Updates on the management of latent tuberculosis infection

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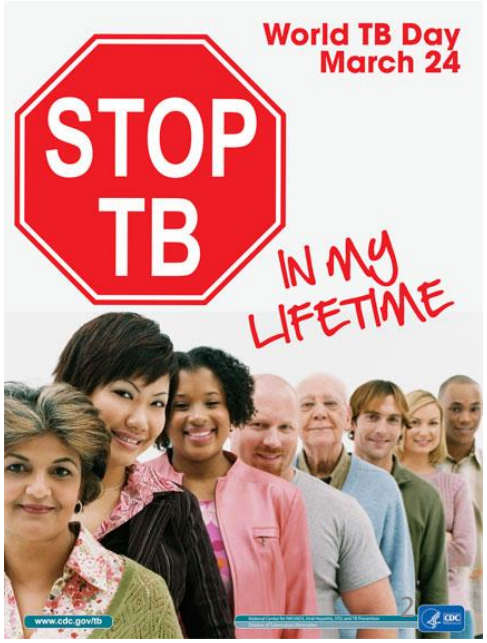
TB Consultant, Virginia Department of Health

Outline

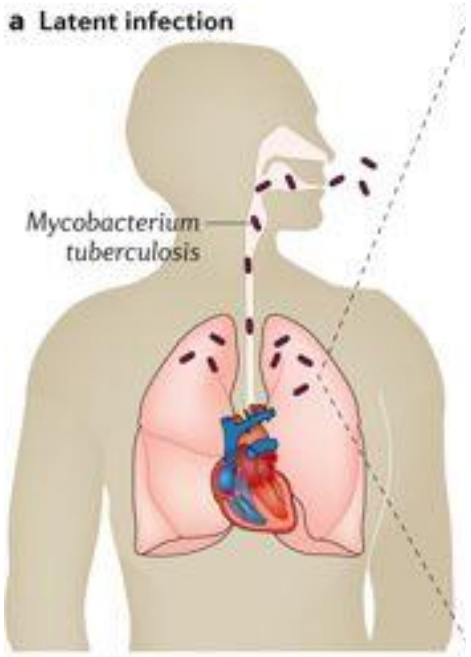
- Definition and Pathogenesis of latent TB
- Global burden of infection
- Who to screen and how
- Review the various treatment options for LTBI and their side effects
- What's on the horizon for LTBI



Latent tuberculosis infection

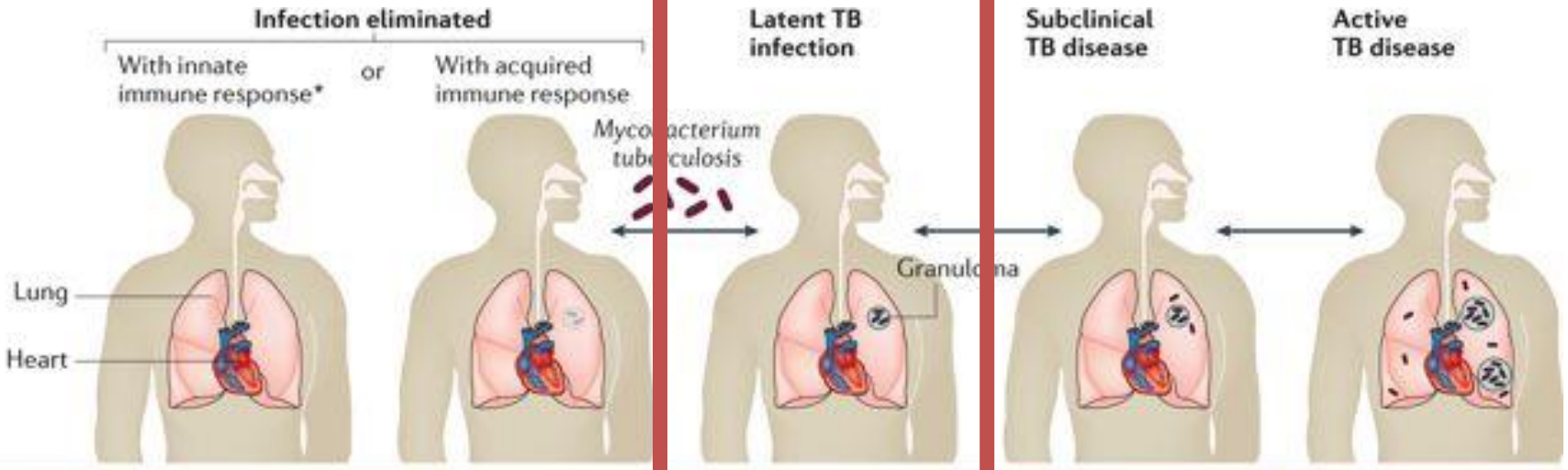
- Immunologic and clinical diagnosis
- Sensitization to mycobacterial proteins
  - Reactive tuberculin skin test
  - Positive interferon-gamma release assay
- Without clinical signs/symptoms of active disease.

M. tuberculosis infection



Pai et al, Nat. Rev. Dis. Primers 2, 16076 (2016)

The spectrum of TB

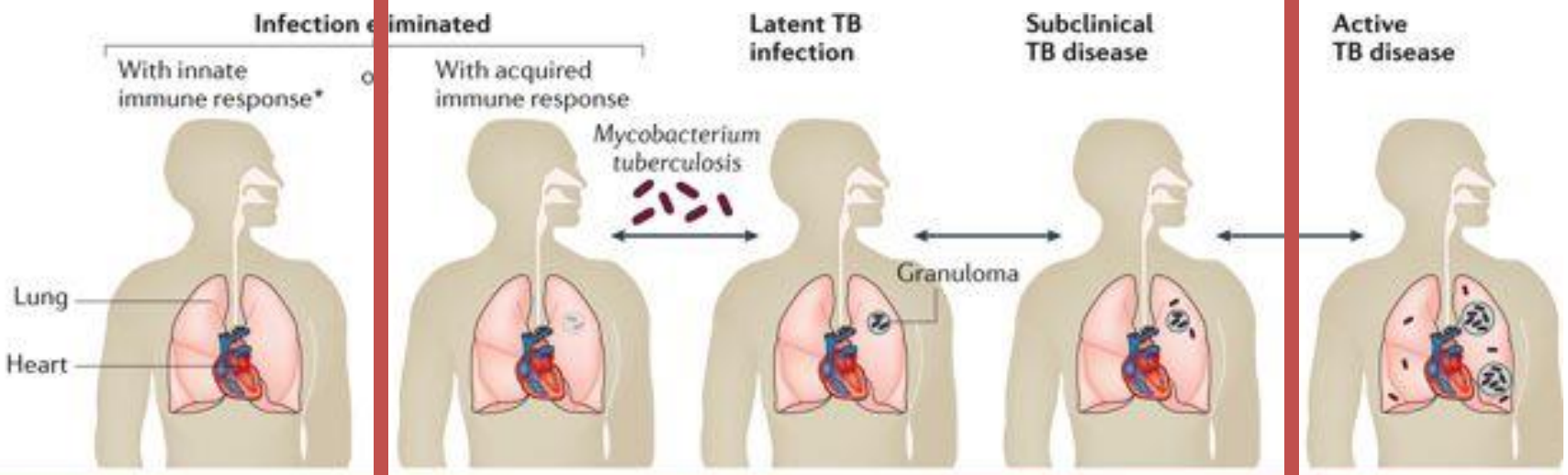


TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms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

Nature Reviews | Disease Primers

Pai et al, Nat. Rev. Dis. Primers 2, 16076 (2016)

The spectrum of TB



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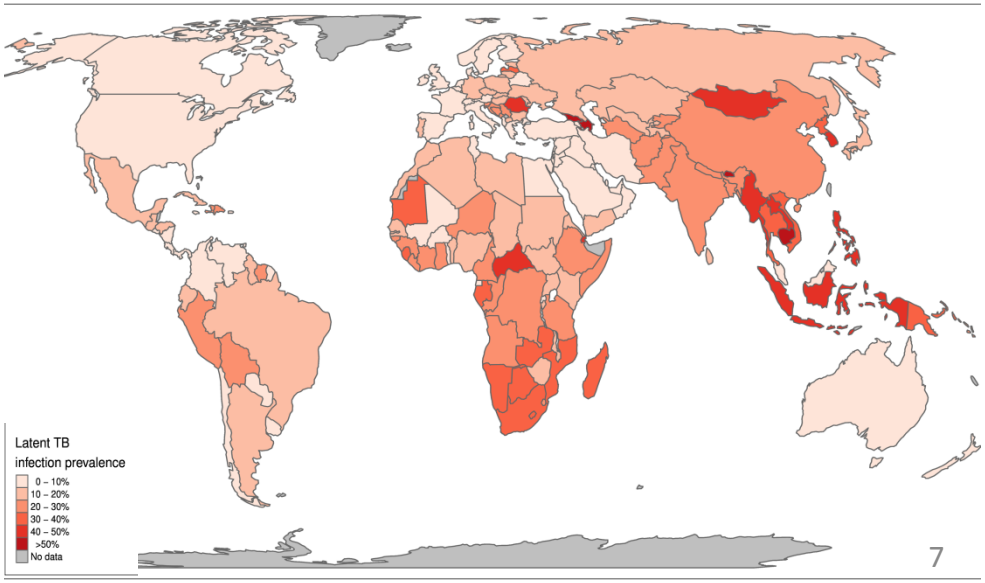
Nature Reviews | Disease Primers

Pai et al, Nat. Rev. Dis. Primers 2, 16076 (2016)

Global Epidemiology of LTBI

- 23% of people are infected with TB (1.7 billion)
  - 80% reside in Asia and Africa
  - ~1-5% reside in USA
  - 6% are children <15years of age
  - ~1% recently infected



Houben/Dodd, PLoS Medicine 13(10) Oct 2016

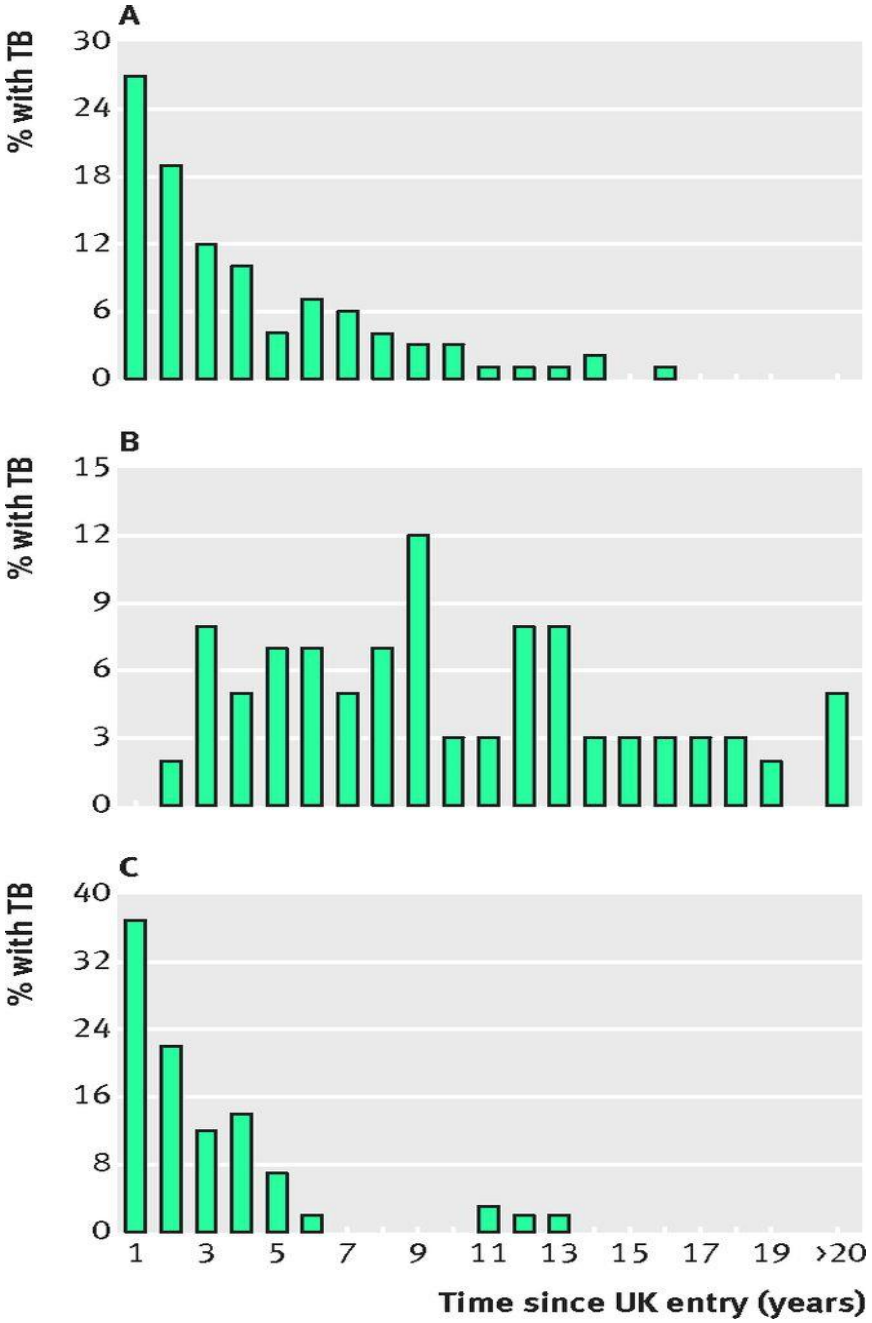
Active TB in Virginia

- 83% are foreign-born:

Figure 6: Top Five Countries of Birth of Tuberculosis Cases, Virginia, 2017

- Develop TB ~9.7 years after being in US

Time of onset of active TB in Asian immigrants to the UK



A) Time of onset of TB in 128 immigrants who neither left the UK nor had known contacts with TB in the UK before receiving a diagnosis of TB.

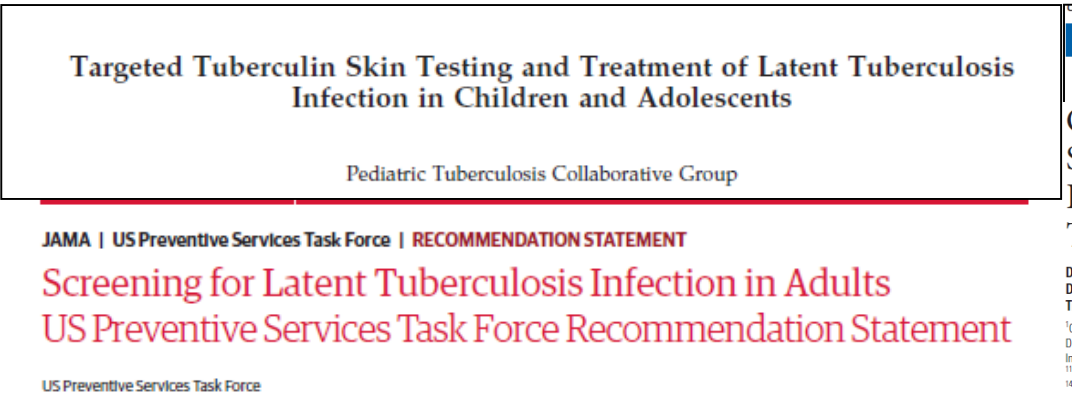
B) Time of onset of TB in 59 immigrants who visited their home countries and had no known contacts with TB in the UK before their diagnosis of TB. Time to onset is based on the time of initial UK entry.

C) Same group shown (B), but with the time to onset measured by the time from re-entry into the UK after their Asian visits.

M Behr et al. BMJ 2018;362
McCarthy, B J Dis Chest. 1984, 78

TB screening guidelines

- Targeted testing and treatment
- Focus on individuals who would benefit from treatment
- “Decision to test is a decision to treat”



Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents

Pediatric Tuberculosis Collaborative Group

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Latent Tuberculosis Infection in Adults
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IDSA GUIDELINE

Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

David M. Lewinsohn,[1,a] Michael K. Leonard,[2,a] Philip A. LoBue,[3,a] David L. Cohn,[4] Charles L. Daley,[5] Ed Desmond,[6] Joseph Keane,[7] Deborah A. Lewinsohn,[1] Ann M. Loeffler,[8] Gerald H. Mazurek,[3] Richard J. O'Brien,[9] Madhukar Pai,[10] Luca Richeldi,[11] Max Salfinger,[12] Thomas M. Shinnick,[3] Timothy R. Sterling,[13] David M. Warshauer,[14] and Gail L. Woods[15]

[1]Oregon Health & Science University, Portland, Oregon, [2]Emory University School of Medicine and [3]Centers for Disease Control and Prevention, Atlanta, Georgia, [4]Denver Public Health Department, Denver, Colorado, [5]National Jewish Health and the University of Colorado Denver, and [6]California Department of Public Health, Richmond; [7]St James's Hospital, Dublin, Ireland; [8]Francis J. Curry International TB Center, San Francisco, California; [9]Foundation for Innovative New Diagnostics, Geneva, Switzerland; [10]McGill University and McGill International TB Centre, Montreal, Canada; [11]University of Southampton, United Kingdom; [12]National Jewish Health, Denver, Colorado, [13]Vanderbilt University School of Medicine, Vanderbilt Institute for Global Health, Nashville, Tennessee, [14]Wisconsin State Laboratory of Hygiene, Madison, and [15]University of Arkansas for Medical Sciences, Little Rock

Screen people at “high risk”

Of infection:

- environmental/behavioral risks
  - Recently exposed/infected (contacts of people with active TB)
  - People in homeless shelters/correctional facilities
  - Health care workers
  - Immigrants from high-burden countries
  - People who use illicit substances

&

Of progression to active TB:

- host-related risk
  - Age <5 years
  - HIV infection
  - Immunocompromised by organ transplant, chemotherapy (incl. prednisone 15mg daily ≥1 month) or malignancy, use of TNF-α blockers
  - Abnormal chest radiograph (apical fibro/nodular changes , “old healed TB”)
  - Silicosis
  - Advanced renal failure
  - Diabetes mellitus

How to test? TST vs IGRAs

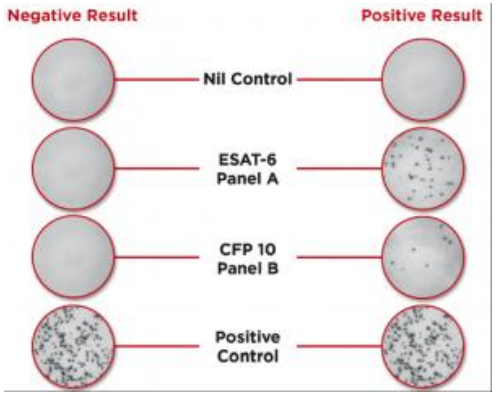
Tuberculin skin test

- ~Century old
- Delayed-type hypersensitivity reaction
- Purified Protein Derivative
  - Mycobacterial antigens from *M.tb*, M.bovis BCG, NTM

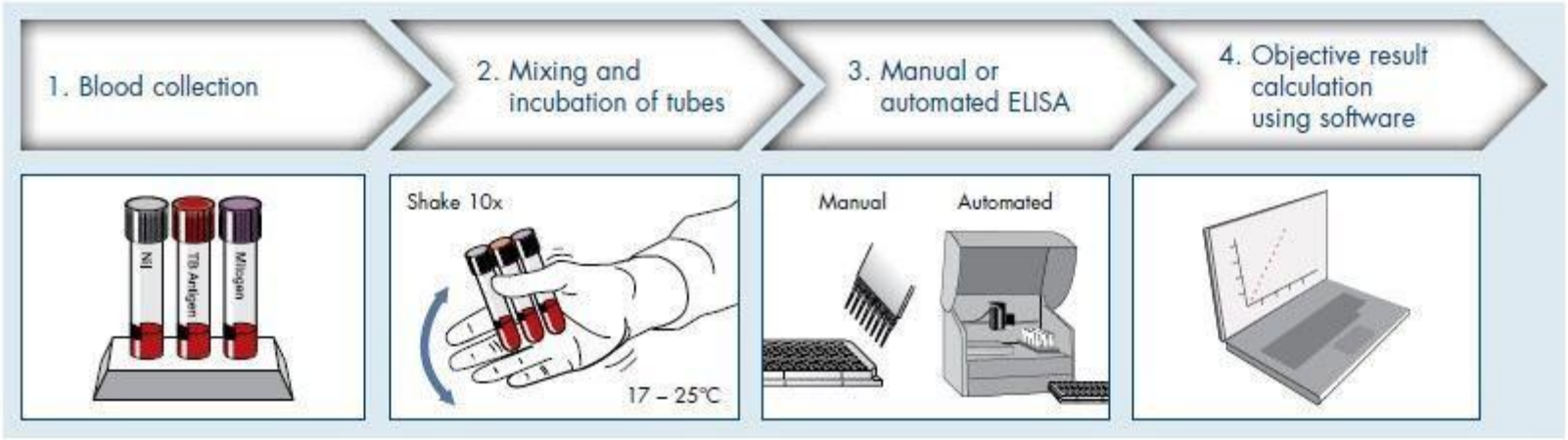
Interferon-γ release assays

- Available since 2005
- Measures IFN-γ response to TB antigens from RD-1 region of *M.tb* in CD4+ T cells
  - Proteins are absent from M. bovis BCG vaccine

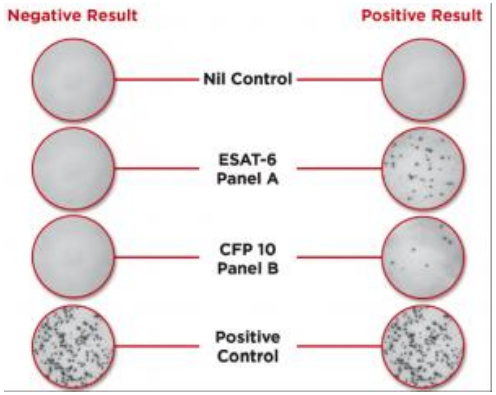
IGRAs



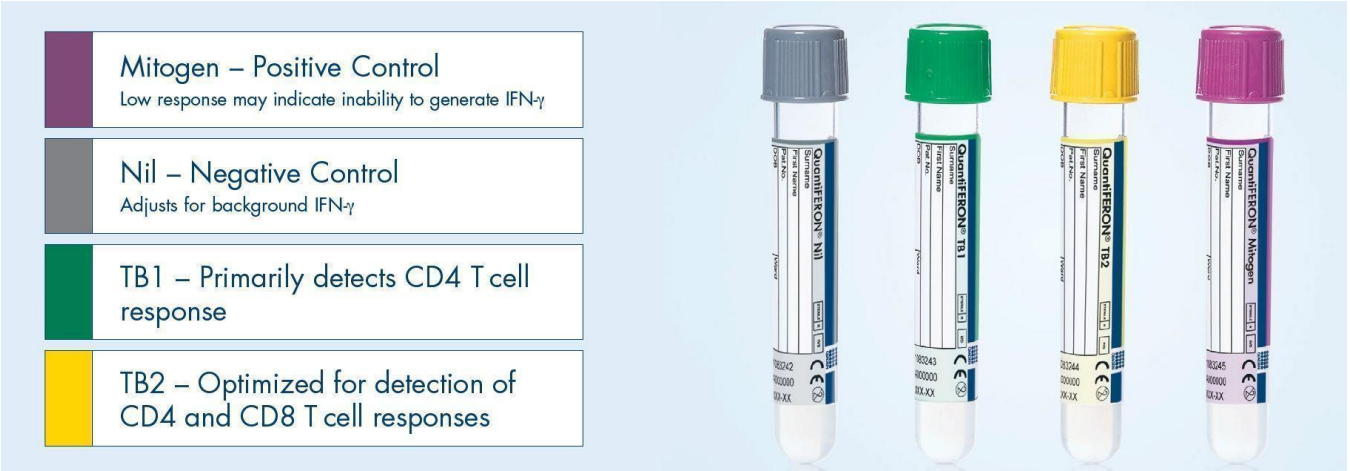
- T-SPOT.TB:
  - ESAT-6 and CFP-10
  - Number of T cells producing IFN-γ
- QuantiFERON-Gold In Tube (QFT-GIT):
  - ESAT-6, CFP-10, TB7.7 (test) & pos/neg controls



IGRAs



- T-SPOT.TB:
  - ESAT-6 and CFP-10
  - Number of T cells producing IFN-γ
- QuantiFERON-Gold In Tube (QFT-GIT):
  - ESAT-6, CFP-10, TB7.7 (test) & pos/neg controls
- QuantiFERON-Plus (4th generation)
  - 2 "TB" tubes, measuring $CD4^+$ and $CD8^+$ T cell responses



Which test to use: TST vs IGRA?

- 2017 Guidelines:
  - **Low to intermediate risk**: IGRA preferred over TST
    - Infected with no known risk factors, smokers, DM, systemic steroid treatment.
  - **High risk**: either can be used, consider dual testing
    - HIV/AIDS, transplantation, immuno-suppressant therapy, silicosis, hemodialysis, recent TB, head/neck cancer, abnormal CXR,

Which test to use in children?

- Children <5 years (CDC/IDSA/ATS): TST preferred
- Children ≥2 years (AAP): either TST or IGRA
  - BCG-vaccinated? Prefer IGRA
  - BCG-vaccinated/TST+? Can check IGRA
- Children <2 years (AAP): TST preferred
- Children <3-6 months (AAP): neither are reliable

Priority candidates for LTBI treatment

TST≥5mm or IGRA+
People living with HIV
Recent contacts of infectious TB
People with fibrotic changes on CXR (“old TB”)
Organ transplant recipients
Otherwise immunosuppressed (TNF-α blockade, steroids, chemo)

Priority candidates for LTBI treatment

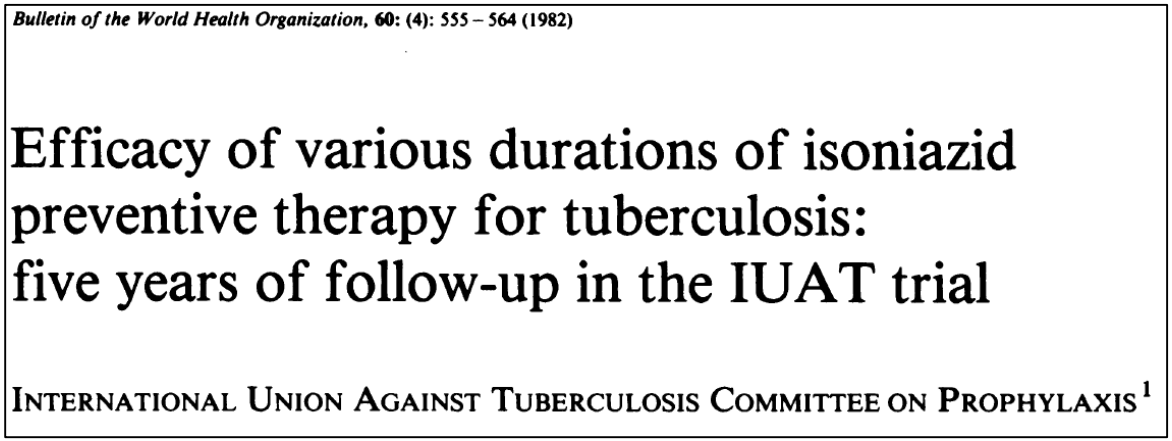
TST≥5mm or IGRA+	TST≥10mm or IGRA+
People living with HIV	People from high-TB-prevalence countries
Recent contacts of infectious TB	Children <4 years of age
People with fibrotic changes on CXR (“old TB”)	At high risk of reactivation (DM, end-stage renal disease, silicosis, some malignancies, injection drug use)
Organ transplant recipients	Residents/employees in high-risk congregate settings (corrections, shelters, health care)
Otherwise immunosuppressed (TNF-α blockade, steroids, chemo)	Mycobacteriology laboratory personnel

http://www.tstin3d.com

LTBI Regimens

Drug(s)	Duration	Notes
Isoniazid (+B6)	9 months 6 months	Daily self-administered or twice-weekly administration via DOT
Rifampicin	4 months	Daily administration.
INH + Rifapentine (+B6)	3 months	Weekly administration, DOT preferred (self administered therapy is acceptable) Not approved for <2yrs or pregnant women

INH for LTBI: 6, 9, or 12 months?



Bulletin of the World Health Organization, **60**: (4): 555 – 564 (1982)

Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial

INTERNATIONAL UNION AGAINST TUBERCULOSIS COMMITTEE ON PROPHYLAXIS[1]

- Rates of completion are inversely related to treatment duration
- 12 months of treatment was associated with 75%-93% reduction in TB incidence

Ferebee et al, Ann NY Acad Sci. 1963
IUAT Committee, WHO Bull Health, 1982

Table 5. Benefit-to-risk ratio by regimen and year

Year of follow-up	Regimen	Cumulative no. of tuberculosis cases prevented[a]	Cumulative no. of hepatitis cases incurred[b]	Benefit-to-risk ratio
First	12-I	2.6	2.5	1.0
	24-I	3.9	3.6	1.1
	52-I	3.6	5.2	0.7

[a] Reduction in cases over placebo regimen (per 1000 persons).
[b] Excess of cases over placebo regimen (per 1000 persons).

- ~50% of hepatitis occurred in first 3 months
- Although 52-wk regimen prevented more cases, the 24-wk regimen prevented more cases of TB per case of hepatitis caused

IUAT Committee, WHO Bull Health, 1982

INT J TUBERC LUNG DIS 3(10):847–850
© 1999 IUATLD

COUNTERPOINT

How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults?

G. W. Comstock

Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland, USA

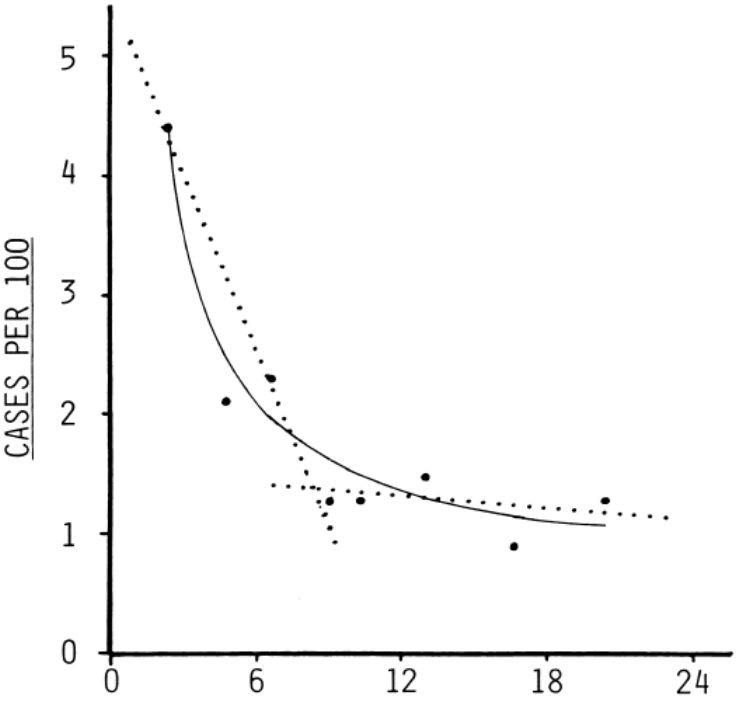


Figure Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve ($y = a + b/x$); and dotted lines, the calculated values based on the first four and last five observations ($y = a + bx$).

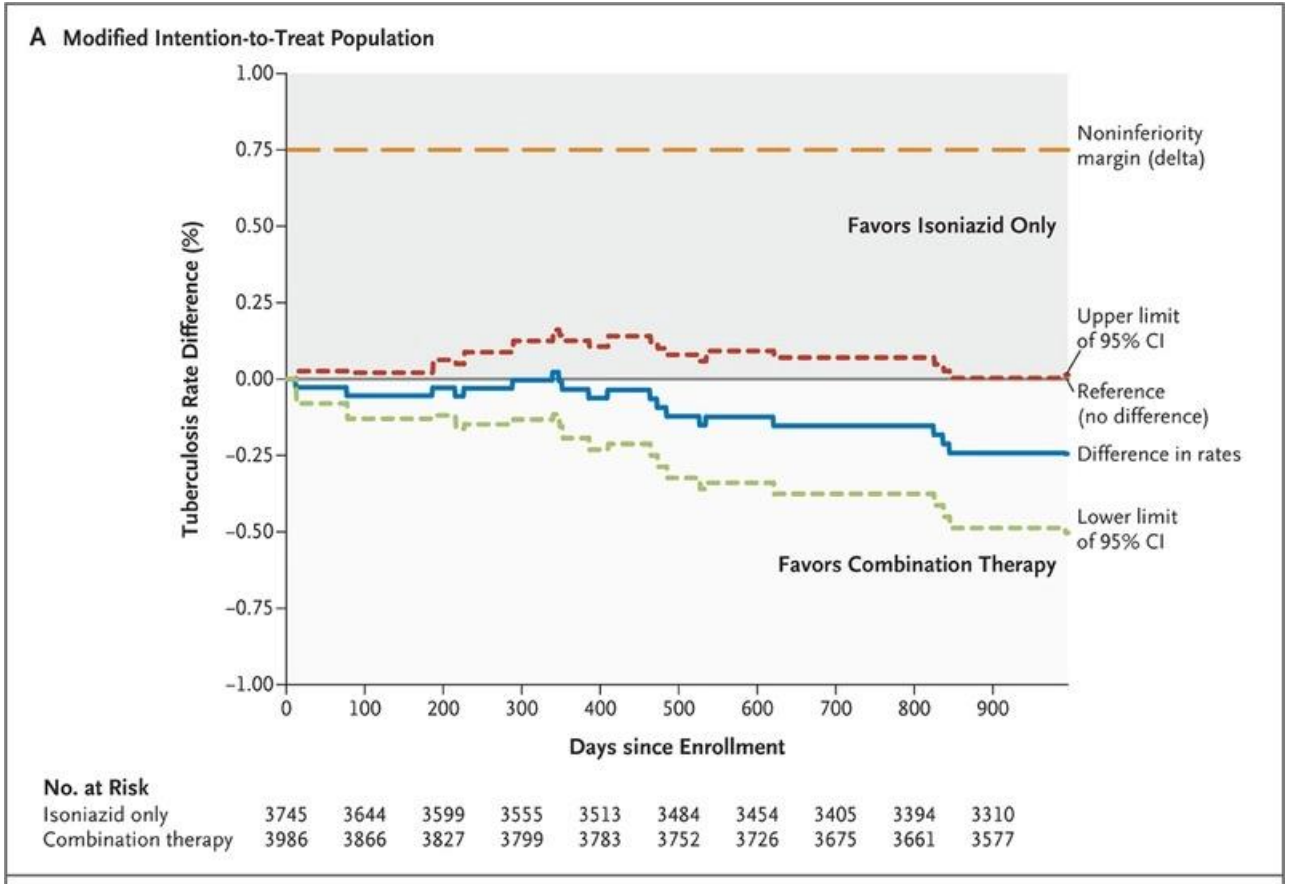
ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

Open label, non-inferiority RCT:

- 3mo weekly INH+RPT under DOT versus
- 9mo daily INH alone Self-administered
- ~8000 children >12yrs and adults
- US, Canada, Brazil, Spain



3HP: 7 cases/3986 participants (0.19%) 82% completion
9H: 15 cases/3745 participants (0.43%) 69% completion

3HP: more dropouts due to hypersensitivity & “other” reaction
9H: more dropouts due to hepatotoxicity

Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons

Timothy R. Sterling[a], Nigel A. Scott[b], Jose M. Miro[c], Guilherme Calvet[d], Alberto La Rosa[e], Rosa Infante[e], Michael P. Chen[b], Debra A. Benator[f,g], Fred Gordin[f,g], Constance A. Benson[h], Richard E. Chaisson[i], M. Elsa Villarino[b], the Tuberculosis Trials Consortium, the AIDS Clinical Trials Group for the PREVENT TB Trial (TBTC Study 26/ACTG 5259)*

- ~400 participants >12 years of age
- US, Canada, Spain, Brazil, Peru, Hong Kong
- 3HP: 1% TB incidence in 33 months of follow up
- 9H: 3.5% TB incidence

Table 3. Safety and tolerability of the study regimens.

Characteristic	3HP, $N=207$, n (%)	9H, $N=186$, n (%)	P value	% Difference (95% CI)[a]
Treatment completion (MITT)	183/206 (89)	123/193 (64)	<0.001	25.0 (17.0, 33.0)
Discontinuation because of adverse drug reaction	7 (3)	8 (4)	0.79	−1.0 (−4.7, 2.9)
Grade 3 toxicity	14 (7)	18 (10)	0.36	−3.0 (−8.4, 2.5)
Grade 4 toxicity	4 (2)	10 (5)	0.10	−3.0 (−7.2, 0.3)
Grade 5 (death)	6 (3)	5 (3)	1.00	0.2 (−3.0, 3.5)
Discontinuation due to hepatotoxicity[b]	2 (1)	8 (4)	0.05	−3.0 (−6.5, −0.1)
Flu-like/systemic drug reaction	2 (1)	0 (0)	0.50	1.0 (−0.4, 2.3)

Original Investigation

Treatment for Preventing Tuberculosis in Children and Adolescents

A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

- ~900 participants 2-17 years of age
- US, Canada, Spain, Brazil, Peru, Honk Kong
- 3HP: 0% TB incidence
- 9H: 0.74% TB incidence

Table 2. Tolerability and Reasons for Discontinuation Among Children in the Modified Intention-to-Treat Population

Characteristic	Patients, No. (%) Isoniazid (n = 434)	Rifapentine Plus Isoniazid (n = 471)	*P* Value[a]	Difference (95% CI)[b]
Treatment completion	351 (80.9)	415 (88.1)	.003	-7.2 (-12.0 to -2.5)
Reason for not completing treatment				
All reasons	83 (19.2)	56 (11.9)	.003	7.2 (2.5 to 12.0)
Discontinuation because of AE[c]	2 (0.5)	8 (1.7)	.11	-1.2 (-2.6 to 0.1)
Withdrawal of informed consent	5 (1.2)	4 (0.9)	.74	0.3 (-1.0 to 1.6)
Lost for ≥3 mo during treatment	26 (6.0)	5 (1.1)	<.001	4.9 (2.5 to 7.4)
Physician decision to cancel other than AE	7 (1.6)	3 (0.6)	.21	1.0 (-0.4 to 2.4)
Participant refusal	15 (3.5)	16 (3.4)	>.99	0.1 (-2.3 to 2.4)
Total dose count and/or administration period outside of protocol guidelines[d]	28 (6.5)	20 (4.3)	.18	2.2 (-0.7 to 5.2)

Directly observed vs Self administered?

iAdhere Study

	DOT	SAT + monthly checks	SAT with weekly text reminders + monthly checks
Completion:	87%	74%	76.4%
In the USA:	85%	78%	77%

– If DOT not available, OK to use SAT.

(recommendations for SAT/parent administered treatment extended to children ≥ 2yrs)

Belknap, Ann Int Med, 2017: 167(10):689

INH + RPT weekly dosing for children and adults

Drug	Weight based dose	Comments	Administration
INH	2-12 yrs: 25 mg/kg	- Max dose: 900mg	- Empty stomach preferred. - May crush tablet & mix in a soft food or liquid, or starch-based pudding
	≥12 yrs: 15 mg/kg	- Round up to nearest 50 or 100 mg dose - Max dose: 900mg	
RPT	10 to 14 kg: 300 mg >14 to 25 kg: 450 mg >25 to 32 kg: 600 mg >32 to 50 kg: 750 mg >50 kg: 900 mg		- With meals preferred - Tablets may be crushed and added to a small amount of semi-solid food and consumed immediately (reduces bioavailability)

LexiComp
Cruz et al, Pediatrics. 2018;141(2)
Peloquin et al, CID, 2007;45(4)

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

D. Menzies, M. Adjobimey, R. Ruslami, A. Trajman, O. Sow, H. Kim, J. Obeng Baah, G.B. Marks, R. Long, V. Hoeppner, K. Elwood, H. Al-Jahdali, M. Gninafon, L. Apriani, R.C. Koesoemadinata, A. Kritski, V. Rolla, B. Bah, A. Camara, I. Boakye, V.J. Cook, H. Goldberg, C. Valiquette, K. Hornby, M.-J. Dion, P.-Z. Li, P.C. Hill, K. Schwartzman, and A. Benedetti

- ~6800 adults, 9 countries, open-label, RCT
- 4R is non-inferior to 9H in preventing TB
- Treatment completion higher in 4R (79% vs 63%)
- 4R: less adverse events
- SAEs noted:
  - rash/allergy, hematologic, GI upset, drug interactions

NEJM, August 2, 2018

Safety and Side Effects of Rifampin versus Isoniazid in Children

T. Diallo, M. Adjobimey, R. Ruslami, A. Trajman, O. Sow, J. Obeng Baah, G.B. Marks, R. Long, K. Elwood, D. Zielinski, M. Gninafon, D.A. Wulandari, L. Apriani, C. Valiquette, F. Fregonese, K. Hornby, P.-Z. Li, P.C. Hill, K. Schwartzman, A. Benedetti, and D. Menzies

- ~850 children with LTBI or TB exposure (<5yrs)
- Treatment completion higher in 4R (87% vs 77%)
- Minor side effects were common (94% in both)
- No Grade 3+ SAEs noted
- 0 TB cases in 4R, 2 TB cases in 9H

NEJM, August 2, 2018

Selecting a regimen?

- Drug interactions (especially with rifamycins)
- Adverse effects
- Adherence
- Concerns with pill burden
  - 9H + B6 : 2 pills/day
  - 4R: 2 pills/day
  - 3HP + B6: upto 10 pills weekly
- Costs
- Pregnancy
- Preferences (patient, provider, system)

Adverse effects: rifamycins

- Hypersensitivity reactions (<0.5-1%)
  - Rash, angioedema, syncope
  - thrombocytopenia/hemolytic anemia
- Cutaneous reactions (mild, 6%)
- Flu-like illness/myalgias (~3%), arthralgias
- GI upset: pain, nausea, vomiting,
- Hepatotoxicity (<1%)
- Orange discoloration of body fluids

Adverse effects: isonazid

- Hepatotoxicity (10-20%: asymptomatic, <1% symptomatic)
  - Underlying liver disease, alcoholism, other hepatically-metabolized medications,
  - Age:
    - <20 yrs: 1/1000
    - 20-34 yrs: 3/1000
    - 35-49 yrs: 12/1000
    - 50-64 yrs: 23/1000
    - >65 yrs: 8/1000
- Peripheral neuropathy (0.2%)
  - DM, HIV, renal failure, alcoholism, meat-deficient diet
- CNS: headaches, insomnia

Ongoing management

- Lab testing at baseline/during treatment
  - If at risk of hepatotoxicity (underlying liver disease)
  - Abnormal LFT results at baseline
  - Anyone with symptoms: fatigue/malaise, anorexia, abd pain, n/v, pale stools, dark urine, fevers/chills
- Follow up visits:
  - Symptom screening
  - Adherence checks, refills

- LTBI testing:
  - “incipient TB” biomarkers
- LTBI treatment:
  - Daily 1HP “ultra short course”:
    - non-inferior to 9H among ~3000 HIV+ adults from TB-endemic regions or TST+. (CROI, 2018)
  - Pediatric-friendly dispersable formulations
- Prevention:
  - New TB vaccines?
- Treatment:
  - Active TB in children: Shorter duration for mild forms of disease in children (SHINE study, 4 mos vs 6 mos)

Thank you

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