TB: A Crash Course Toward Confidence and Expertise in a Dynamic Time

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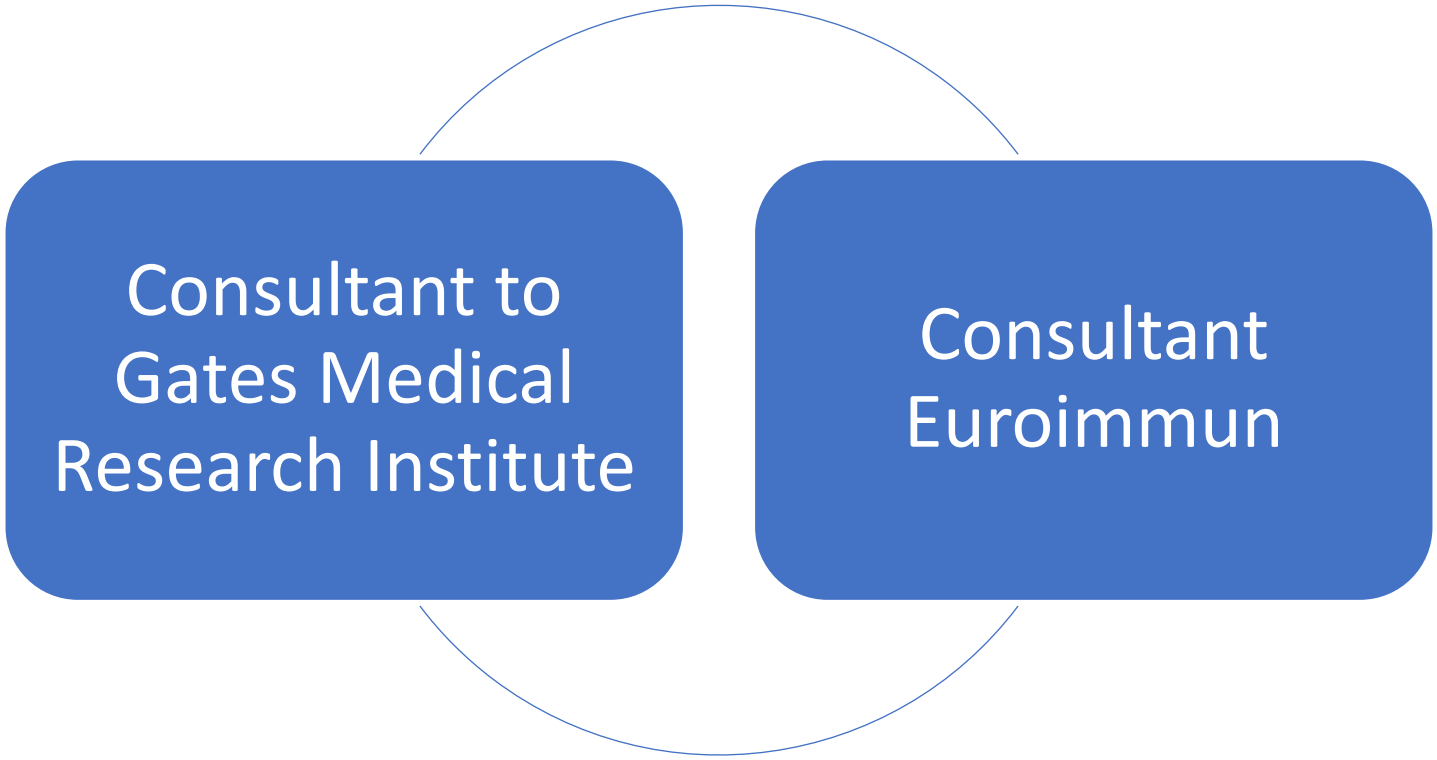
Disclosure


Consultant to Gates Medical Research Institute
Consultant Euroimmun

Outline

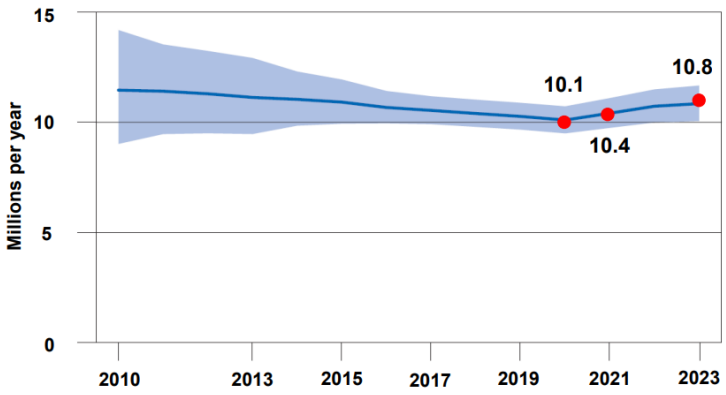
- Epidemiology: “TB Disease” and “TBI”
  - New research re continuum of TB disease and TBI
- Local sitrep
- TBI updates
- TB changing paradigm
- TB future

Getting on the Same Page

- TBI: TB infection, newer term for latent TB infection
- TB disease: newer term for active TB or tuberculosis
- TST: tuberculin skin test which uses PPD
- IGRA: interferon-gamma release assay
- TB screening: TB risk assessment, TB symptom evaluation, test for *M. tuberculosis* infection
- TB risk assessment: who is at risk for TB disease?

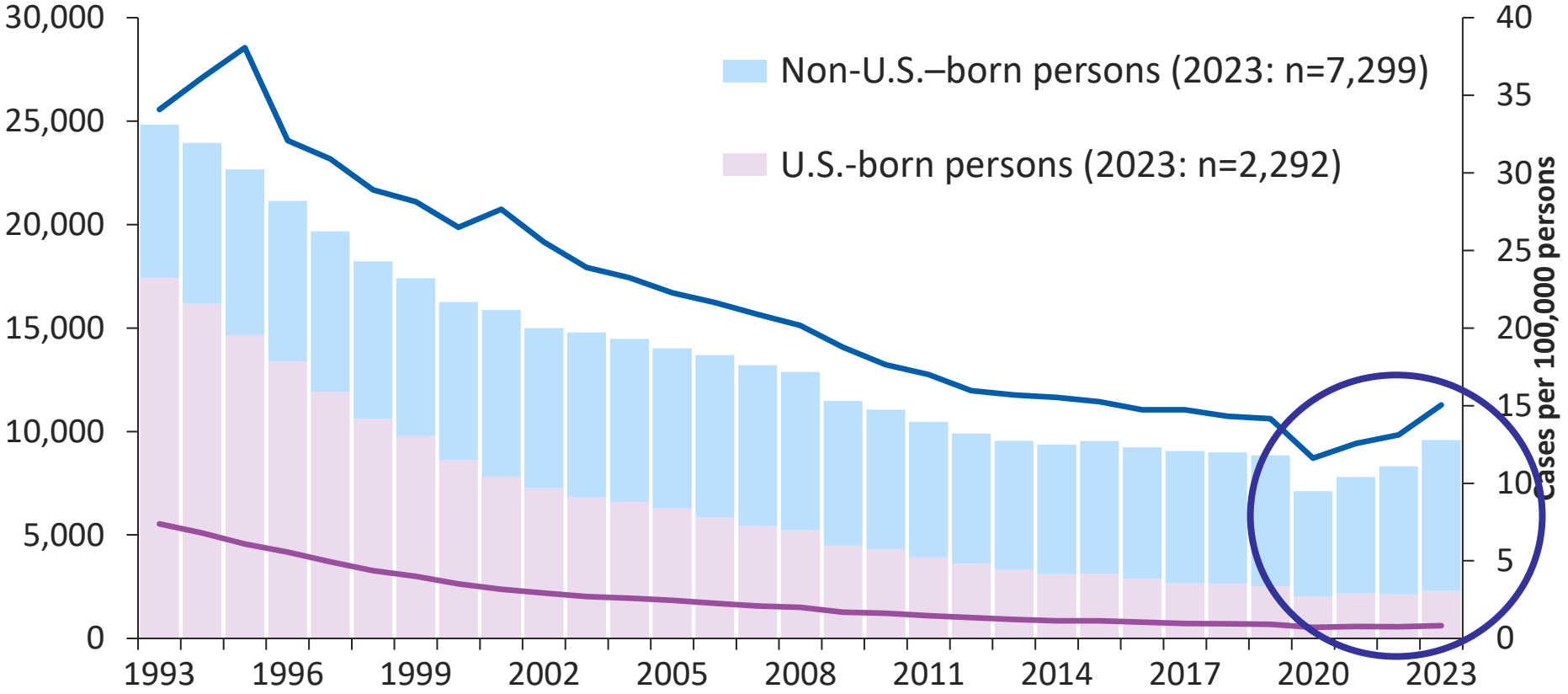
Global tuberculosis report 2024

- Estimated 10.8M people developed TB disease in 2023
  - Estimated rate 134/100,000 population
  - 55% men, 33% women, 12% <15y
  - “Global rise in TB incidence is slowing”
  - India (26%), Indonesia (10%), and China, the Philippines, and Pakistan (~6%)
- Estimated 1.25M global deaths



WHO Global TB Report 2024

Cases and Incidence Rates by Origin of Birth*
US, 1993–2023

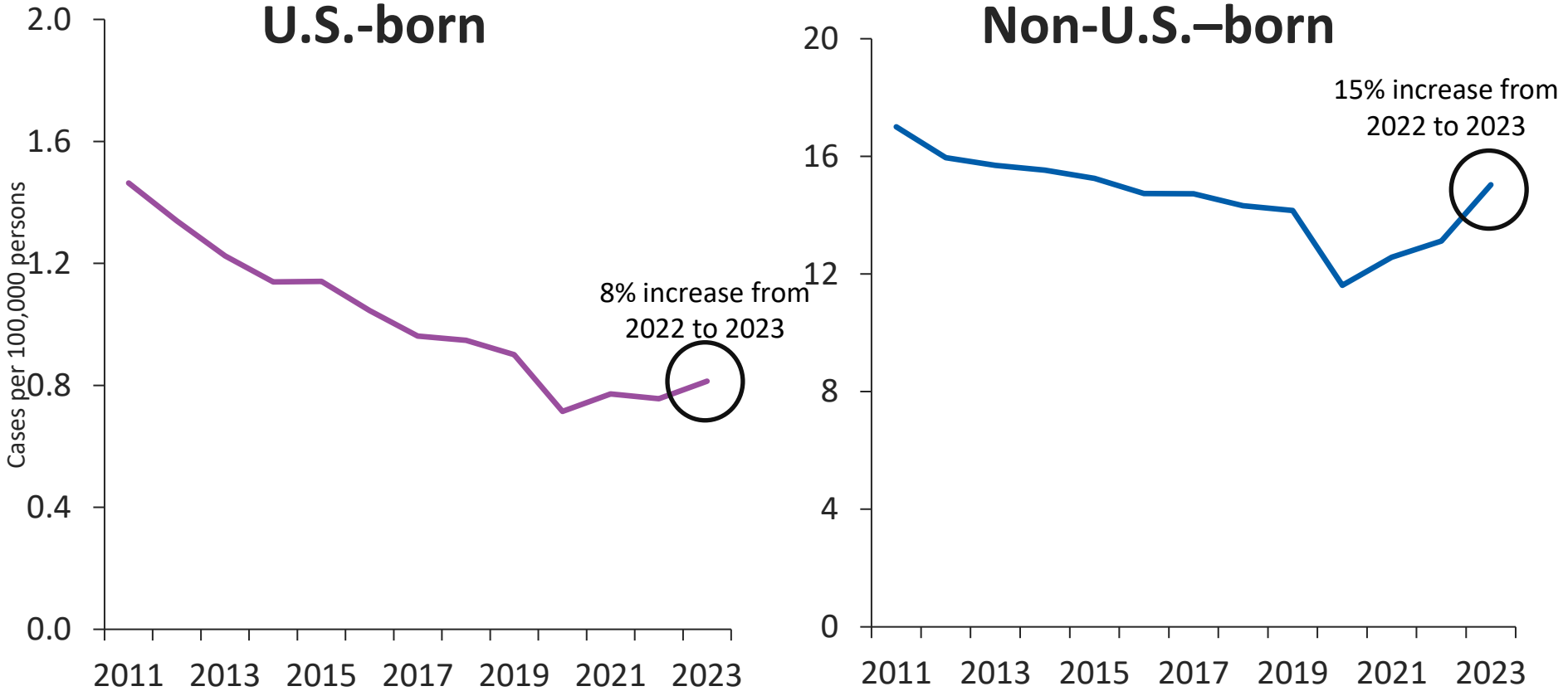


*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

2023 REPORTED TUBERCULOSIS IN THE UNITED STATES

CDC TB Surveillance

Increases by Origin of Birth,* US, 2011–2023



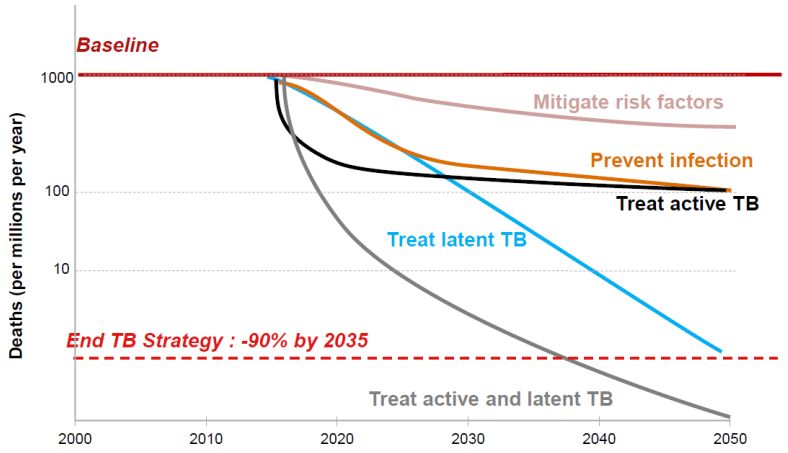
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

2023 REPORTED TUBERCULOSIS IN THE UNITED STATES

CDC TB Surveillance

TB Disease Elimination in the US Requires Focus on TBI

- >80% of TB disease in the US is due to reactivation of TBI
- ~13M (4.5%) in US have TBI (stable)
- Progress towards global TB disease elimination (<1 case/M) requires:
  - Continued management of those with infectious TB disease
  - Expanded detection and treatment of TBI, especially in high-risk groups



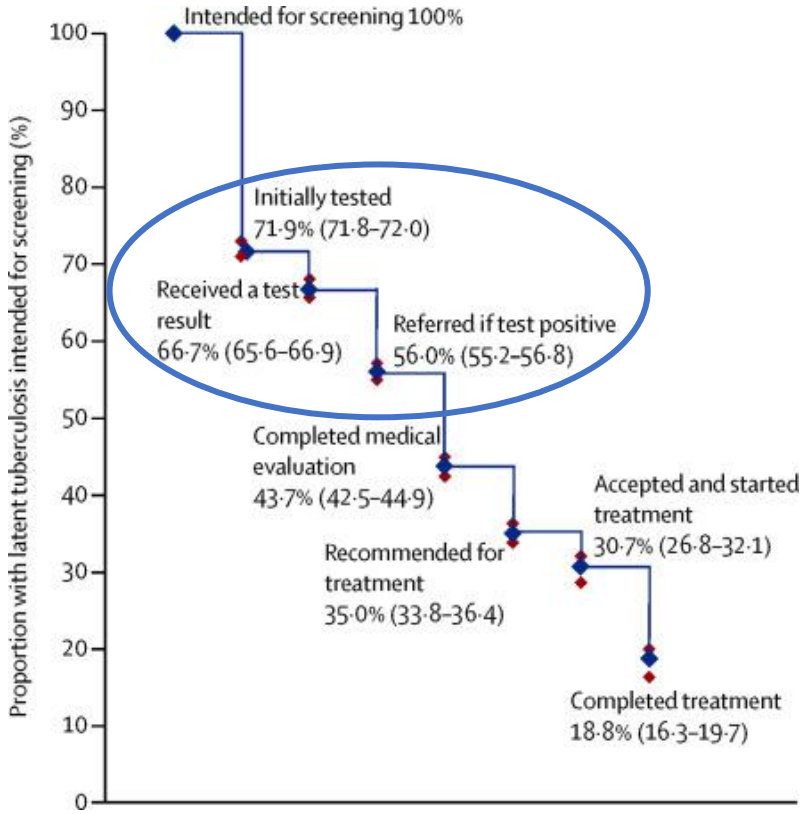
Dye C et al., Prospects for Tuberculosis Elimination. Ann Rev Public Health 2013. 34:271-86

TBI: The Tip of the Iceberg

Estimated TB disease incidence: 10.8M/year

TB infection prevalence: 2B

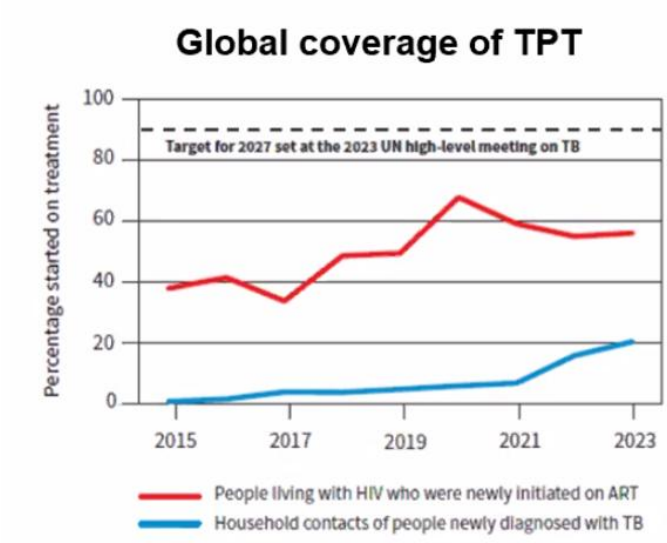
Cascade of Care for TBI



Alsdurf et al Lancet ID 2016

TBI Management Hesitancy

- Asymptomatic
- 3 testing options
- Testing turnaround time
- Expensive
- Conversions and reversions
- Dynamic guidance



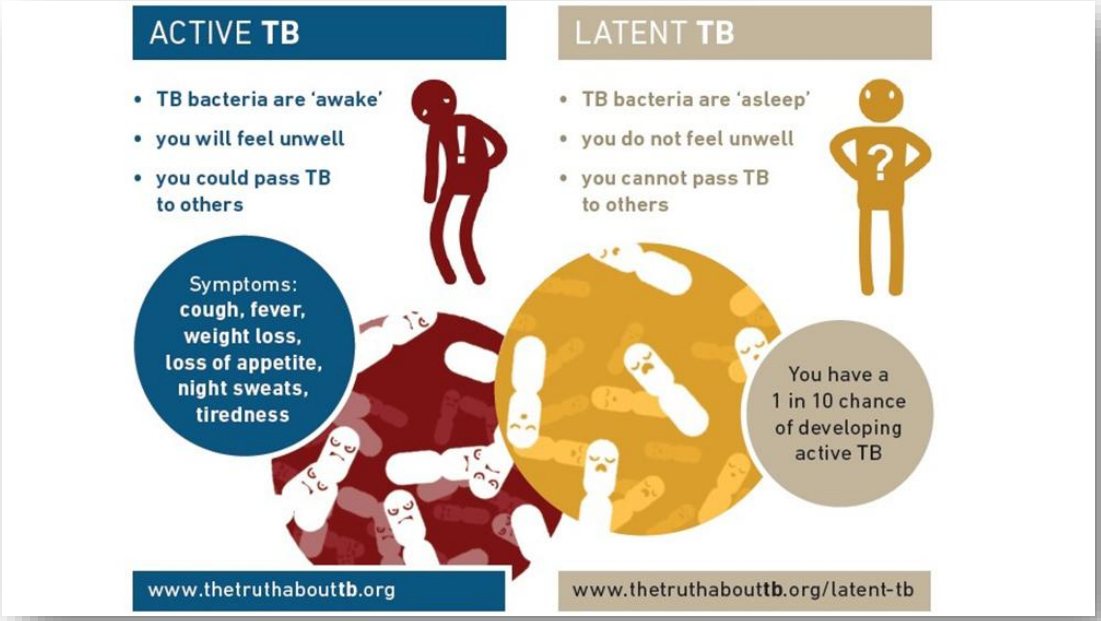
WHO Global TB Report 2024

Case: Positive IGRA

- Foreign-born, homebody author from rural Maine who reports no known TB contact has had his first IGRA because **he will start** TNF-alpha inhibitor for steroid-resistant rheumatoid arthritis
- QFTG-Plus (Qiagen) comes back as positive:
  - TB1-nil=1.3
  - TB2-nil=2.4
- What should be your next steps?

Next Steps on Cascade of Care

- The patient confirms he is fully asymptomatic. Afebrile, stable weight and cardiopulmonary exam is negative
- CXR shows ‘RUL infiltrate”. You call the radiologist who says this appears to be subtle fibronodular opacities
- What do you next?
- Xpert MTB/RIF positive

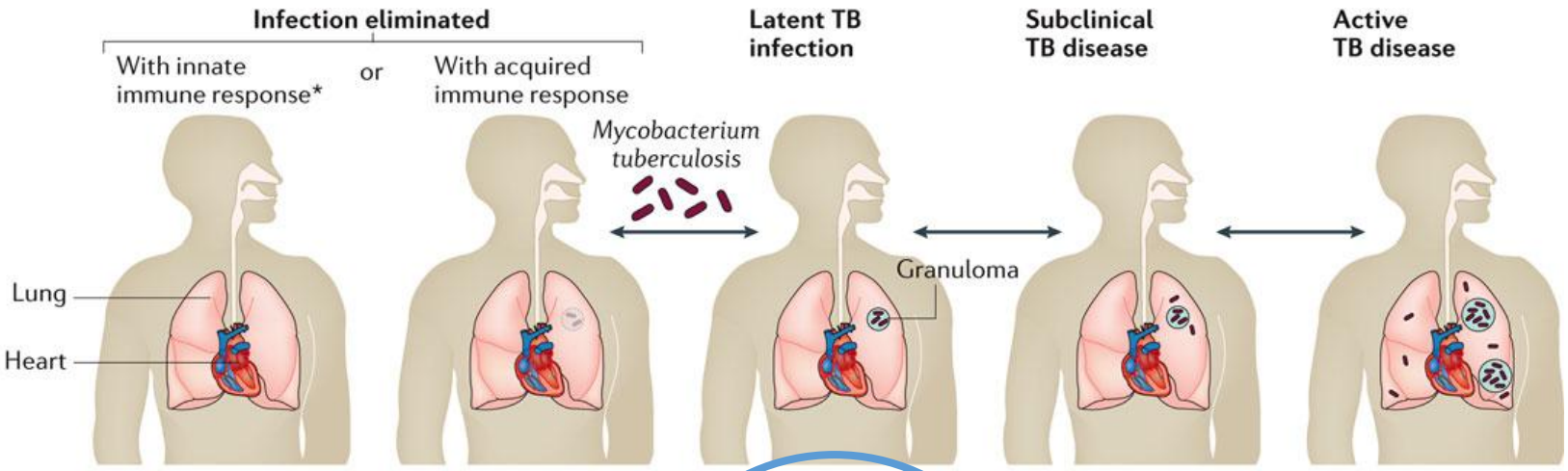


Traditional Contrast

TB Infection	TB Disease
M. tuberculosis bacteria have been seen by immune system TST and IGRAs are usually positive	
• No symptoms • CXR not suggestive of TB disease • Negative AFB smear, culture, NAAT • Never infectious to others	• Cough, sputum production, weight loss, fever, night sweats, etc. • CXR suggestive of TB disease • Positive AFB smear, culture, NAAT • Often infectious to others

AFB: acid fast bacilli; NAAT: nucleic acid amplification such as Cepheid GeneXpert

TBI vs TB Disease

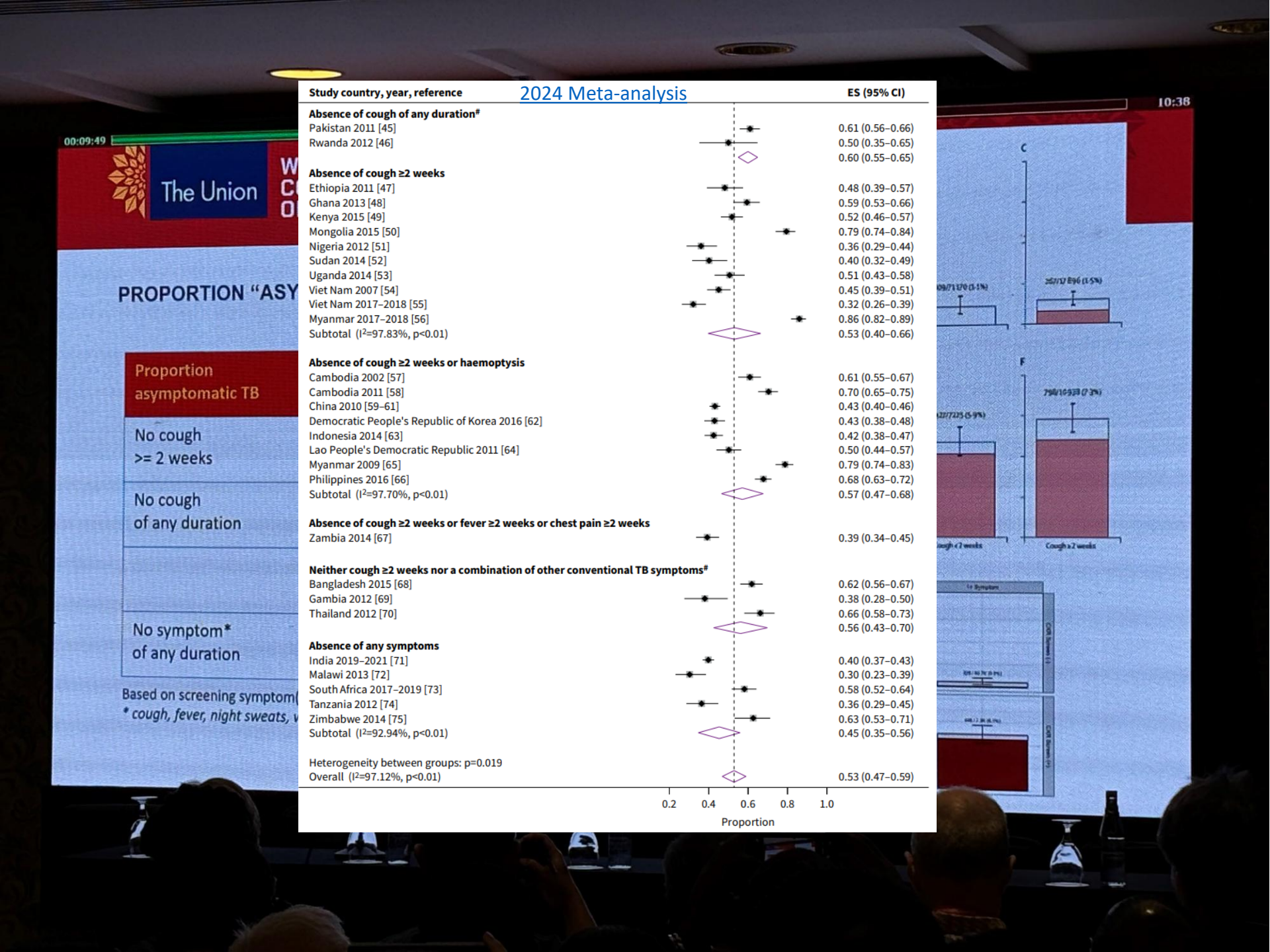


TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai M. *et al.* (2016) Tuberculosis. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76

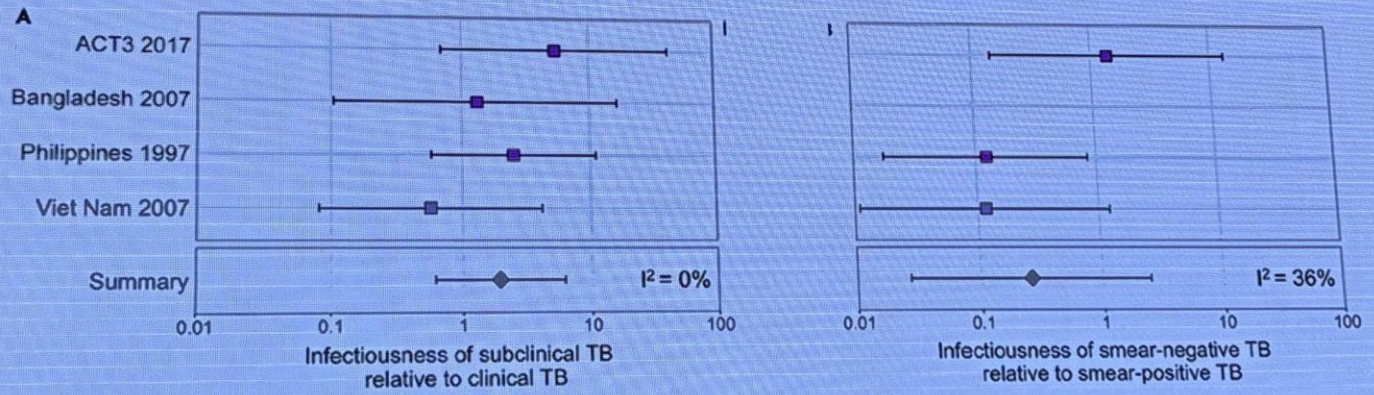
Evolving Recognition of Asymptomatic TB

- 2005: Dar-Dar collaborators published about “subclinical TB” within context of vaccine trial
- In meta-analysis of 1990-2022 data, identified “absence of cough of any duration” or completely asymptomatic patients made up ~half of people with bacteriologically confirmed pulmonary TB
  - 29 national TB prevalence surveys
  - 71 case finding studies
- Uncertain impact, whether majority of persons progress or regress
- Growing evidence that A-TB contribute substantively to TB transmission and global TB burden
  - Analysis of data from 14 countries in Africa and Asia suggests that about two-thirds of global TB transmission may be from asymptomatic TB (95% prediction interval: 27–92%)


00:09:49
The Union
PROPORTION "ASY
Proportion asymptomatic TB
No cough >= 2 weeks
No cough of any duration
No symptom* of any duration
Based on screening symptom(
* cough, fever, night sweats,
10:38
Study country, year, reference
2024 Meta-analysis
ES (95% CI)
Absence of cough of any duration#
Pakistan 2011 [45] 0.61 (0.56–0.66)
Rwanda 2012 [46] 0.50 (0.35–0.65)
0.60 (0.55–0.65)
Absence of cough ≥2 weeks
Ethiopia 2011 [47] 0.48 (0.39–0.57)
Ghana 2013 [48] 0.59 (0.53–0.66)
Kenya 2015 [49] 0.52 (0.46–0.57)
Mongolia 2015 [50] 0.79 (0.74–0.84)
Nigeria 2012 [51] 0.36 (0.29–0.44)
Sudan 2014 [52] 0.40 (0.32–0.49)
Uganda 2014 [53] 0.51 (0.43–0.58)
Viet Nam 2007 [54] 0.45 (0.39–0.51)
Viet Nam 2017–2018 [55] 0.32 (0.26–0.39)
Myanmar 2017–2018 [56] 0.86 (0.82–0.89)
Subtotal (I²=97.83%, p<0.01) 0.53 (0.40–0.66)
Absence of cough ≥2 weeks or haemoptysis
Cambodia 2002 [57] 0.61 (0.55–0.67)
Cambodia 2011 [58] 0.70 (0.65–0.75)
China 2010 [59–61] 0.43 (0.40–0.46)
Democratic People's Republic of Korea 2016 [62] 0.43 (0.38–0.48)
Indonesia 2014 [63] 0.42 (0.38–0.47)
Lao People's Democratic Republic 2011 [64] 0.50 (0.44–0.57)
Myanmar 2009 [65] 0.79 (0.74–0.83)
Philippines 2016 [66] 0.68 (0.63–0.72)
Subtotal (I²=97.70%, p<0.01) 0.57 (0.47–0.68)
Absence of cough ≥2 weeks or fever ≥2 weeks or chest pain ≥2 weeks
Zambia 2014 [67] 0.39 (0.34–0.45)
Neither cough ≥2 weeks nor a combination of other conventional TB symptoms#
Bangladesh 2015 [68] 0.62 (0.56–0.67)
Gambia 2012 [69] 0.38 (0.28–0.50)
Thailand 2012 [70] 0.66 (0.58–0.73)
0.56 (0.43–0.70)
Absence of any symptoms
India 2019–2021 [71] 0.40 (0.37–0.43)
Malawi 2013 [72] 0.30 (0.23–0.39)
South Africa 2017–2019 [73] 0.58 (0.52–0.64)
Tanzania 2012 [74] 0.36 (0.29–0.45)
Zimbabwe 2014 [75] 0.63 (0.53–0.71)
Subtotal (I²=92.94%, p<0.01) 0.45 (0.35–0.56)
Heterogeneity between groups: p=0.019
Overall (I²=97.12%, p<0.01) 0.53 (0.47–0.59)
0.2
0.4
0.6
0.8
1.0
Proportion

11:38

INFECTION RATES IN CONTACTS ARE SIMILAR FOR ASYMPTOMATIC AS FOR SYMPTOMATIC INDEX PATIENTS



3 TB prevalence surveys and one active case finding trial in which children in households with a TB patient had tuberculin skin testing

Emery et al, eLife 2024

2025 NH TB SitRep

- NH DPHS to report 18 TB cases for 2025
- >650 identified as TB exposed
  - 17.8% screened
  - 7.4% positive by IGRA
- Public places with potential unidentified exposures

THIS IS AN OFFICIAL NH DHHS HEALTH ALERT

Distributed by the NH Health Alert Network
DHHS.Health.Alert@dhhs.nh.gov
October 1, 2025, 0900 EDT (9:00 AM EDT)
NH-HAN 202510011

Department of HEALTH & HUMAN SERVICES

Tuberculosis (TB) Transmission Identified in Southern New Hampshire Homeless and Correctional Settings

Key Points and Recommendations:

- Three people with active tuberculosis (TB) have been identified who were present while infectious in homeless and correctional facility settings from January 1, 2025 to July 17, 2025 in the Manchester and Nashua areas (see Background Information).
  - TB isolates from two of the individuals are genetically related indicating local transmission has occurred.
  - Hundreds of exposures have been identified, but many more unidentified exposures are possible.
  - Latent TB infection (LTBI) testing has identified nine individuals (7.7% of persons tested) positive for LTBI.
- Screen your patients for exposure to homeless or correctional facility settings in southern New Hampshire.
- Evaluate for active TB in any person presenting with signs/symptoms of active TB who also reports risk factors, including living or working in homeless or correctional facility settings, and then:
  - Isolate the person under airborne isolation precautions.
  - Enact the appropriate workup, including collecting a sputum specimen.
  - Notify the NH Division of Public Health (DPH) and coordinate specimen submission to the NH Public Health Laboratories by calling 603-271-4496 (after hours call 603-271-5300 and request the Public Health Nurse on-call).
- Test for latent TB infection (LTBI) using an interferon-gamma release assay (IGRA, preferred), or a tuberculin skin test (TST) in persons who are asymptomatic but report living or working in homeless or correctional facility settings.
  - Notify NH DPH of persons who report exposure and are positive on LTBI testing by calling 603-271-4496 (after hours call 603-271-5300 and request the Public Health Nurse on-call).
  - Immunocompromised persons are more likely to have false negative IGRA or TST; please notify NH DPH of these exposed patients.
- Report symptomatic and asymptomatic patients who report exposure to homeless or correctional facilities in southern NH to the NH DPH at 603-271-4496 (after hours call 603-271-5300 and request the Public Health Nurse on-call).

Public Health Collaborative Contact Investigation

- Public health is working with leadership in the HCDOC, community and at affected settings to
  - Investigate to identify all possible TB contacts
  - Facilitate an evaluation to determine need for TB preventive treatment
  - Public notification for those who cannot be identified
    - 1269 Café at 456 Union St: Jan 1-March 1
    - 'Loads of Love' event at Wash Street Laundromat, 1231 Elm St: Jan 1-July 17 Monday and Thursday 10pm-1am
    - Hillsborough County Dept of Corrections, 445 Willow St: Apr 16-25 and May 9-Aug 15

TBI Testing Access for This Event

- Primary care provider
- Anyone without PCP call 211 to get connected to care
- Free TB testing is also available:
  - MHD, 1528 Elm St
    - Monday-Thursday, 8am-4pm
  - MHD Outreach Van, Pearl St Parking Lot, 45 Orange St
    - Wednesdays 9am-12pm through Oct 29
  - Nashua Div of PH and Community Services, 18 Mulberry St
    - 589-4512 option 2 to schedule an appointment
  - Call DPHS at 603-271-4496
  - Not advising emergency rooms, but aware patients may choose

IGRA Performance Acc. Package Inserts

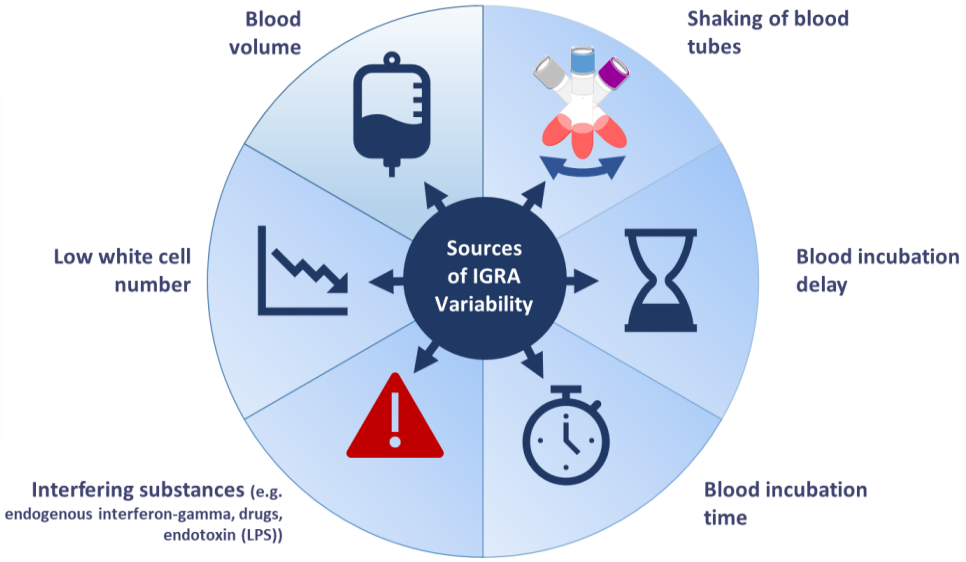
	Sensitivity	Specificity	Indeterminate / Invalid rate
T-SPOT.TB ELISPOT	95.6%	97.1%	3.4%
QFT-Plus ELISA	94.8%	97.3%	2.5–9%

*Indeterminate rate differs between sensitivity and specificity studies

Oxford Immunotec. T-SPOT.TB Package Insert TB-PI-US-0001 V12. Abingdon, UK. March 2023.
Qiagen. QuantiFERON-TB Gold Plus (QFT-Plus) ELISA Package Insert. 1095849 Rev. 09. Jan 2023.

Studies of IGRA Performance

- Sensitivity
  - TST 80%
  - T-SPOT 90%
  - QFT-GIT 80%
- Specificity
  - TST:
    - **97%** in populations without routine BCG
    - **~60%** in populations receiving BCG
    - Varies depending on timing of BCG
  - IGRAs: **>95%** in low-TB-incidence settings



Pai, M, et al. Gamma Interferon Release Assays for Detection of Mycobacterium tuberculosis Infection. Clinical Microbiology Reviews 27(1), 3-20, 2013.

TST and IGRA Comparison

TST
Visits
Method
BCG
NTM
TAT
Results
Costs

- Both cost money, including for false positives
- Both are less sensitive for immunocompromised
- Both have specificity (false positive) potential
- Quantitative results are important
- Neither differentiates between TBI and TB disease
- Neither predicts risk for progression from TBI to TB disease

Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. *Lancet*. 2000;356(9235):1099-1104
Altet et al. Ann Am Thor Soc 2015; 12(5):680; Andrews J et al. Serial QFT Lancet 2017

QFT-Plus vs. T-SPOT®.*TB* for TB Disease

Received: 21 January 2022 | Accepted: 29 May 2022
DOI: 10.1111/jebm.12477

ARTICLE

WILEY

Comparison of diagnostic accuracy of QuantiFERON-TB Gold Plus and T-SPOT.TB in the diagnosis of active tuberculosis in febrile patients

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Lifan Zhang and Zhengrong Yang contributed equally to this work.

Abstract

Objective: This study aimed to compare the accuracy of QuantiFERON-TB Gold Plus (QFT-Plus) and T-SPOT.TB for diagnosing active tuberculosis (ATB) in febrile patients, to explore influencing factors of positive results and to verify the potential value of QFT-Plus in the identification of ATB and latent tuberculosis infection (LTBI).

Methods: A total of 240 febrile patients with ATB ($n = 80$) and non-ATB ($n = 160$) were recruited to assess the accuracy of QFT-Plus and T-SPOT.TB for diagnosing ATB. Multivariable logistic regression was used to analyze the influencing factors of positive results.

Results: The proportion of indeterminate results (ITRS) in QFT-Plus and T-SPOT.TB were 3.3% and 0%, respectively. The consistency between the results of the QFT-Plus and T-SPOT.TB was substantial. The area under the receiver operating characteristic curve (AUROC) of the QFT-Plus and T-SPOT.TB for diagnosing ATB was 0.792 and 0.849 ($p = 0.070$), respectively. The sensitivity of differentiating ATB from non-ATB was 92.2% in QFT-Plus versus 95.0% in T-SPOT.TB. The influencing factors of T-SPOT.TB positive result were male (odds ratio (OR) = 2.33, 95% confidence interval (CI) 1.27–4.26, $p = 0.006$), evidence of previous TB (OR 11.36, 95% CI 4.62–27.94, $p < 0.001$), while male (OR = 3.17, 95% CI 1.73–5.84, $p < 0.001$), evidence of previous TB (OR = 7.58, 95% CI 3.60–15.98, $p < 0.001$), and use of immunosuppressant (OR = 0.49, 95% CI 0.260.94, $p = 0.030$) were influencing factors for QFT-Plus positive result. There was no significant difference in QFT-Plus in differentiating ATB from LTBI in febrile patients.

Conclusion: There was no significant difference between QFT-Plus and T-SPOT.TB for diagnosing ATB in febrile patients. QFT-Plus is prone to ITRS. The influencing factors including males, evidence of the previous TB, and use of immunosuppressant should be considered when interpreting positive results.

KEYWORDS
active tuberculosis, diagnostic accuracy, febrile, QFT-Plus, T-SPOT.TB

n=240 (TB) n=160 (not TB)

Results	T-SPOT.*TB*	QFT-Plus
Sensitivity (58 confirmed active TB)	**96.6 %**	**93.1 %**
Indeterminates (240 febrile patients)	**0%**	**3.3%** (8/240)
AUROC for diagnosing active TB	**0.849** (95% CI 0.799–0.900)	**0.792** (95% CI 0.734–0.851)

- No significant difference between QFTG-Plus and T-SPOT.TB in differential diagnosing TB in febrile patients
- QFTG-Plus prone to indeterminate results, especially in immunocompromised patients

Zhang L, et al. *J Evid Based Med*. 2022;15:97-105.

WHO- and CDC-Approved Molecular TB Screening and Diagnostic Tool

- Xpert MTB/RIF: automated, RT PCR, modular system
  - 100min to TB and rifampin resistance (RR)
    - Xpert LOD 131 organisms/ml
    - 98% sensitivity for RR
- In US, Xpert MTB/RIF FDA-approved ONLY for diagnosis using respiratory secretions
- Xpert valuable role in US to release presumptive TB from airborne infection isolation

Furthering the Power of Xpert

- Xpert MTB/RIF **Ultra** increases TB diagnostic sensitivity by incorporating two different multicopy amplification targets
  - Analytical lab studies show ~1 log improvement in lower limit of detection for Ultra compared with Xpert MTB/RIF
  - Clinical diagnostic accuracy studies consistently show Ultra is more sensitive than Xpert MTB/RIF in
    - Paucibacillary pulmonary disease
    - PLWH
    - Children
    - Extrapulmonary specimens
- 2017 WHO endorsed Ultra for P/EP TB diagnosis
  - Not pending FDA review

Chakravorty et al. *MBio.* 2017; 8: e00812-e00817
Dorman SE et al. Lancet ID. 2018; 18: 76-84
Zifodya JS et al. Cochrane Database Syst Rev. 2021; 2: CD009593
Kay AW et al. Cochrane Database Syst Rev. 2020; 8: CD013359
Kohli M et al. Cochrane Database Syst Rev. 2021; 1: CD012768

The Union WORLD CONFERENCE ON LUNG HEALTH BALI • 2024 NOV 12-16

Clinical sputum study

FIND sputum biobank

- 55 Cx+/smear +
- 55 Cx+/smear –
- 55 smear +/- with INH-R, RIF-R, or INH-R + RIF-R
- 55 Cx -
  - 5 MDR errors
  - 9 Ultra errors
  - 1 MDR/Ultra error
  - 1 Ultra invalid
  - 4 low sample volume
  - 2 labeling errors

198 tested with both MDR and Ultra

Sensitivity TB Detection

All Cx +

Ultra	139/149 = 93.2%
MDR	136/149 = 91.2%

Smear +

Ultra	97/99 = 97.9%
MDR	97/99 = 97.9%

Smear –

Ultra	42/50 = 84%
MDR	39/50 = 78%

Specificity TB Detection

Ultra	48/49 = 97.9%
MDR	48/49 = 97.9%

Sensitivity RIF-R Detection

Ultra	73/73 = 100% (3 indeterminant)
MDR	75/75 = 100% (1 indeterminant)

Specificity RIF-R Detection

Ultra	43*/46 = 93.47% (3 indeterminant)
MDR	45*/48 = 93.75% (1 indeterminant)

Sensitivity INH-R

MDR 76/77 = 98.7% (1 indeterminant)

Specificity INH-R

MDR 38/38 = 100% (2 indeterminant)

IMPACT OF ON-SITE TESTING

SAME DAY TEST-AND-TREAT IS FEASIBLE

FIND

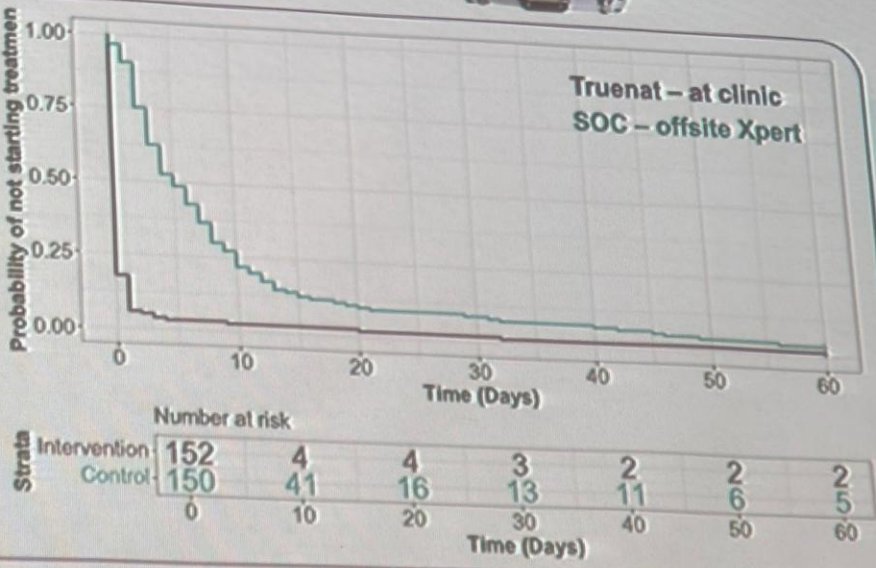
Impact of point-of-care implementation of the Truenat MTB assays on TB diagnosis and treatment initiation.

Intervention:

On-site Truenat at PHC clinics + rapid communication of results vs SOC (off-site Xpert testing in all clinics and on-site smear microscopy when available).

Main results:

- Placement of molecular diagnostics in primary health care clinics is feasible
- Majority can initiate Rx on day 0 at PHC



TB-CAPT consortium submitted. TB-CAPT.org

EDCTP

TB·CAPT

IFAKARA HEALTH INSTITUTE

cism

Truenat MTB Ultima Pilot Study Results

Study Population: Consecutive people ≥12 years with presumed TB presenting to outpatient clinics in Uganda, India and Vietnam from Feb-August 2024

Clinical Performance Against Microbiological Reference Standard (liquid culture x 2)			
MTB Ultima	**Sensitivity:** n/N (%, 95% CI)	**Specificity:** n/N (%, 95% CI)	**Error Rate:** n/N (%)
Tongue swab	111/144 (77%, 69-84)	735/750 (98%, 97-99)	11/905 (1.2%)*
Sputum swab	42/46 (91%, 79-98)	122/125 (97.6%, 93-100)	0/171 (0.0%)
Comparator tests	**Sensitivity:** n/N (%, 95% CI)	**Specificity:** n/N (%, 95% CI)	**Error Rate:** n/N (%)
Sputum Xpert	125/135 (93%, 87-97)	741/749 (99%, 98-100)	1/885 (0.1%)^
Sputum Smear	85/145 (58%, 50-67)	760/763 (99%, 99-100)	N/A

*Includes 905 of 908 participants who had a tongue swab collected
^Excludes 23 participants with a trace result on Sputum Xpert Ultra

For details see **TBS-EP-91 A multi-country evaluation of the diagnostic performance of Molbio Truenat MTB Ultima** in TBS-EP-05 Mechanisms underlying heterogeneous disease manifestations | Part 1, Friday November 15, 12:15 PM – 02:10 PM

Case: New American Presents with Cough

- During Civil Surgeon exam for adjustment of immigration status, 50y M BCG=vaccinated from Thailand endorses
  - Chronic cough
    - “I should quit smoking”
  - Weight loss
    - “Lots of stress”
  - Low-grade temperatures
    - “Room is hot”
- TST is 9mm, the QFTG-Plus is indeterminate and the T-SPOT.TB is positive
- What is next?

Case: Borderline IGRA in Low TBI Risk

- Farmer from northern Maine who never left his farm needs an IGRA because **he will start** TNF-alpha inhibitor for steroid-resistant rheumatoid arthritis
- T-SPOT.TB comes back borderline
- What is the clinician's next best step?

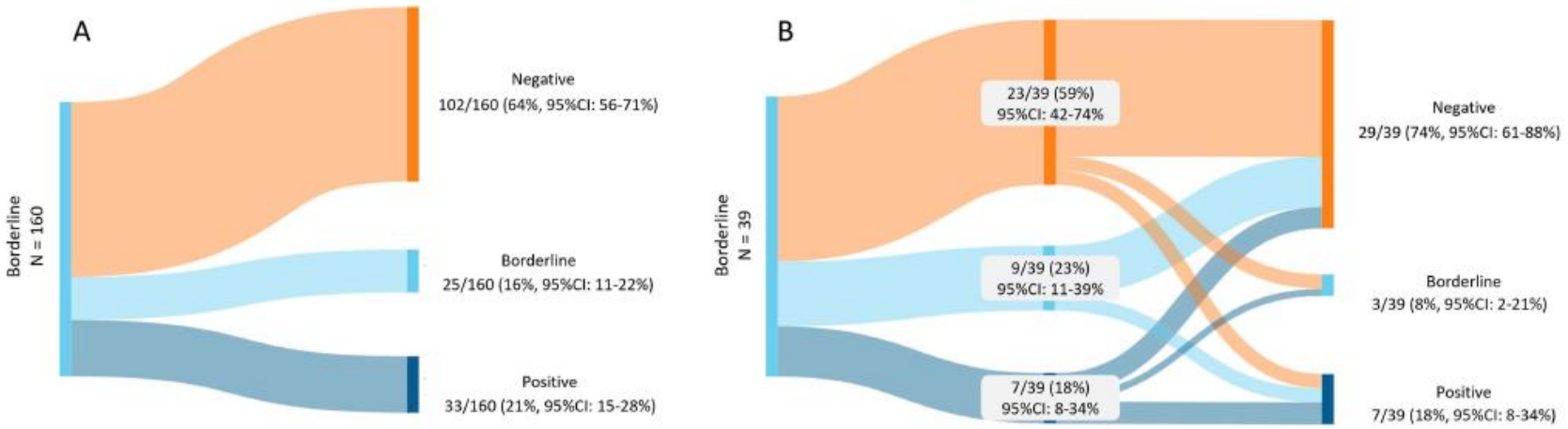
New Study of Borderline T-SPOT.TB Results

- Denmark retrospective review 2010-2017
- Of 11,268 T-SPOT.TB tests
  - 9,132 (81%) negative
  - 1,402 (12%) positive
  - 518 (4.6%) borderline
  - 216 (1.9%) invalid
- Of 489 patients with borderline results
  - Compared to patients with negative results
    - Fewer had immune suppression (15% vs. 25%, P=0.001)
    - More were foreign-born (64% vs. 38%, P=0.001)
  - Compared to patients with positive results
    - More patients with borderline results had immune suppression (15% vs. 10%, P=0.005)

Pedersen OS et al. Int J Tuberc Lung Dis 2025. 29(9): 422.

Retesting Borderline Results Clarifies

- Of 160 patients with borderline results who were retested once
  - 64% resolved to negative
  - 21% to positive
  - 16% remained borderline
- Of 39 patients retested twice, all who had borderline after first retest resolved to definitive result
- Patients with borderline results were significantly more likely than those with negative results to present with prevalent TB during testing or to progress to incident TB: borderline as a transitional result?



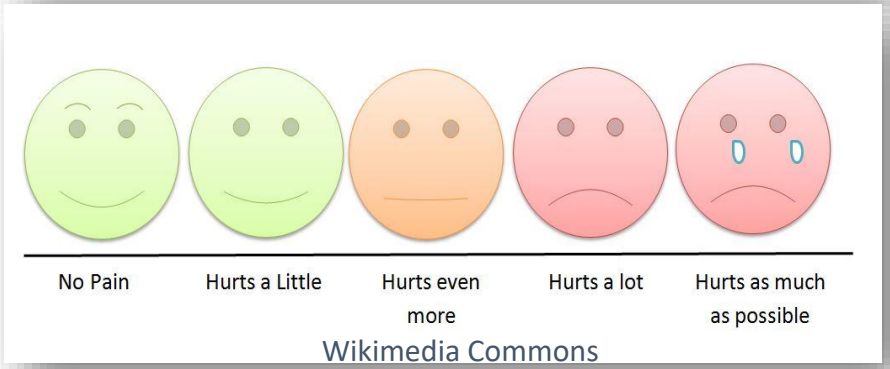
Pedersen OS et al. Int J Tuberc Lung Dis 2025. 29(9): 422. Prevalent TB: TB diagnosis 3m before or after testing; Incident TB: TB diagnosis ≥3m from test; immune suppressed as registered 6m-3y before testing

How to Test if Low LTBI Risk

- Do NOT test. But …
- Suggest performing an IGRA instead of TST*
  - *Conditional recommendation, low-quality evidence*
- If initial test is positive, suggest second diagnostic test, either IGRA or TST
  - When such testing is performed, person is considered infected only if both tests are positive
  - *Conditional recommendation, very low-quality evidence*

Lewinsohn DM, Leonard MK, LoBue PA, *et al.* Official ATS/IDSA/CDC Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases*. 2017;64(2):e1-e33.

Case: Indeterminate IGRA in Immunocompromised Patient



Wikimedia Commons

- Retired businessman from NYC needs an annual IGRA because **he is on** TNF-alpha inhibitor for steroid-resistant psoriasis
- QFTG-Plus comes back indeterminate
- What does the clinician do now?

Performance of IGRAs in Immunocompromised Patients

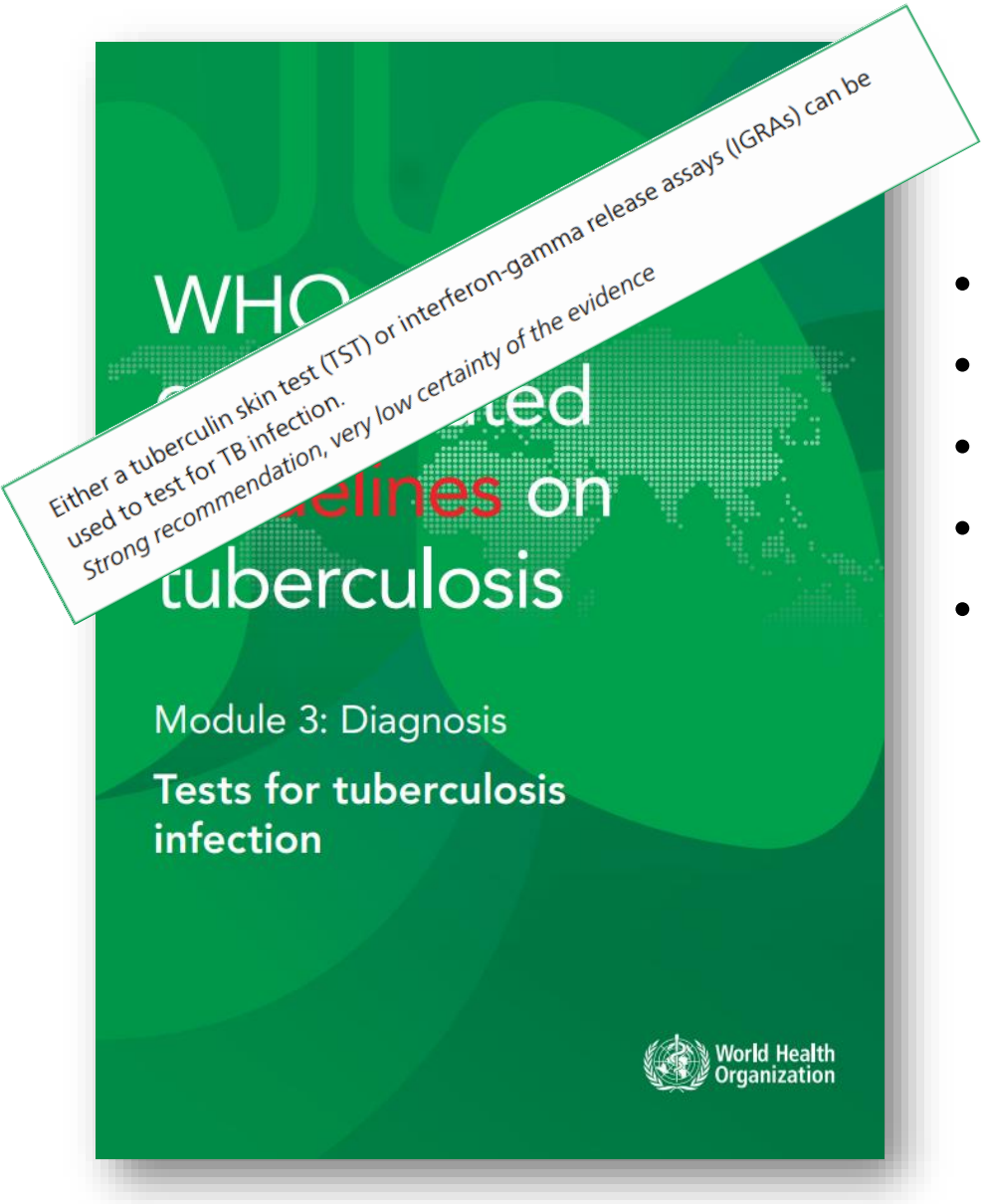
Conclusions

- *QuantiFERON-TB Gold Plus and T-SPOT.TB test demonstrate **similar sensitivity and specificity in healthy populations**. However, immunosuppressed patients are more likely to have an indeterminate or invalid IGRA due to an inadequate immune response*
- *In this single-center autoimmune disease population, **T-SPOT.TB test provided a definitive result significantly more often** than the QFT-Plus test*
- *"In the case of a QFT-Plus test indeterminate result, the T-SPOT.TB test should be the **first-line** TB-screening test in the autoimmune skin disease population."*

Yan DY, et al. *J Am Acad Dermatol*. 2022;86(4):948-949.

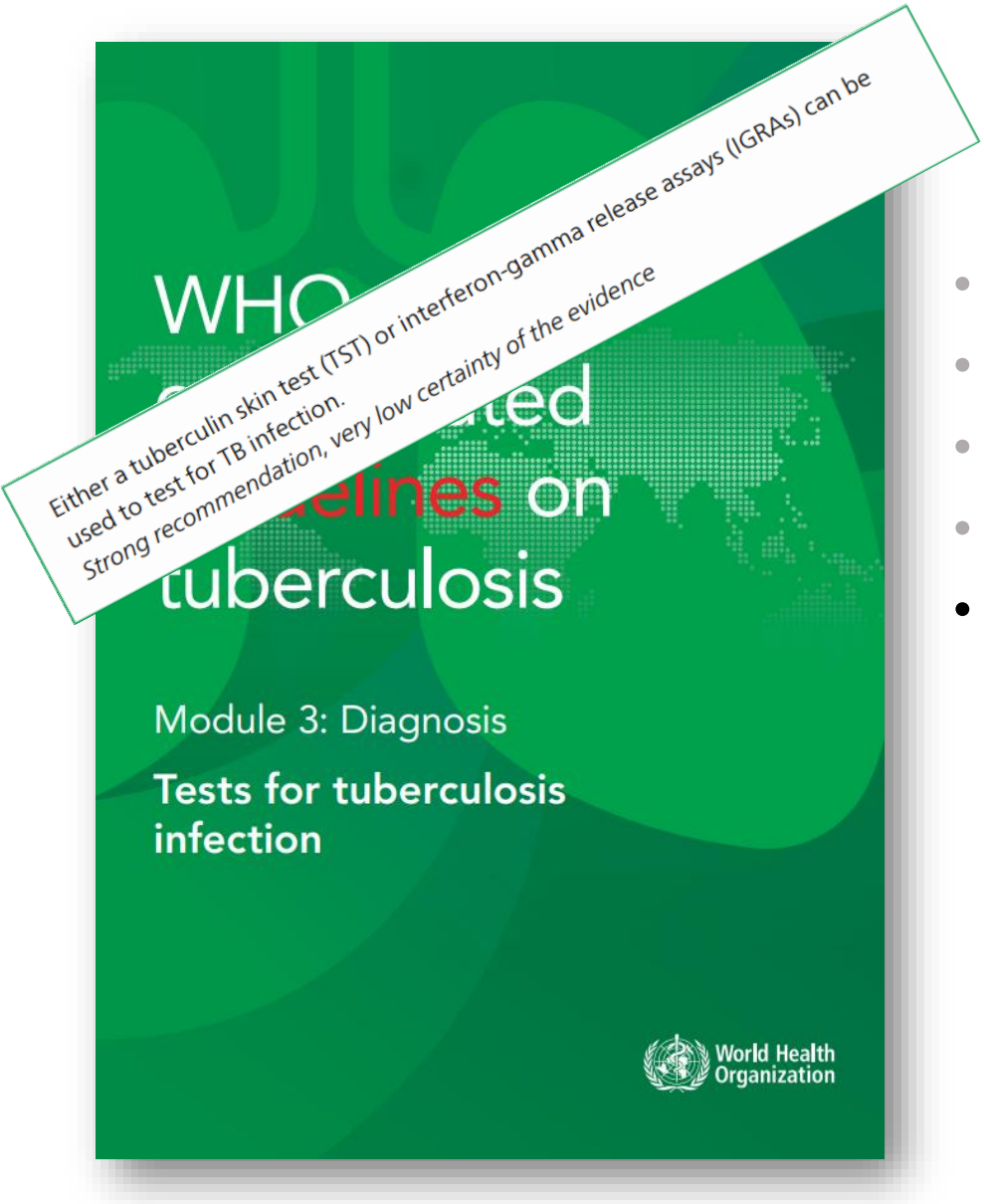
Better TBI Tests!

When??



- TST
- T-SPOT®.TB
- QuantiFERON-TB Gold Plus
- Beijing Wantai's TB-IGRA
- Mtb antigen-based skin tests
  - Cy-Tb (Serum Institute of India, India)
  - Diaskintest® (Generium, Russian Federation)
  - C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China)

WHO consolidated guidelines on tuberculosis: module 3: diagnosis: tests for TB infection



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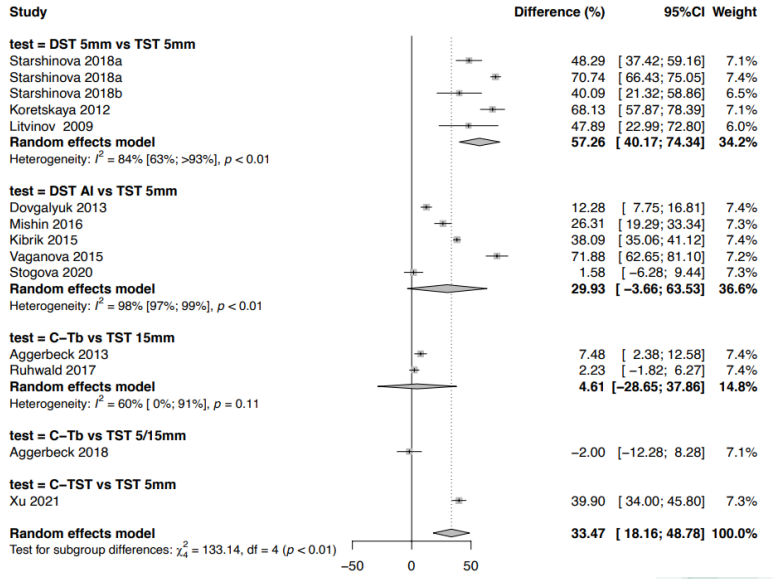
WHO consolidated guidelines on tuberculosis: module 3: diagnosis: tests for TB infection

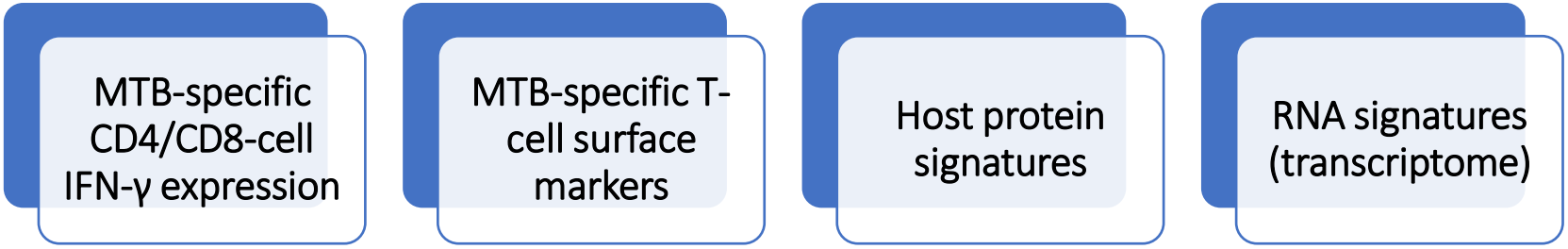
M. tuberculosis Antigen-Based Skin Tests

- Based on ESAT-6 and CFP-10
- Same 48-72h in vivo incubation
- Simplifying 5mm cutoff
- In 2022, WHO Guideline Development Group concluded that diagnostic accuracy of TBSTs is similar to that of IGRAs and greater than that of the TST
  - 89% agreement with IGRA
- Not for use to predict progression from TBI to TB nor to diagnose of TB

Fig. 6. Difference in specificity – TBSTs versus the TST



Pipeline of Better Tests for Predicting TB Disease



TBI Treatment in the US

Drug(s)	Duration	Dose	Frequency	Doses
Isoniazid (INH)* and Rifapentine (RPT)†	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years: INH*: 25 mg/kg; 900 mg maximum RPT†: as above	Once weekly	12
Rifampin (RIF)§	4 months	Adults: 10 mg/kg Children: 15–20 mg/kg‖ Maximum dose: 600 mg	Daily	120
Isoniazid (INH)* and Rifampin)§	3 months	Adults: INH*: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum Children: INH*: 10-20 mg/kg; 300 mg maximum RIF§: 15-20 mg/kg; 600 mg maximum	Daily	90
Isoniazid (INH)	6 months	Adults: 5 mg/kg Children: 10–20 mg/kg¶ Maximum dose: 300 mg	Daily	180
		Adults:15 mg/kg Children: 20–40 mg/kg¶ Maximum dose: 900 mg	Twice weekly‡	52
	9 months	Adults: 5 mg/kg Children: 10–20 mg/kg¶ Maximum dose: 300 mg	Daily	270
		Adults: 15 mg/kg Children: 20–40 mg/kg¶ Maximum dose: 900 mg	Twice weekly‡	76

Case: New American Presents with Cough Xpert+

- Rifampin resistance not detected
- What is next?

AMERICAN THORACIC SOCIETY DOCUMENTS

Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis

An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Jussi J. Saukkonen*, Raquel Duarte*, Sonal S. Munsiff*, Carla A. Winston*, Manoj J. Mammen, Ibrahim Abubakar, Carlos Acuña-Villaorduña, Pennan M. Barry, Mayara L. Bastos, Wendy Carr, Hassan Chami, Lisa L. Chen, Terence Chorba, Charles L. Daley, Anthony J. Garcia-Prats, Kelly Holland, Ioannis Konstantinidis, Marc Lipman, Giovanni Battista Migliori, Farah M. Parvez, Adrienne E. Shapiro, Giovanni Sotgiu, Jeffrey R. Starke, Angela M. Starks, Sanket Thakore, Shu-Hua Wang, Jonathan M. Wortham, and Payam Nahid; on behalf of the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

This official clinical practice guideline was approved by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) September 2024, was cleared by the U.S. Centers for Disease Control and Prevention (CDC) September 2024, and was approved by the European Respiratory Society (ERS) October 2024

Time to Shorten DS-TB Regimens for Adults and Children

Morbidity and Mortality Weekly Report (*MMWR*)

Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

Weekly / February 25, 2022 / 71(8);285–289

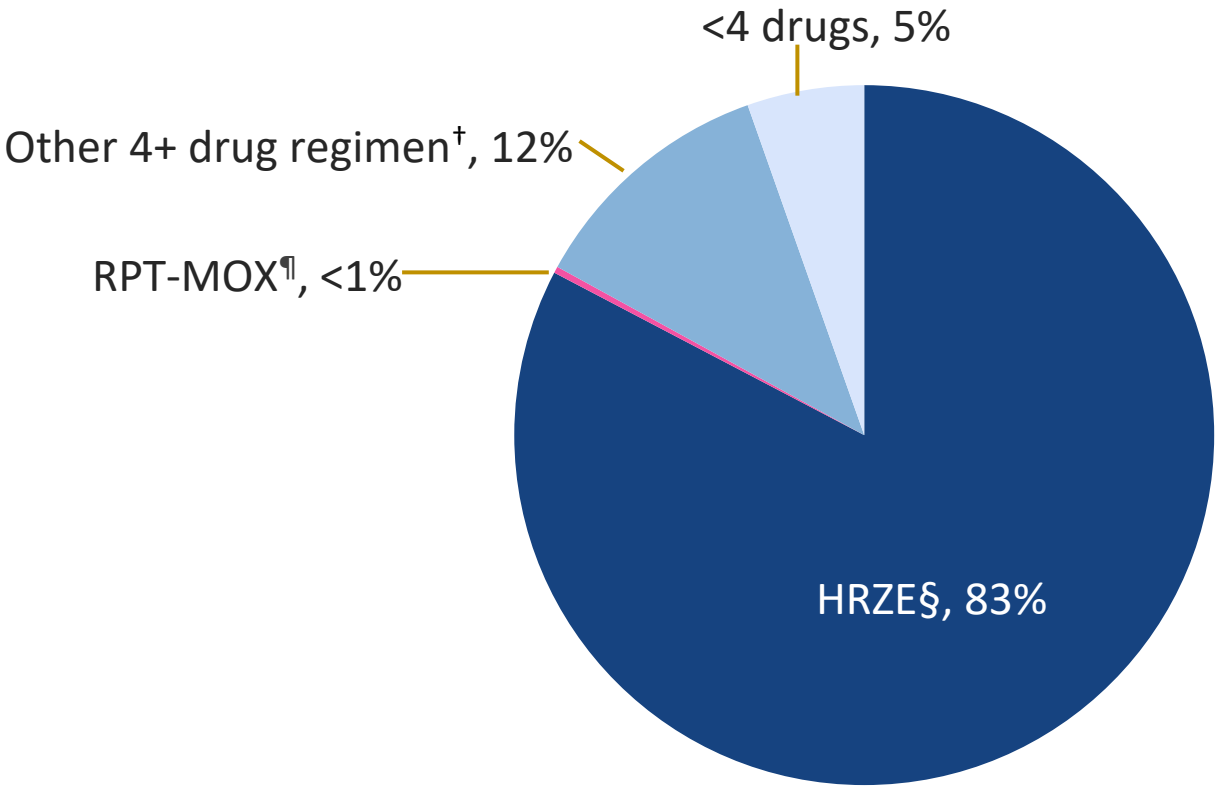
Wendy Carr, PhD[1]; Ekaterina Kurbatova, MD[1]; Angela Starks, PhD[1]; Neela Goswami, MD[1]; Leeanna Allen, MPH[1]; Carla Winston, PhD[1] (VIEW AUTHOR AFFILIATIONS)

CDC recommends the 4-month regimen as a treatment option for U.S. patients aged ≥12 years with drug-susceptible pulmonary TB and provides implementation considerations for this treatment regimen (conditional recommendation, moderate certainty of evidence)

In people 3 months - 16 years with nonsevere TB* (without suspicion or evidence of MDR]/RR-TB), we recommend the use of a 4m regimen of 2HRZ(E)/2HR rather than the 6m regimen of 2HRZ(E)/4HR (strong recommendation, moderate certainty of evidence).”

*Nonsevere TB is defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion; or paucibacillary and noncavitary disease confined to one lobe of the lungs or without a miliary pattern

% of TB Cases* by Initial Drug Regimen US, 2023 (N=9,334)



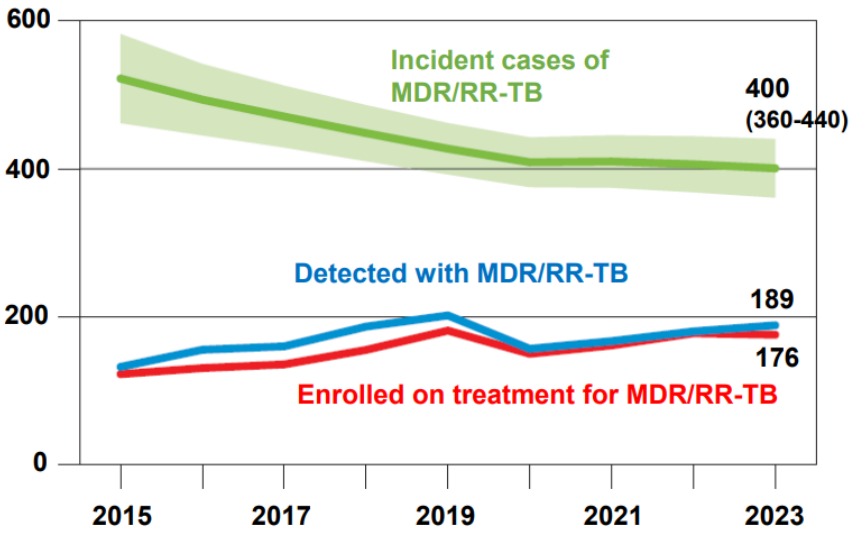
* Persons alive at diagnosis with initial drug regimen information.
† A drug regimen with at least four drugs, other than HRZE and RPT-MOX.
¶ Daily 4-month regimen with rifapentine, isoniazid, pyrazinamide, and moxifloxacin, first recommended by CDC in 2022.
§ H, isoniazid; R, rifampin; Z, pyrazinamide; E, ethambutol.

Case: New American Presents with Cough Xpert+

- Rifampin resistance detected
- What is next?

RR/MDR TB

- 400k estimated persons with RR/MDR-TB globally: stable
- 1 in 3 with MDR/RR-TB were tested and started on appropriate regimen
  - 44% of people diagnosed with RR/MDR-TB enrolled on treatment
- 68% treatment success rate for MDR/RR-TB enrolled in 2021
  - Substantially increased!
  - 88% for DS-TB (stable)

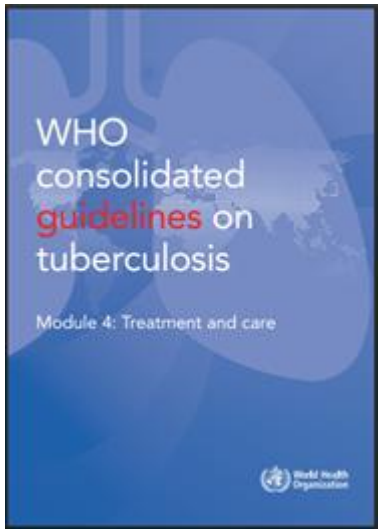


WHO Global TB Report 2024

RR/MDR = rifampin resistant or resistant to at least both INH and rifampin; DS-TB = drug sensitive

New Standard for RR/MDR-TB

Bedaquiline, Pretomanid, Linezolid +/- Moxifloxacin (BPaL/BPaLM)



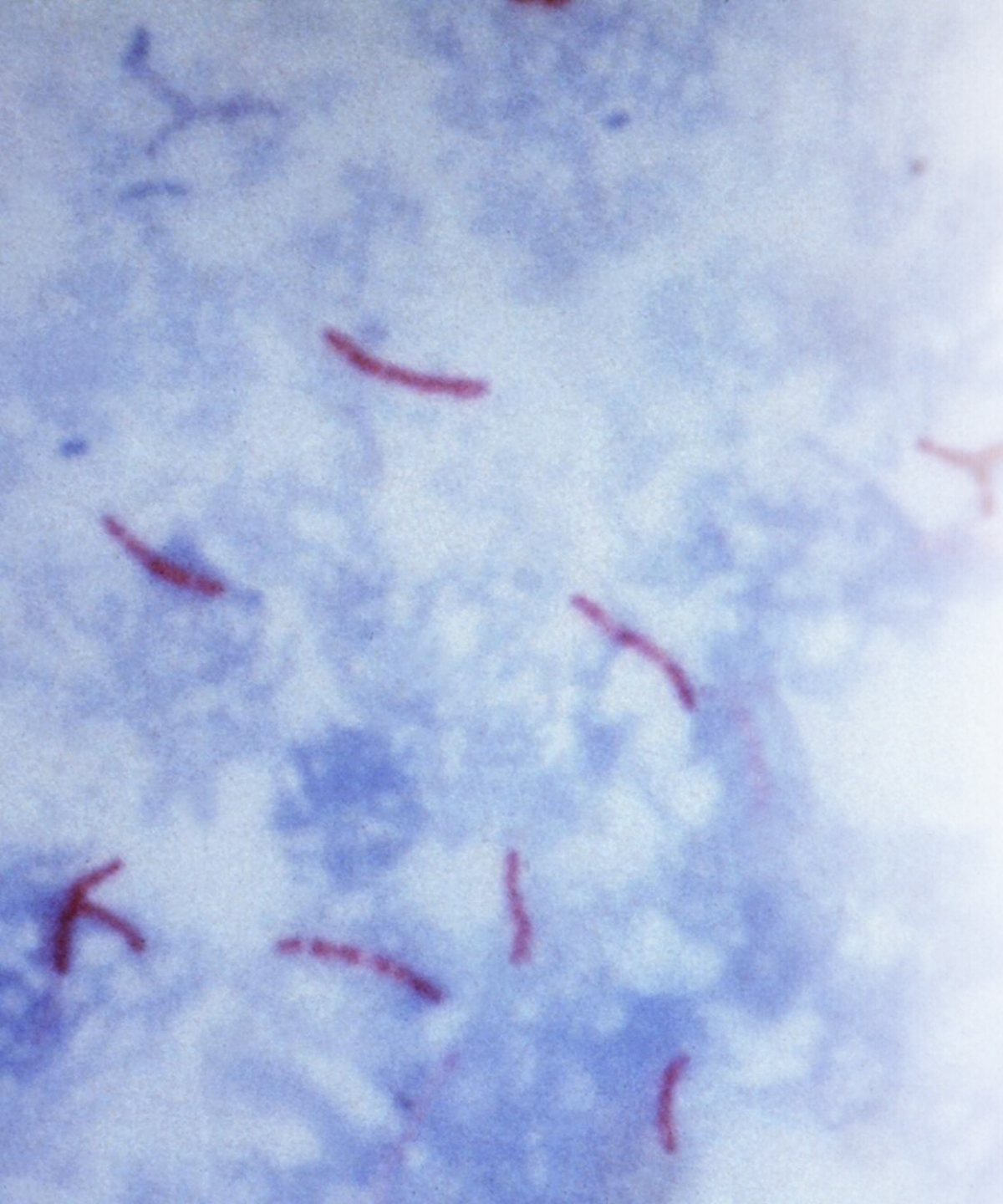
- In people ≥14y with RR/MDR pulmonary TB
  - FQ-susceptible: 6m **BPaLM**, rather than ≥15m regimens
  - Resistance or intolerance to FQs
    - No or <1m exposure to bedaquiline and linezolid
    - **BPaL**, rather than ≥15m regimens
- Prospective study 15 sites July 2022 - March 2023 84 patients with RR/MDR-TB, 82 (97.6%) successful tx
  - Of 61 (72.6%) with positive cultures at baseline, all 61 converted within 3m (median 32d, IQR 30–56)

Emergence of BPaL Resistance Two Years After WHO Endorsement

Now **published** analysis of *Mycobacterium tuberculosis* genomes from 27 countries identified >500 strains of MDR-TB with resistance to ≥1 compound in BPaL/M

Genomic analysis of 81,576 genomes from 26 countries identified 454 highly drug-resistant strains (with resistance to ≥1 drug in BPaL) and concluded that 117 of 420 (28%) were linked to direct transmission

- 9 strains carried resistance mutations to all BPaL/M drugs



Summary

- TB is leading infectious cause of death in the world
- TB elimination depends on getting those with TBI on an effective cascade of care
- TBI diagnostics include TST, IGRAs and now TBSTs
- IGRAs
  - Offer advantages over TSTs and TBSTs
  - Have similarities and important differences
- Better TBI diagnostics that predict TB disease are needed