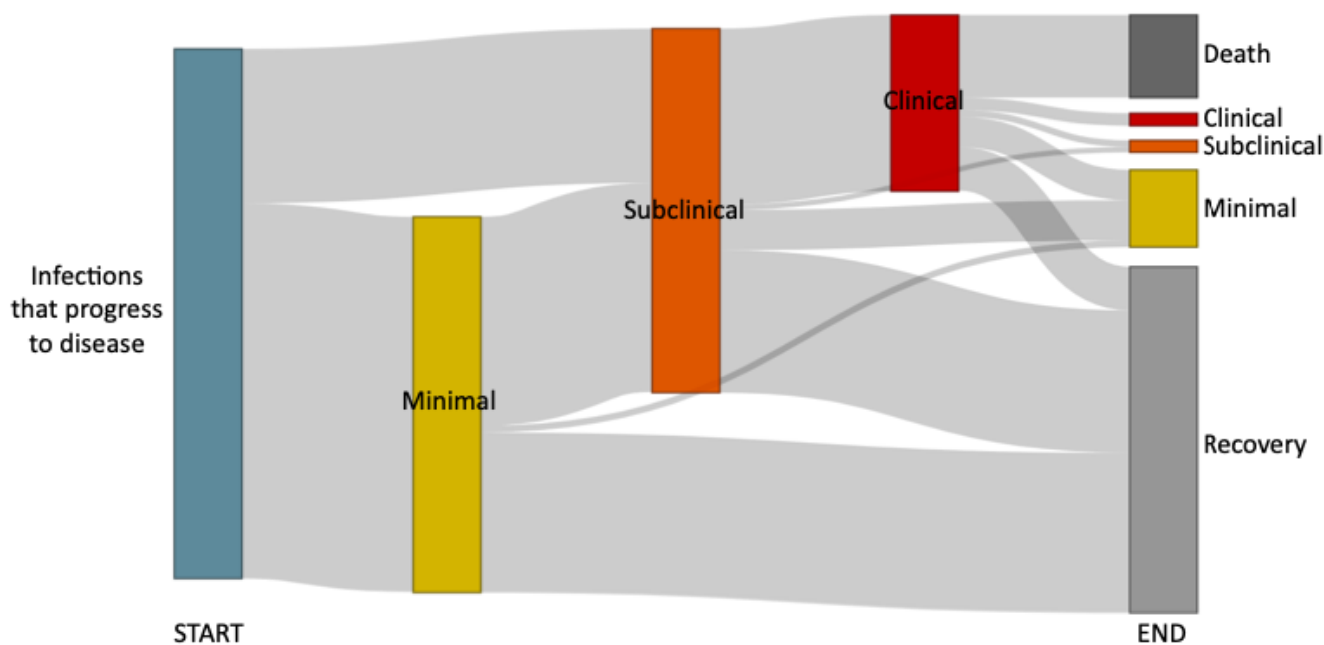
Classification of early tuberculosis states to guide research for improved care and prevention: an international Delphi consensus exercise

Anna K Coussens*, Syed M A Zaidi, Brian W Allwood, Puneet K Dewan, Glenda Gray, Mikashmi Kohli, Tamara Kredo, Ben J Marais, Guy B Marks, Leo Martinez, Morten Ruhwald, Thomas J Scriba, James A Seddon, Phumeza Tisile, Digby F Warner, Robert J Wilkinson, Hanif Esmail*, Rein M G J Houben*, on behalf of the International Consensus for Early TB (ICE-TB) group†

	Disease dimensions*			
	Macroscopic pathology	Infectiousness	Symptoms and signs	
Mycobacterium tuberculosis infection				Infection
Subclinical tuberculosis, non-infectious				Disease
Subclinical tuberculosis, infectious				
Clinical tuberculosis, non-infectious				
Clinical tuberculosis, infectious				

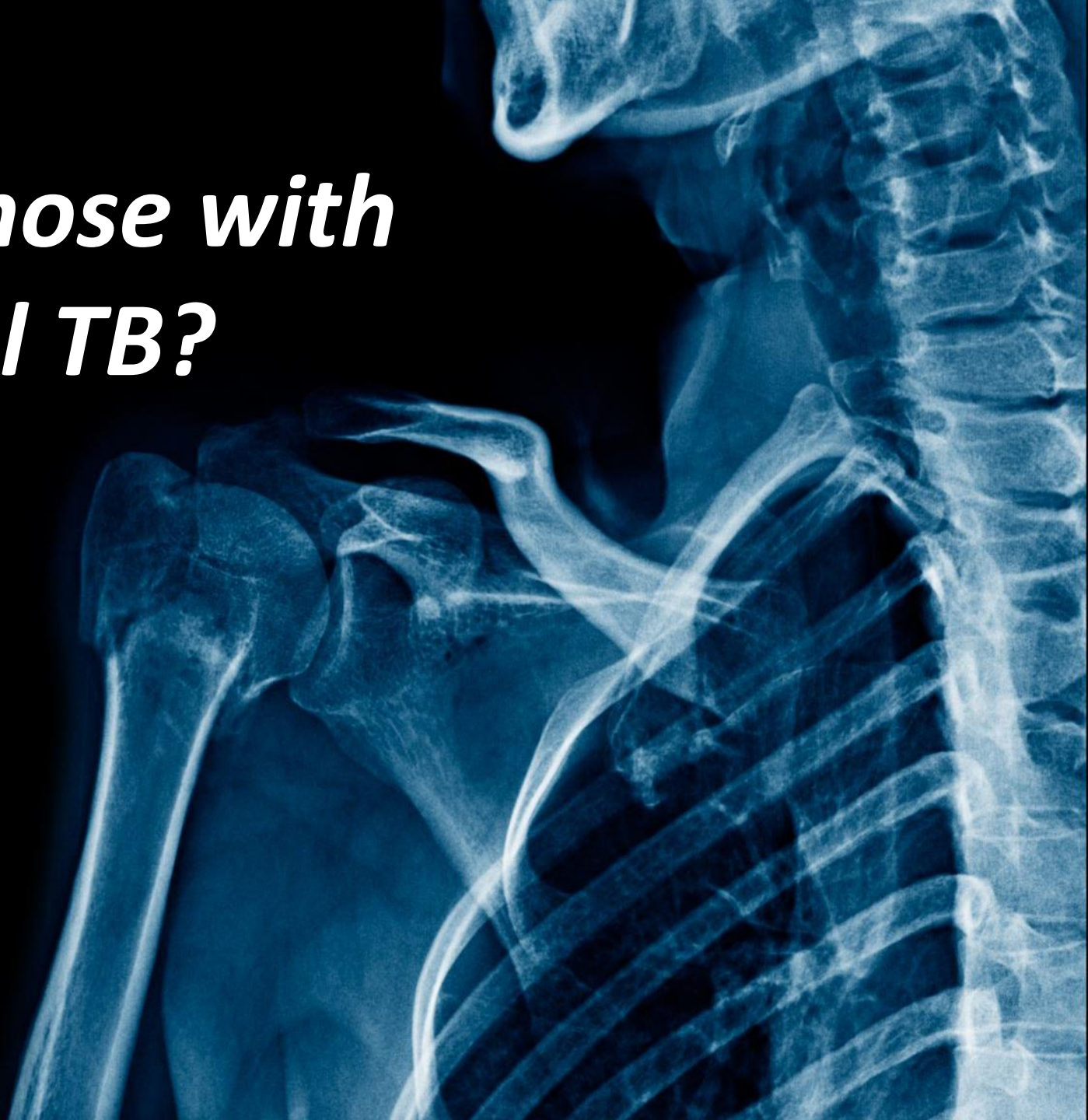
Reevaluating progression and pathways following *Mycobacterium tuberculosis* infection within the spectrum of tuberculosis

Katherine C. Horton ^{a,2,1}, Alexandra S. Richards ^{a,1}, Jon C. Emery^a, Hanif Esmail^b, and Rein M. G. J. Houben ^a



50% subclinical
don't progress???

***How to find those with
subclinical TB?***



Classification of early tuberculosis states to guide research for improved care and prevention: an international Delphi consensus exercise

Anna K Coussens*, Syed M A Zaidi, Brian W Allwood, Puneet K Dewan, Glenda Gray, Mikashmi Kohli, Tamara Kredo, Ben J Marais, Guy B Marks, Leo Martinez, Morten Ruhwald, Thomas J Scriba, James A Seddon, Phumeza Tisile, Digby F Warner, Robert J Wilkinson, Hanif Esmail*, Rein M G J Houben*, on behalf of the International Consensus for Early TB (ICE-TB) group†

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Clinical tuberculosis, non-infectious				
Clinical tuberculosis, infectious				

How to find those with subclinical TB?

Active TB

Passive case finding

(patients self-presenting to HFs)

Entry point:

- TB suggestive symptoms
- CXR -> HRCT -> Sputum
- Other imaging/samples for EPTB
- Decision to start anti-TB treatment

Subclinical TB

Active case finding

(contacts screening, migrants screening, PLHIV, candidates to anti-TNF, transplant candidates, other comorbidities follow up)

Entry point:

- Positive TST/IGRA and/or abnormal imaging
- HRCT/PET -> Sputum/Induced sputum/BAL
- Decision to start anti-TB treatment



How to treat subclinical TB?

Mind the gap — Managing tuberculosis across the disease spectrum

Hanif Esmail,^{a,b,c,} Liana Macpherson,^a Anna K. Coussens,^{c,d,e} and Rein M.G.J. Houben^{f,g}*

^aMRC Clinical Trials Unit at University College London, UK

^bInstitute for Global Health, University College London, UK

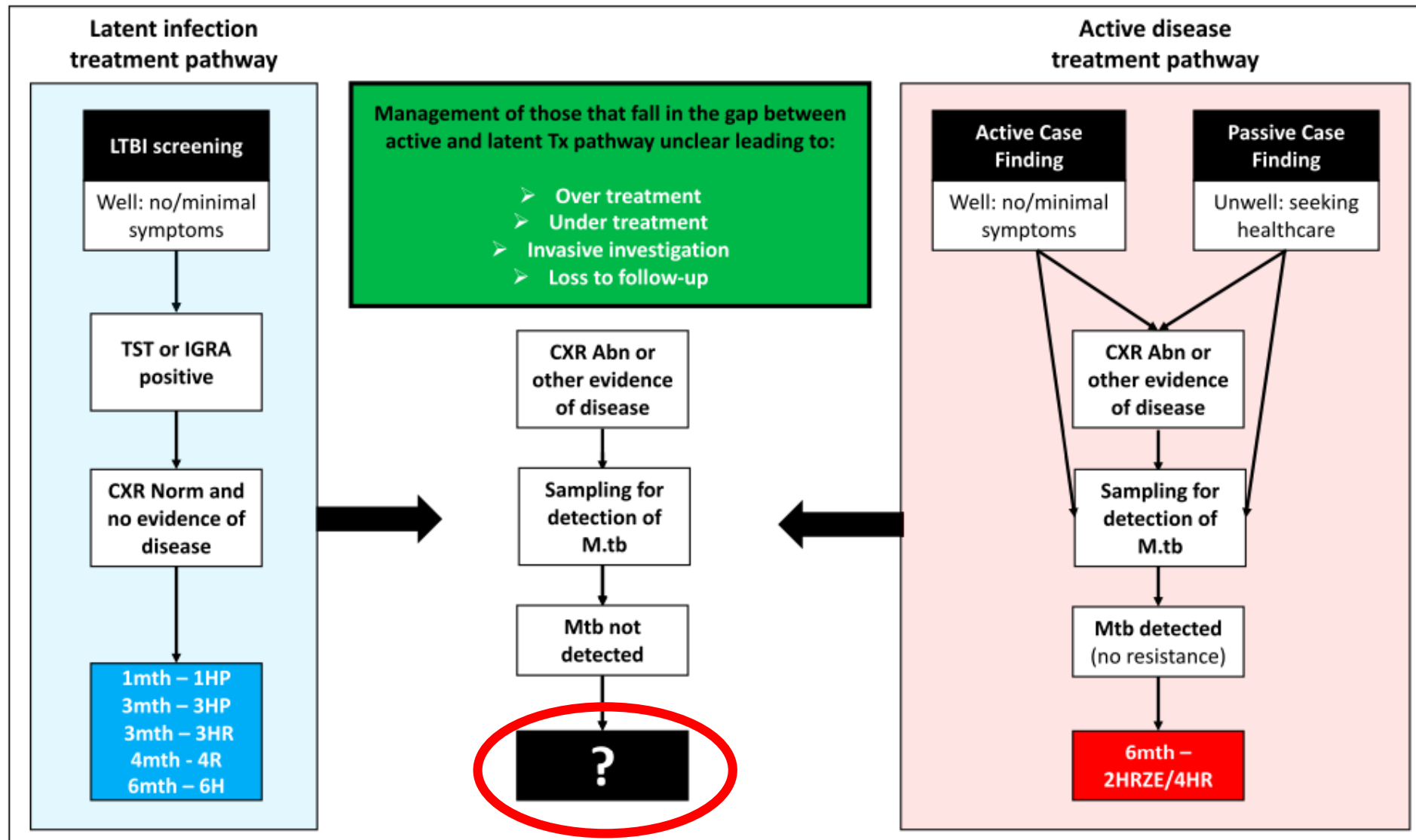
^cWellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa

^dInfectious Diseases and Immune Defense Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia

^eDepartment of Medical Biology, University of Melbourne, Parkville, Australia

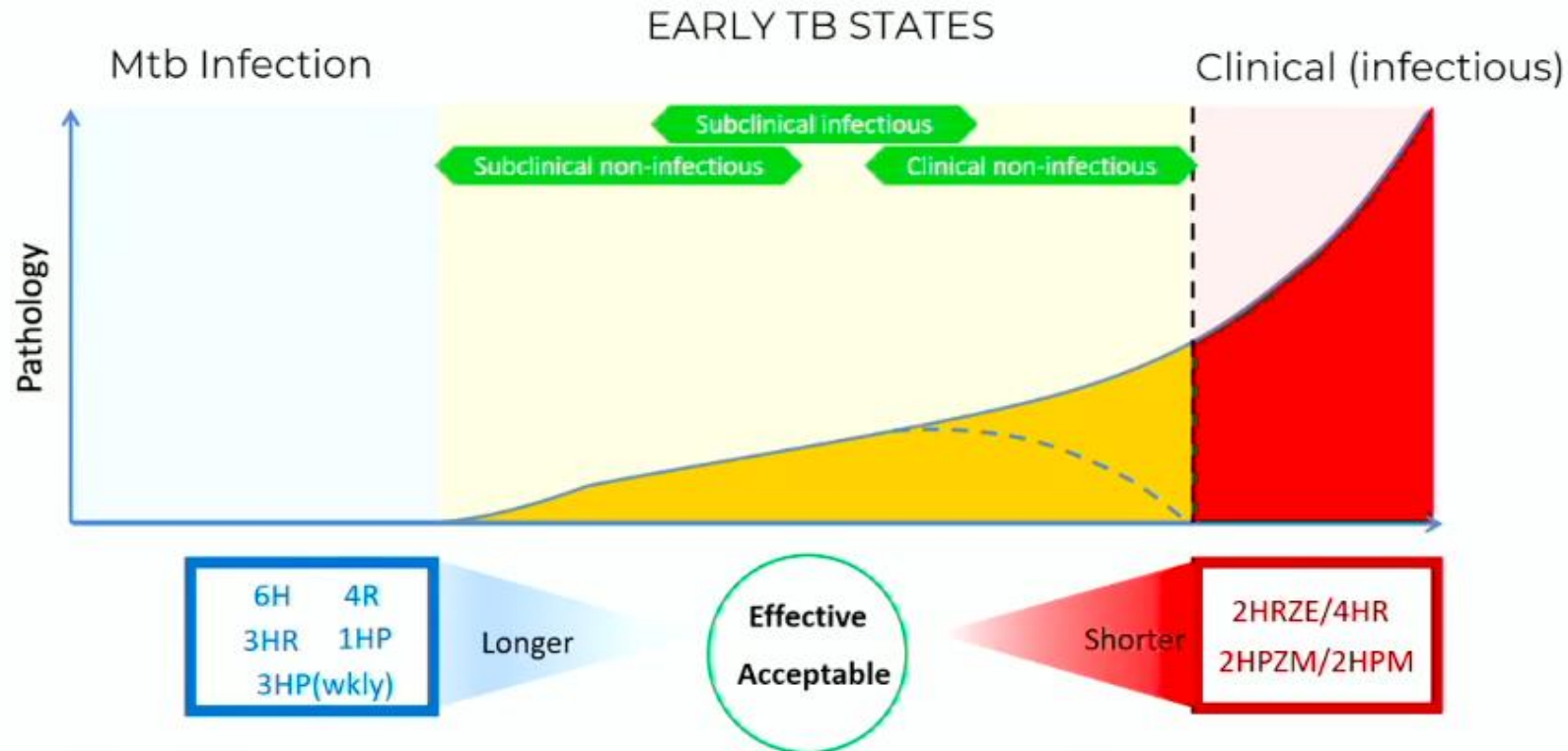
^fTB Modelling Group, TB Centre, London School of Hygiene and Tropical Medicine, UK

^gDepartment of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, UK



How to treat subclinical TB ?

TB SPECTRUM AND TREATMENT



Clinical trials on subclinical TB treatment are needed!



WHO Technical consultation on Subclinical TB

14 – 15 October 2024, WHO HQ, Geneva, Switzerland

Salle V1-V2 – B Building (main entrance)

Draft Provisional agenda

From subclinical TB to **asymptomatic TB**

Asymptomatic TB definition

Current WHO definitions of TB

TB disease:

A person with disease caused by the *M. tuberculosis* complex.

Bacteriologically confirmed TB:

A person from whom a biological specimen is positive by a WHO-recommended rapid diagnostic test, culture or smear microscopy.

Clinically diagnosed TB (being reworded to bacteriologically unconfirmed):

A person who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with TB disease by a medical practitioner....

New definitions for asymptomatic TB

Asymptomatic TB:

A person with TB disease who did not report symptoms suggestive of TB during screening.

Asymptomatic TB, bacteriologically confirmed:

A person with bacteriologically confirmed TB who did not report symptoms suggestive of TB during screening.

Asymptomatic TB, bacteriologically unconfirmed:

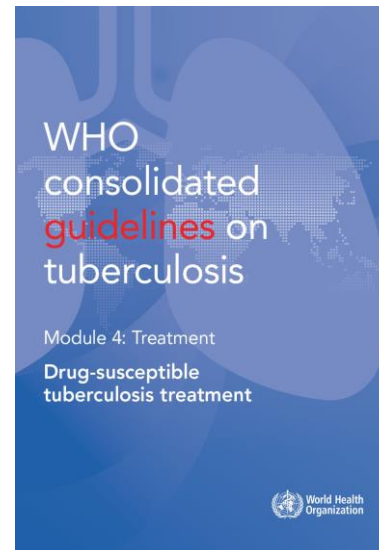
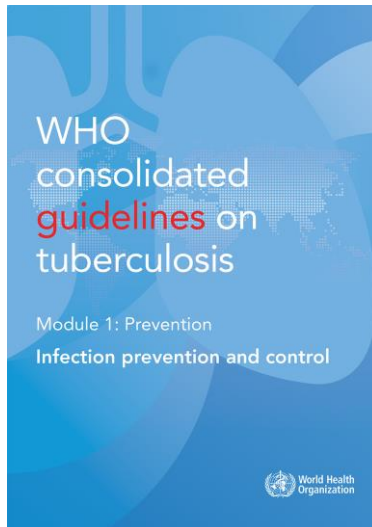
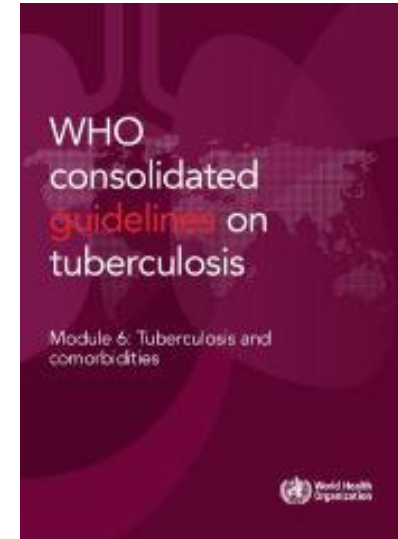
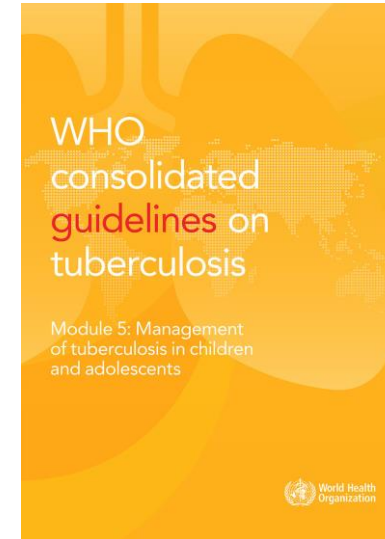
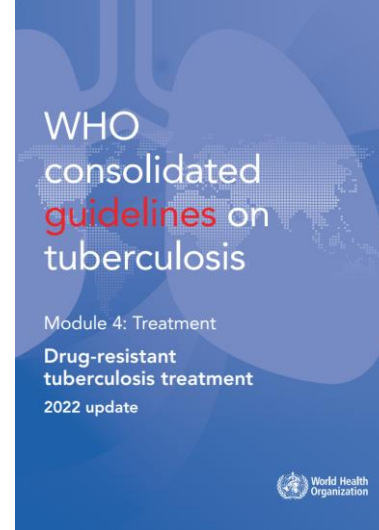
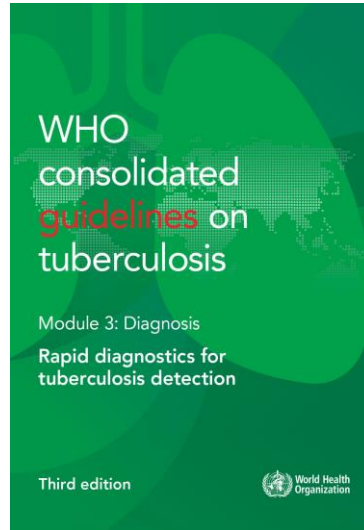
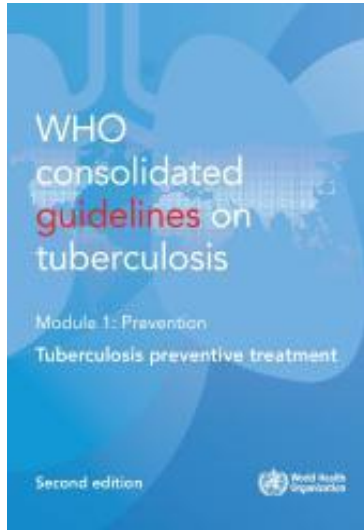
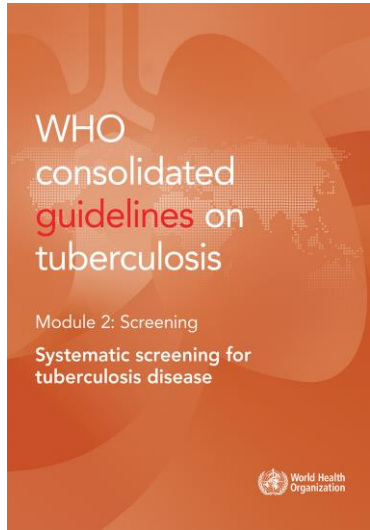
A person with bacteriologically unconfirmed TB who did not report symptoms suggestive of TB during screening.

Consolidated guidance on tuberculosis data generation and use
Module 1

Tuberculosis surveillance



Asymptomatic TB: Policy implications



Summary

Natural history of TB is composed by a continuum of phases, with undulating and dynamic pathways over time

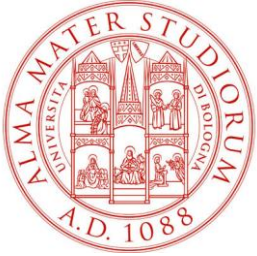
TB disease $\neq$ presence of symptoms!!!

Finding asymptomatic TB could be an important way to prevent transmission, future symptomatic disease, and post-TB health consequences

**Passive case finding/symptoms screening miss a considerable amount of disease!!
Symptoms agnostic screening algorithms are needed.**

Research studies should explore **how to treat asymptomatic TB**

THANKS TO



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Elisa Vanino, Caterina Monari



World Health
Organization

Irwin Law, Ikushi Onozaki, Cecily Miller,
Dennis Falzon, Matteo Zignol, Katherine Floyd



Characteristics of culture-negative subclinical pulmonary tuberculosis: a single-center observation



Figure 2. A-C) Pre- and post-treatment chest images of a 26-year-old female with culture-positive subclinical pulmonary TB. A) Pre-treatment chest radiograph shows reticulonodular opacities at the right apical lung. B) Axial CT image in lung window performed 1 month after A. reveals multiple centrilobular nodules with tree-in-bud pattern in the apical segment of the right upper lobe. C) Post-treatment chest radiograph (7 months after A.) shows resolution of the abnormalities of the right apical lung.

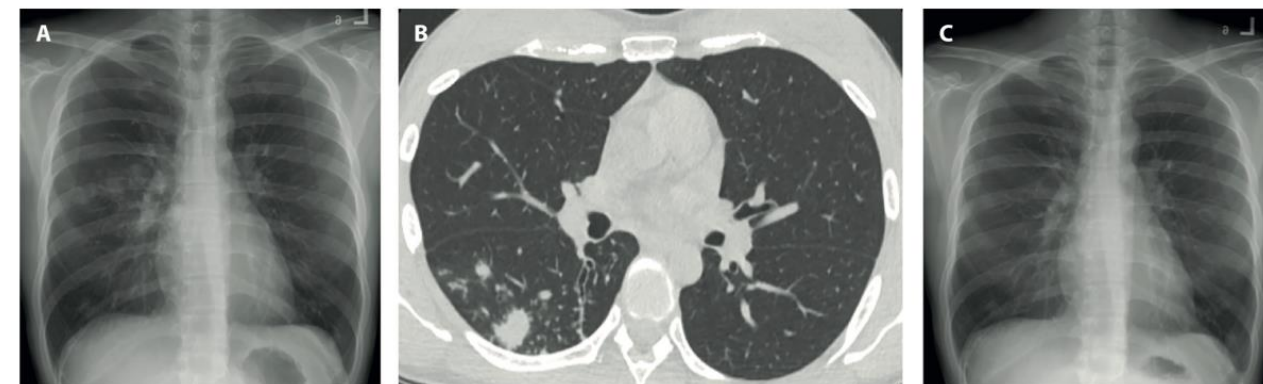


Figure 3. A-C) Pre- and post-treatment chest images of a 32-year-old female with culture-negative subclinical pulmonary TB. A) Pre-treatment chest radiograph shows patchy nodular opacities at the right middle lung zone. B) Axial CT image in lung window performed on the same date as A. reveals solid pulmonary nodules with adjacent centrilobular and tree-in-bud opacities in the superior segment of the right lower lobe as well as bronchial wall thickening and bronchiectasis. C) Post-treatment chest radiograph (10 months after A.) shows resolution of the abnormalities with minimal residual fibrosis at the right middle lung zone.

Subclinical - Culture positive

Subclinical - Culture negative

Symptoms screening?

Persistent cough?

Any cough?

4 WHO symptoms?

Or any symptom?

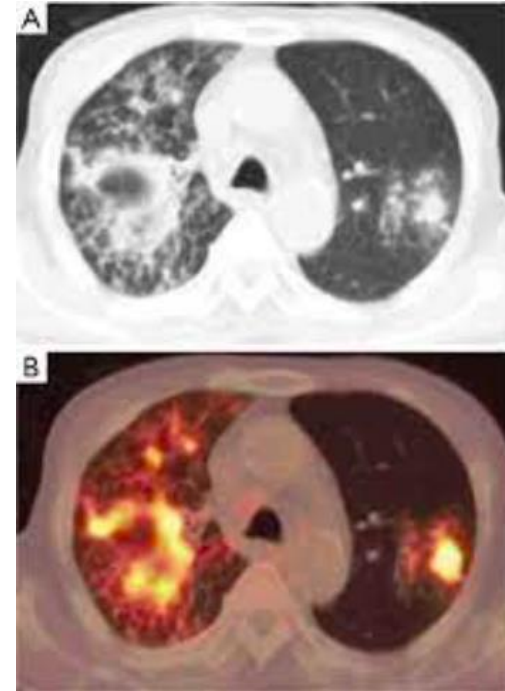
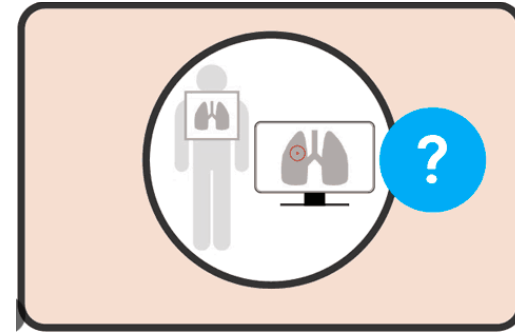


Imaging?

CXR?

Chest HRCT?

PET/TC?



Bacteriological tests?

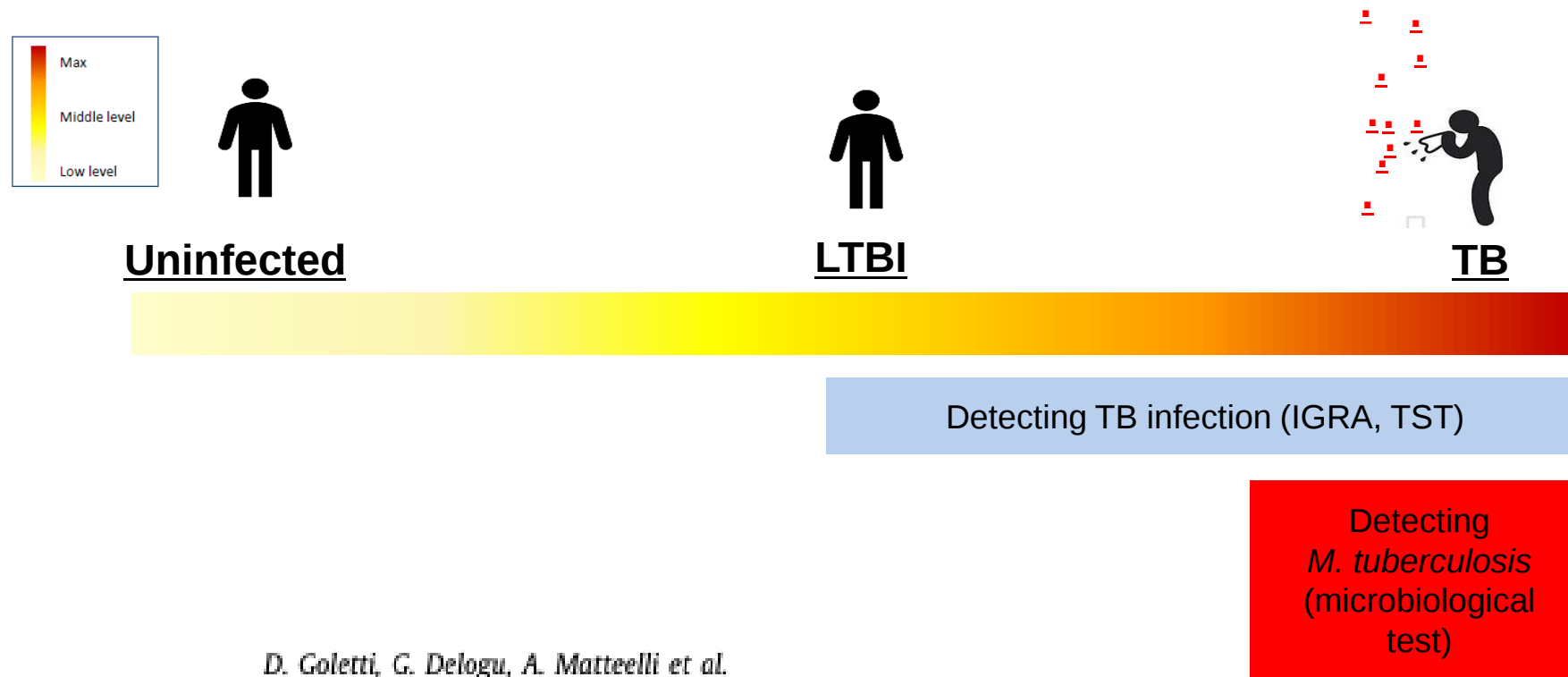
Xpert? Trace? 1 is enough?
Culture?



On sputum? Induced sputum? BAL?

TST? IGRA? New skin tests?

Other biomarkers?



D. Goletti, G. Delogu, A. Matteelli et al.

International Journal of Infectious Diseases 124 (2022) S12–S19