Tuberculosis: 13 million in US Infected Treatment Needed Now

2018 PA Refugee Health Consultation

Ed Zuroweste, MD
TB Medical Consultant
PA Dept. of Health

November 29, 2018

Disclosure and Disclaimer

Faculty:

Ed Zuroweste, MD

Disclosure: I have no real or perceived vested interests that relate to this presentation nor do we have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas.

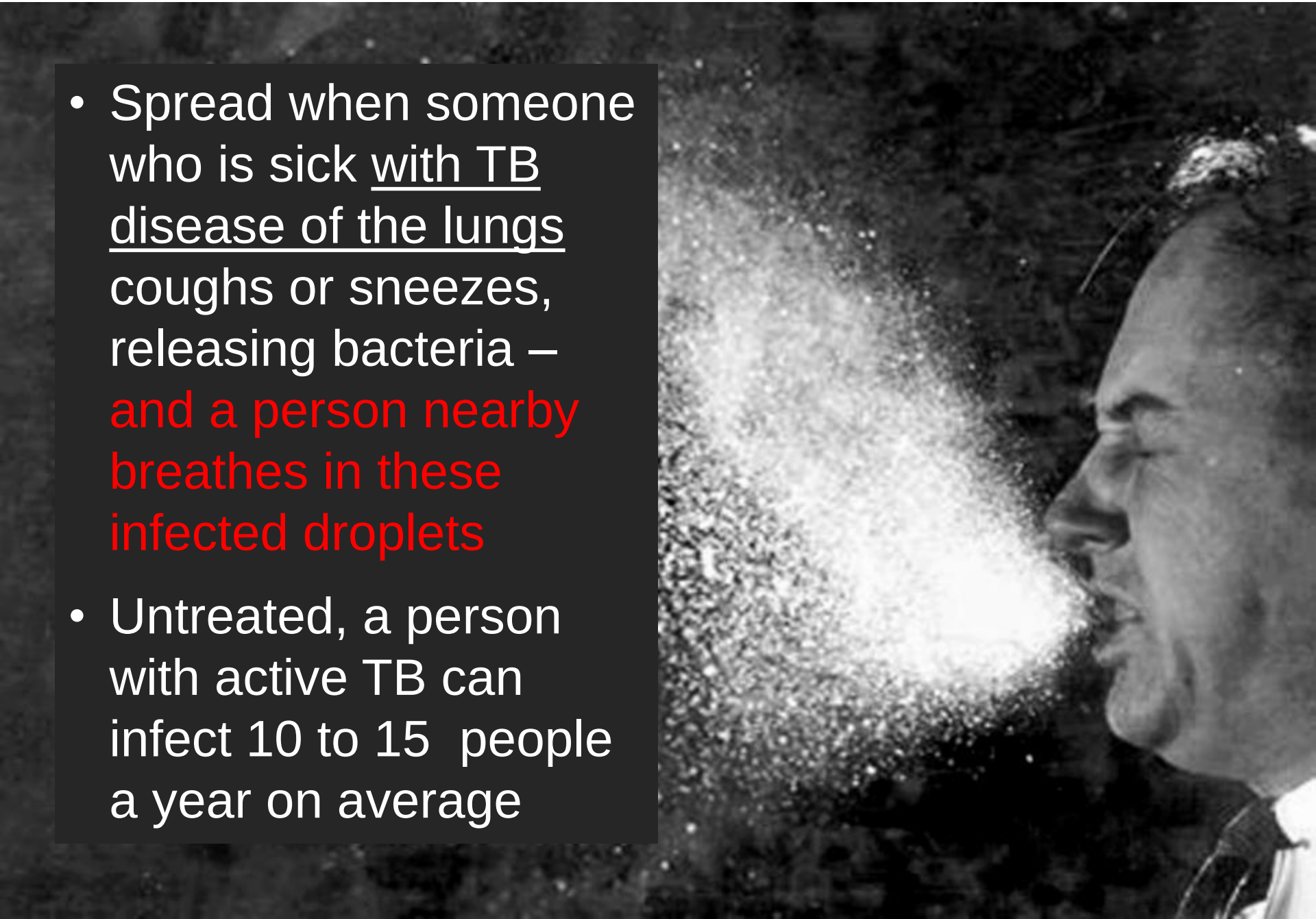
Objectives

- TB Global, US, PA current stats
- State the benefits of screening for TB with the interferon gamma-release assay (IGRA) blood test.
- Screening and treatment of TB infection
- Explain the benefits of collaborating with the state and the local public health department to diagnose and treat patients TB infection.

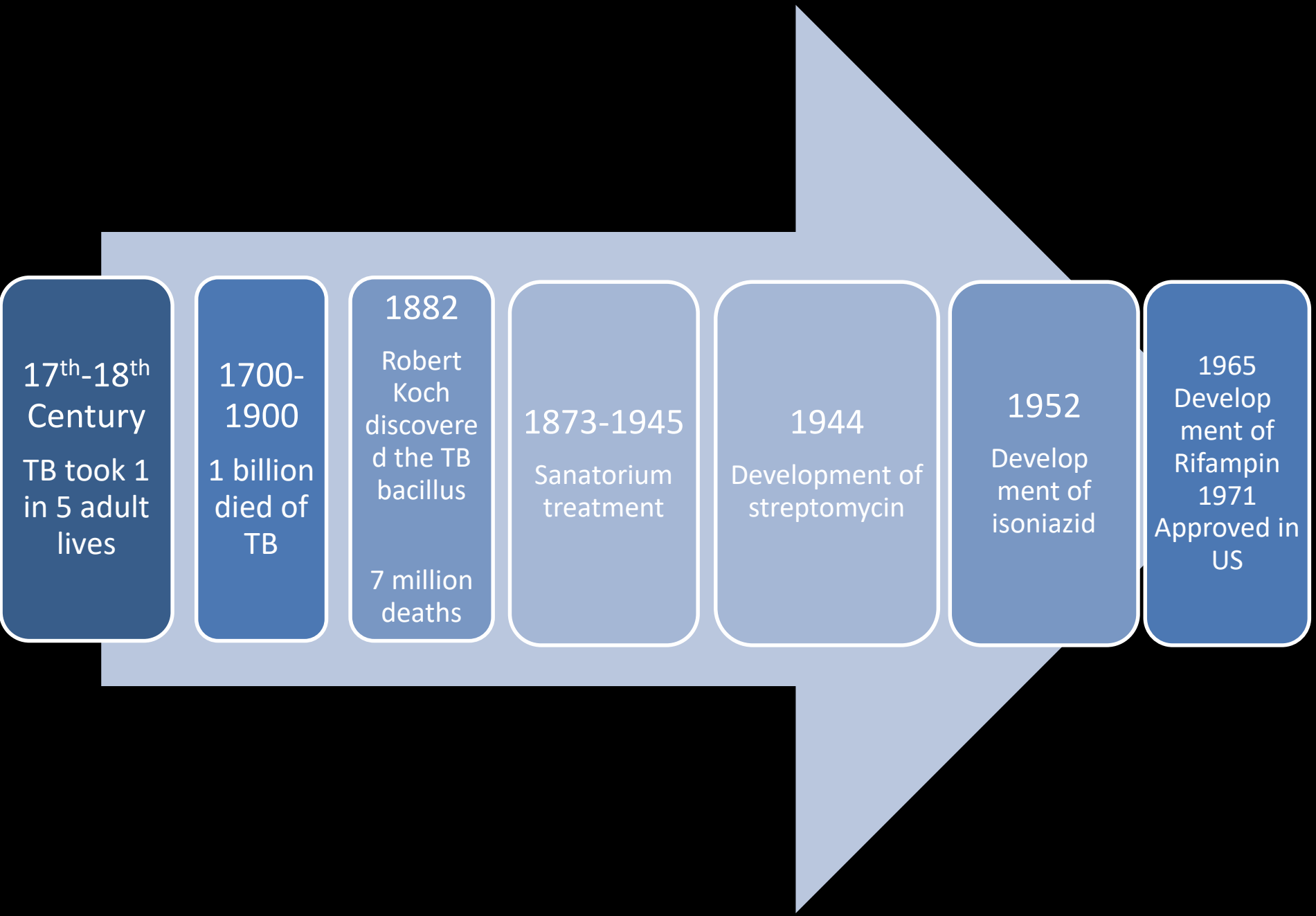
MIGRANT CLINICIANS NETWORK
MCN

“Tuberculosis is a social problem with a medical aspect”

Sir William Osler, 1904



- Spread when someone who is sick with TB disease of the lungs coughs or sneezes, releasing bacteria – and a person nearby breathes in these infected droplets
- Untreated, a person with active TB can infect 10 to 15 people a year on average


17th-18th Century
TB took 1 in 5 adult lives
1700-1900
1 billion died of TB
1882
Robert Koch discovered the TB bacillus
7 million deaths
1873-1945
Sanatorium treatment
1944
Development of streptomycin
1952
Development of isoniazid
1965
Development of Rifampin
1971
Approved in US

Global Burden Of Tuberculosis

Global Burden of TB, 2017

WHO Global TB Report, 2017

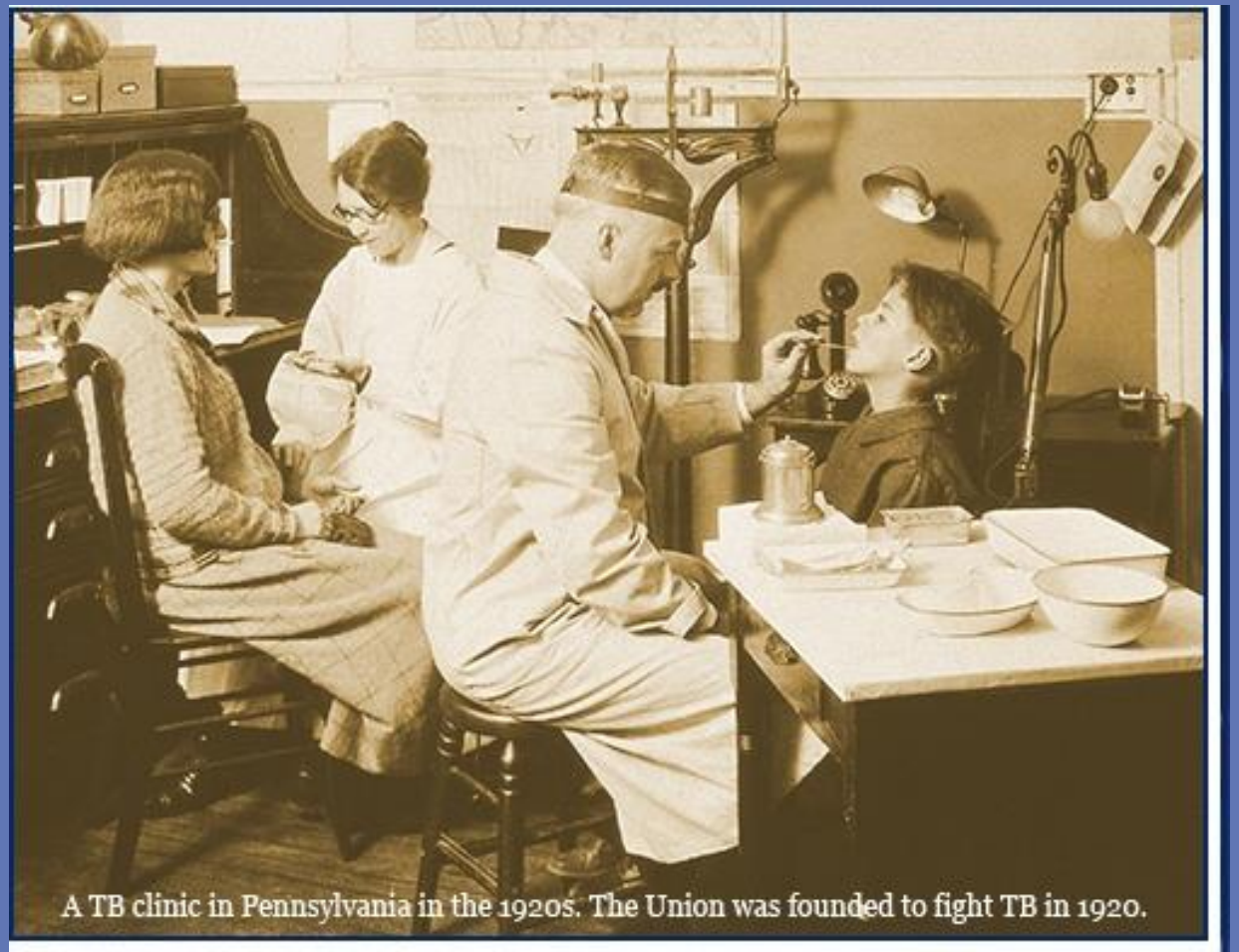
	Estimated Number of Cases	Estimated Number of Deaths
All forms of TB	**10.4 million (9.6 in 2014)**	**1.7 million***
HIV-Associated TB	**1.2 million (12%)**	**374,000**
Multidrug-resistant TB (MDR-TB)	**490,000****	**~150,000**

- Approx. 1/3 of the world (2 billion people) is infected with *M.tb*
- Estimated that 53 million lives were saved between 2000 and 2016 through effective diagnosis and treatment of TB and HIV
- In Children 1,000,000 cases and 140,000 deaths a year

*including 0.374 million deaths among PLHIV

**Fewer than 25% of those thought to have MDR TB were detected

2015 Tuberculosis Surpassed HIV as the Leading Cause of Death by Infectious Disease



A TB clinic in Pennsylvania in the 1920s. The Union was founded to fight TB in 1920.

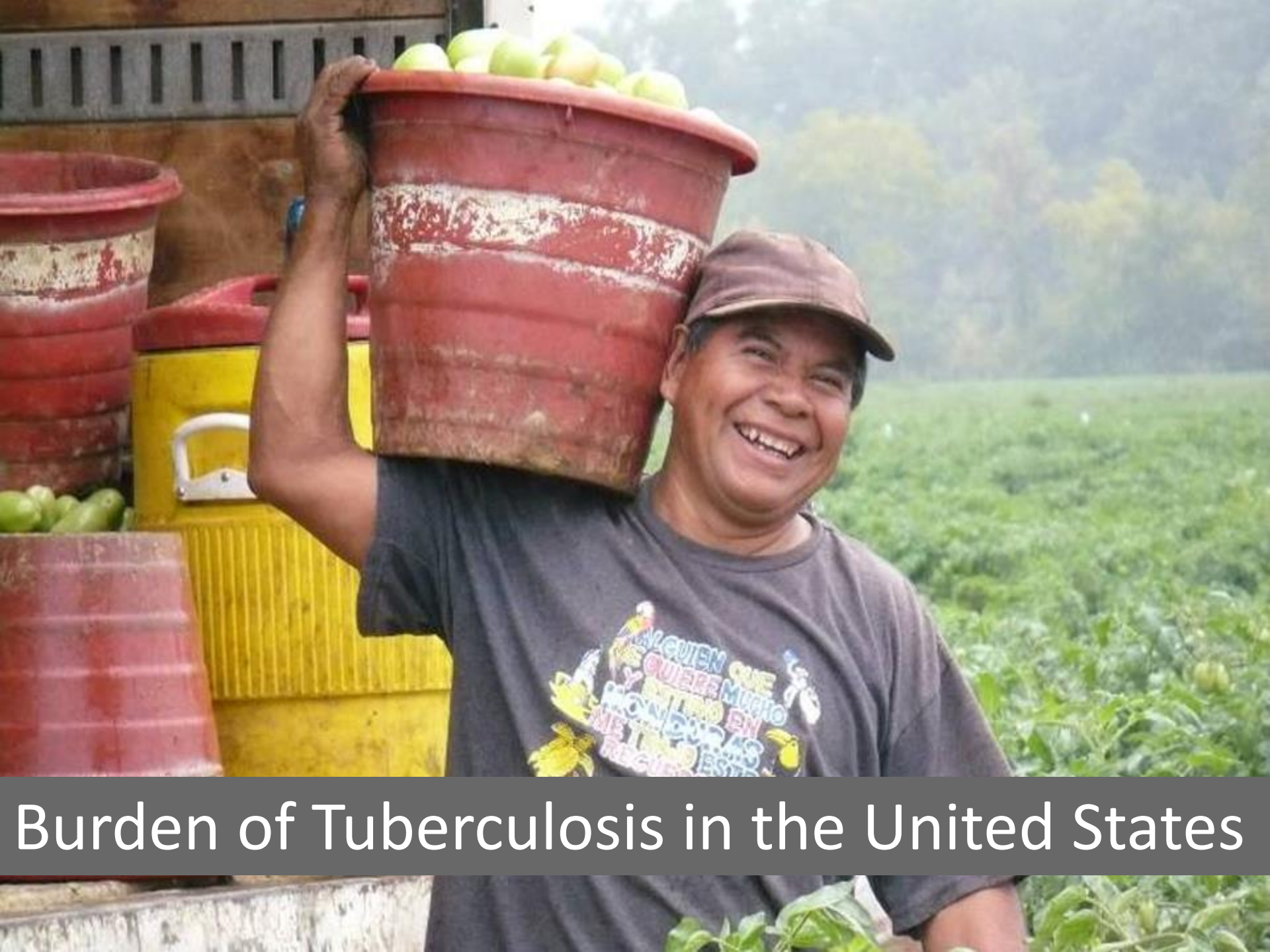
TB causes more deaths among women than all causes of maternal mortality

Every day 20,000 people develop TB disease and 4,400 die (< 12,000 Total Ebola Deaths)

Each year over 10 million people around the world become sick with TB disease.

On average, one person dies of TB every 15 seconds

TB accounts for more than ¼ of all preventable adult deaths in developing countries



Burden of Tuberculosis in the United States

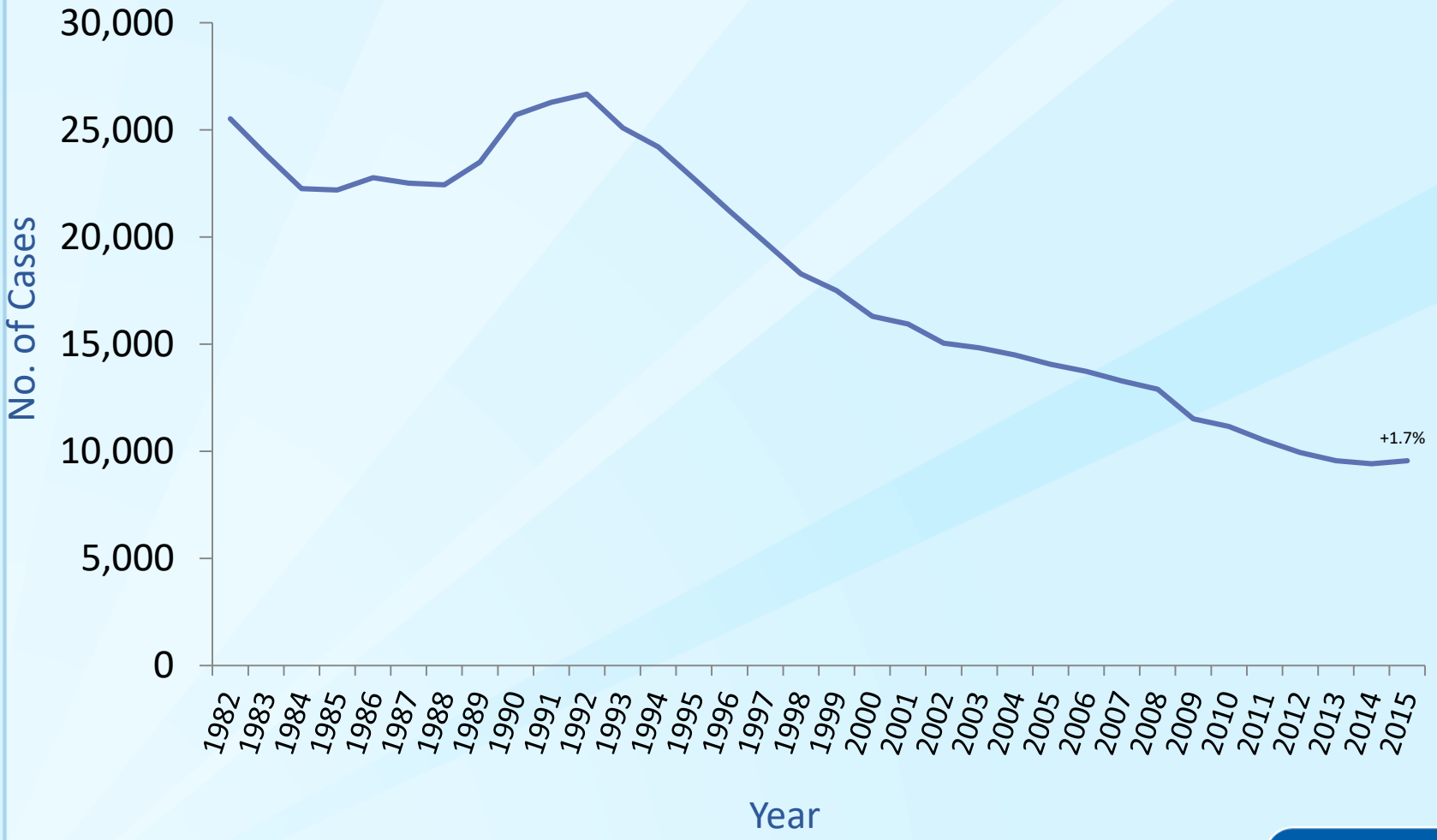
TB Morbidity

United States, 2005-2017

Year	No. of Cases	Rate (per 100,000)	
2005	14, 065	4.7	
2006	13, 754	4.6	
2007	13, 299	4.4	
2008	12, 898	4.2	
2009	11, 540	3.8	
2010	11, 181	3.6	
2011	10, 521	3.4	
2012	9,951	3.2	
2013	9,588	3.0	
2014	9,406	2.95	
2015	9,557	3.0	*1.6% increase*
2016	9,287	2.9	
2017	9,105*	2.8	*2.1% decline*

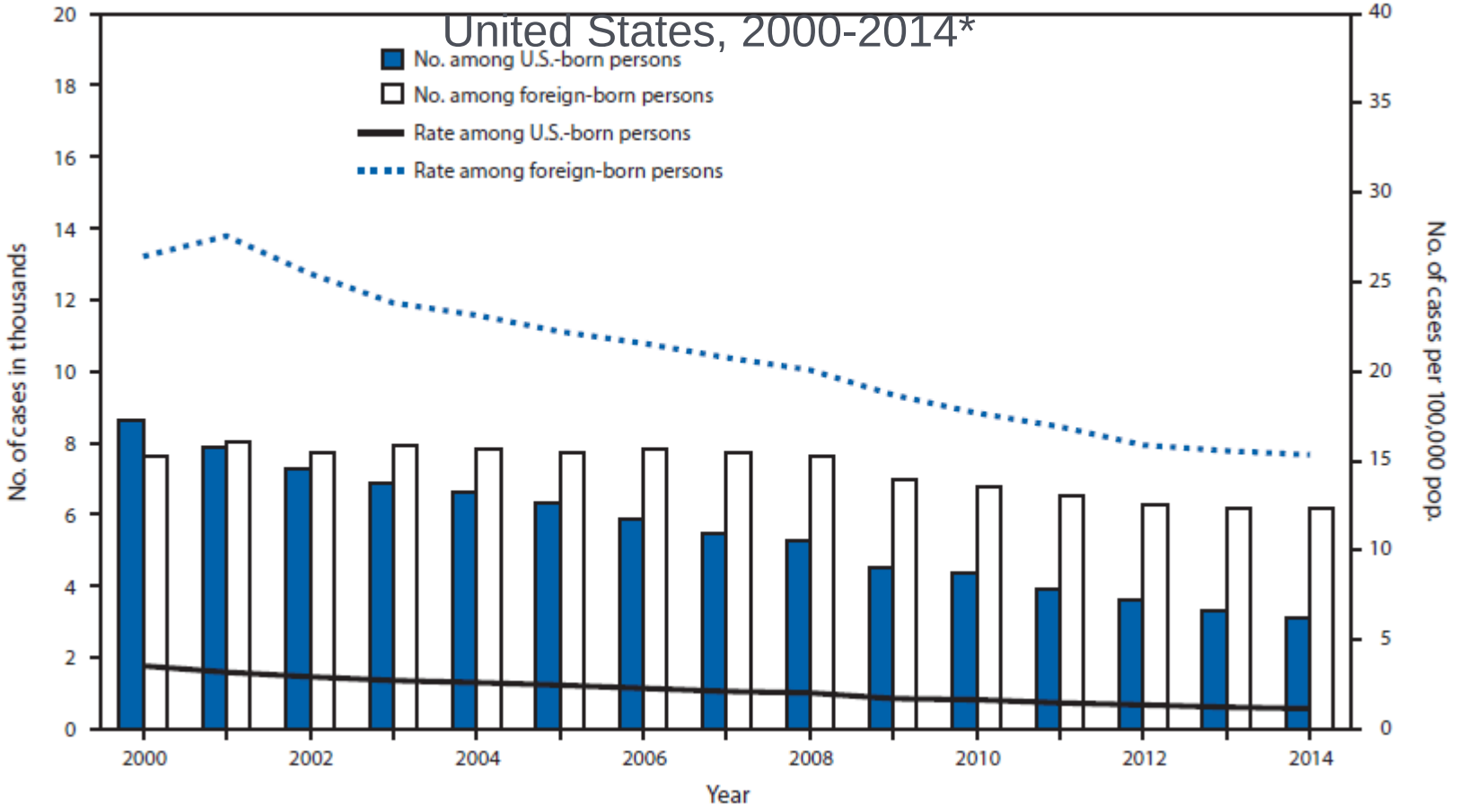
**Lowest since 1953*

Reported TB Cases
United States, 1982–2015*



*Updated as of March 25, 2016.

TB Cases in US-born vs Non-US-born persons



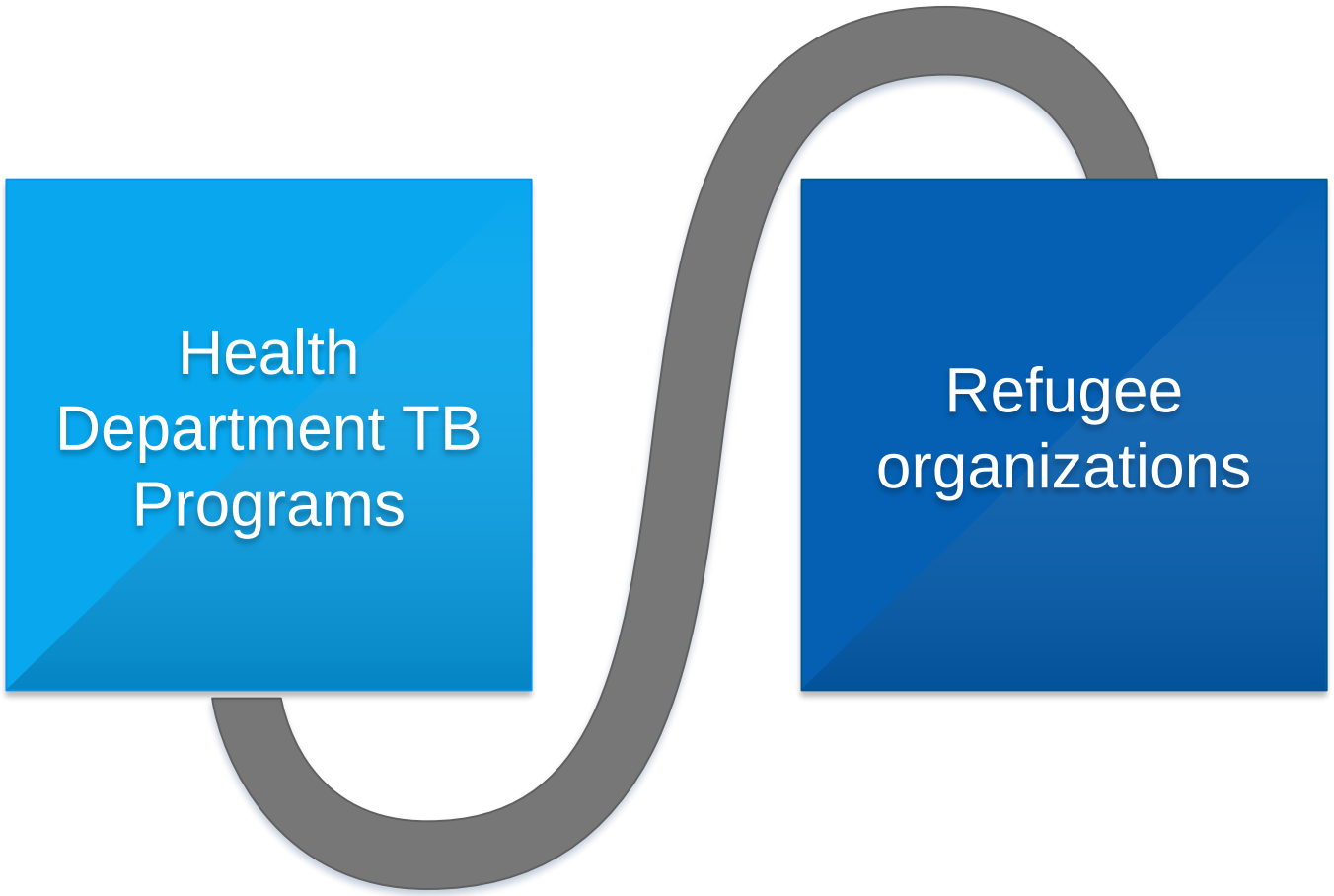
*Updated March 24, 2018 with provisional 2017 data

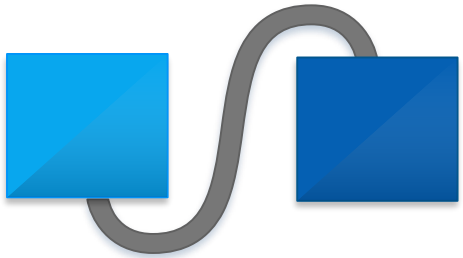
69.8% Foreign-born

What are the “Hidden Stats” on TB

- Active TB cases 9,105
- Contact investigation* identifies average of 17.9 contacts/active case; 1% new active case identified; 20% LTBI; estimated over 163,000 individuals that need to be evaluated, tested and offered preventive treatment if infected.
- TB Infection (LTBI) Estimated >13,000,000 with ~ 10% risk of active TB in lifetime

Natural Partners

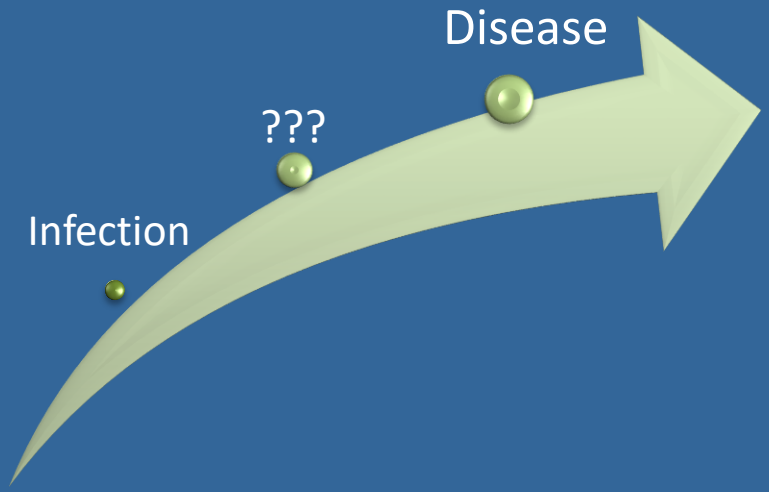




- Concern for High risk populations
- Prevention is core function
- Safety net health care/Non-exclusion policies
- Services for all life cycles
- Concern for all of public health issues (DM/HIV/Immunization etc.)

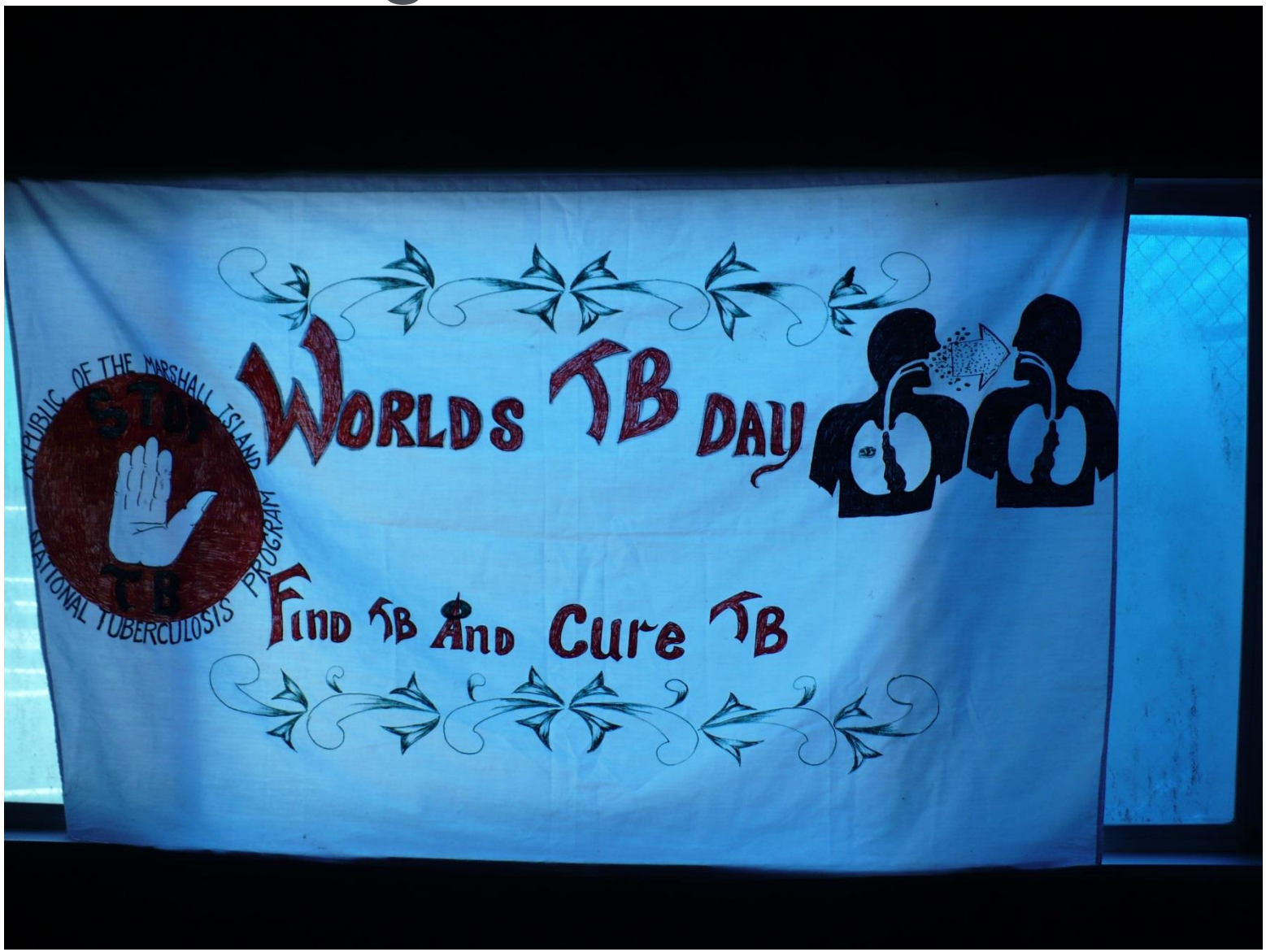

129 Lake Shore Dr.
ERNIE'S
PLUMBING
SALVAGE
&
CENTER FOR
INTERPRETIVE
DANCE

Conditions that increase the risk of progression to TB disease…



- HIV infection
- Recent infection
- Chest radiograph findings suggestive of previous TB
- Diabetes mellitus
- Prolonged corticosteriod therapy
- Other immunosuppressive therapy (chemo for CA)
- History of inadequately treated TB

Testing for TB Infection



Who is NOT REQUIRED to be TB Tested before entering the US??

- Student Visa holders
- Temporary Work Visa holders
- Tourist Visa holders
- Diplomats
- Undocumented Individuals

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

- The USPSTF recommends screening for LTBI in populations at increased risk. **(B recommendation)** The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

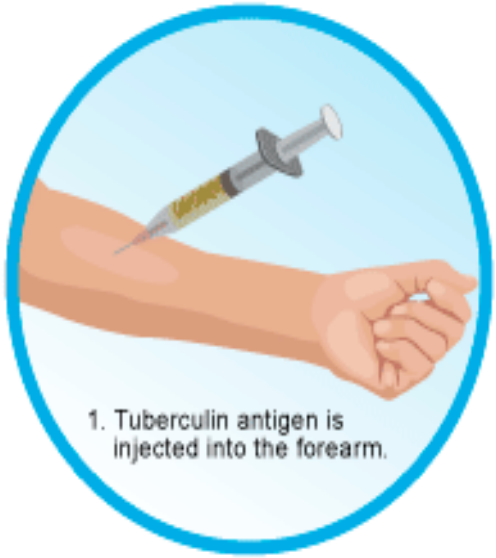
- This recommendation applies to asymptomatic adults 18 years and older at increased risk for tuberculosis

- Populations **at increased risk for LTBI include persons who were born in, or are former residents of, countries with increased tuberculosis prevalence and persons who live in, or have lived in, high-risk congregate settings (eg, homeless shelters and correctional facilities).** Local demographic patterns may vary across the United States; clinicians can consult their local or state health departments for more information about populations at risk in their community.

* JAMA September 6, 2016 Volume 316, Number 9

Approved tests for LTBI

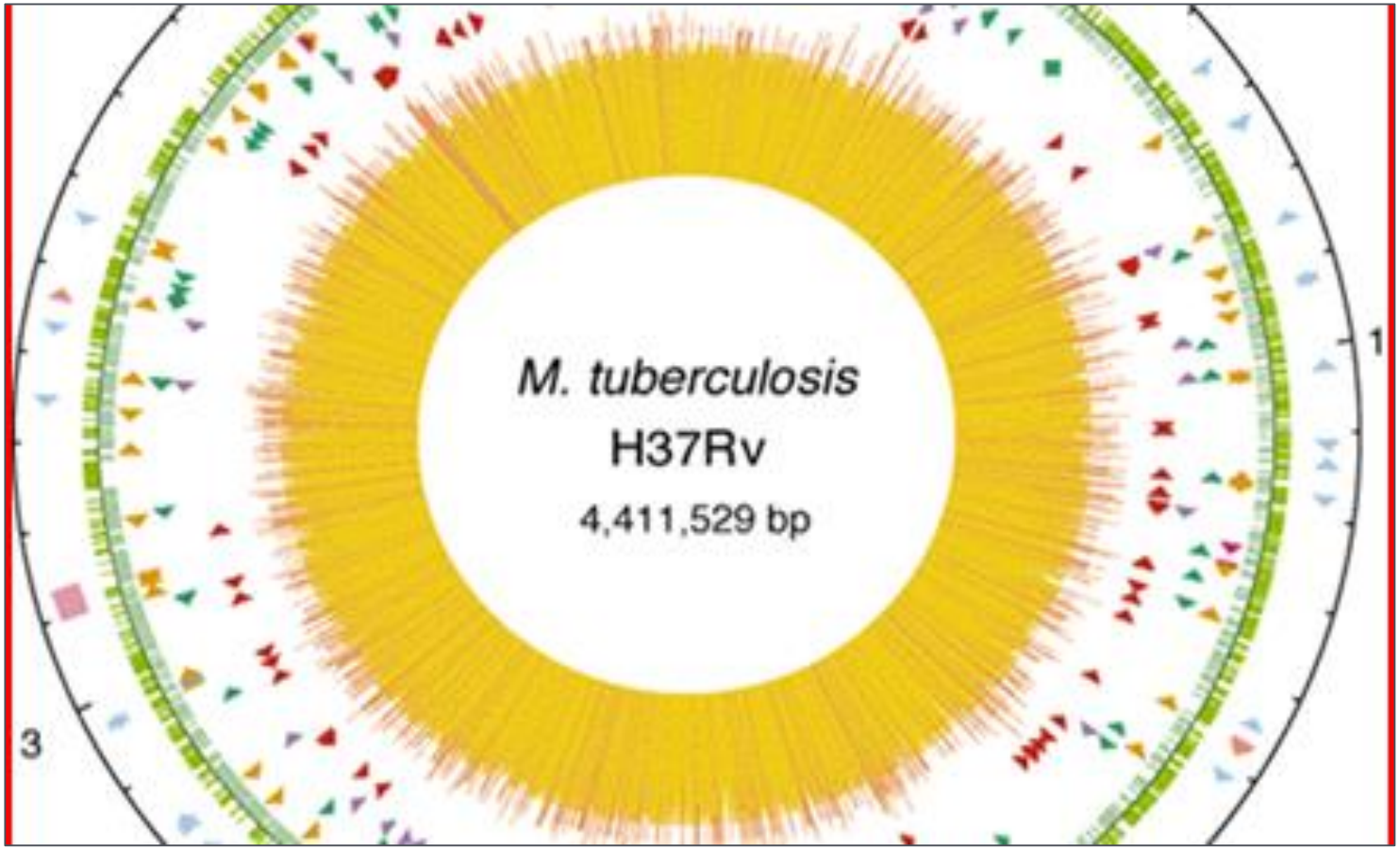
QuantiFERON®-TB Gold In-Tube (Qiagen) measures interferon gamma



Tuberculin Skin Test

T-SPOT®.*TB* test (Oxford Immunotec) measures peripheral blood mononuclear cells that produce interferon gamma

Interferon γ Release Assays



Beware of data….

TST Return Rates

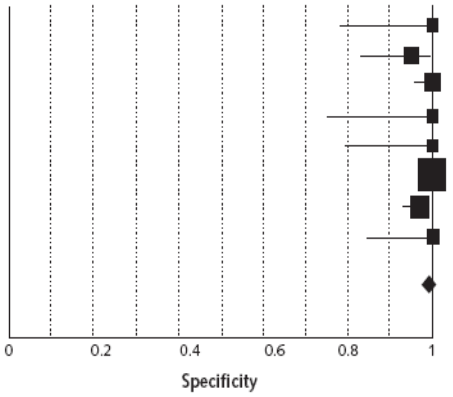
- **Return rates vary from 18% to 72%** depending on the population*
- This is especially important in high risk groups

Population	LTBI screening completion rate	Source
HIV	57%	Cheallaigh et al. (2013) *Plos One*
Immigration employees	39%	De Perio et al. (2011) *J Occup Environ Health*
Children	< 50%	Jacono et al. (2006) *Arch Pediatr Adolesc Med*

Failure to come for result reading undermines the TST

* Cheng et al. (2011) *Pediatrics* 100;210

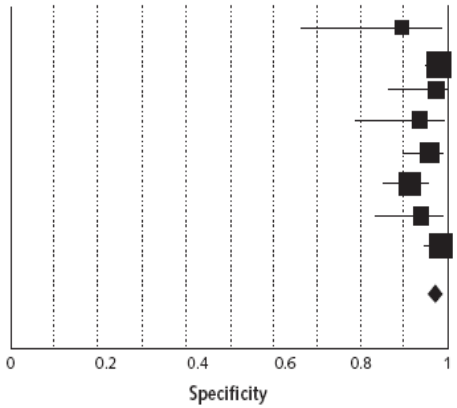
Specificity of QFT-Gold and QFT-GIT and effect of BCG vaccination



Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	1.00 (0.78–1.00)
Brock et al., 2004 (36)	0.95 (0.83–0.99)
Taggart et al., 2006 (37)	1.00 (0.96–1.00)
Palazzo et al., 2008 (24)	1.00 (0.75–1.00)
Bua et al., 2007 (18)	1.00 (0.79–1.00)
Mazurek et al., 2007 (38)	1.00 (0.99–1.00)
Franken et al., 2007 (39)	0.97 (0.93–0.99)
Detjen et al., 2007 (25)	1.00 (0.85–1.00)

Pooled specificity = 0.99 (0.98–1.00)
Chi-square = 15.88; $P = 0.026$
Inconsistency $I^2 = 55.9\%$

BCG-nonvaccinated
Pooled specificity **99%**



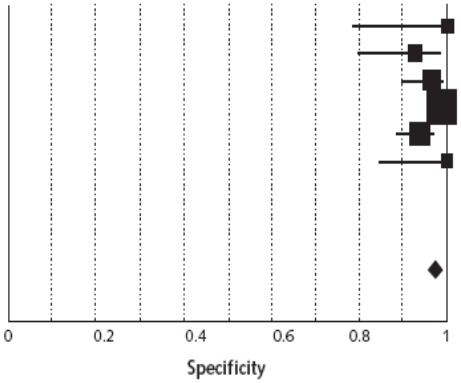
Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	0.89 (0.67–0.99)
Mori et al., 2004 (7)	0.98 (0.95–0.99)
Ravn et al., 2005 (9)	0.97 (0.87–1.00)
Brock et al., 2004 (36)	0.94 (0.79–0.99)
Kang et al., 2005 (10)	0.96 (0.90–0.99)
Lee et al., 2006 (11)	0.92 (0.85–0.96)
Kobashi et al., 2006 (15)	0.94 (0.83–0.99)
Soborg et al., 2007 (40)	0.99 (0.95–1.00)

Pooled specificity = 0.96 (0.94–0.98)
Chi-square = 13.81; $P = 0.055$
Inconsistency $I^2 = 49.3\%$

BCG-vaccinated
Pooled specificity **96%**

Pai M et al Annals Intern Med 2008

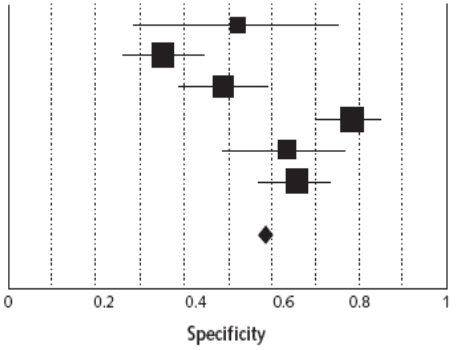
Specificity of the TST and effect of BCG vaccination



Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	1.00 (0.78–1.00)
Brock et al., 2004 (36)	0.93 (0.80–0.98)
Taggart et al., 2006 (37)	0.96 (0.90–0.99)
Mazurek et al., 2007 (38)	0.98 (0.97–0.99)
Franken et al., 2007 (39)	0.94 (0.89–0.97)
Detjen et al., 2007 (25)	1.00 (0.85–1.00)

Pooled specificity = 0.97 (0.95–0.99)
Chi-square = 12.25; $P = 0.032$
Inconsistency $I^2 = 59.2\%$

BCG-nonvaccinated
Pooled specificity **97%**



Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	0.53 (0.29–0.76)
Mori et al., 2004 (7)	0.35 (0.27–0.45)
Kang et al., 2005 (10)	0.49 (0.39–0.60)
Lee et al., 2006 (11)	0.79 (0.71–0.85)
Kobashi et al., 2006 (15)	0.64 (0.49–0.77)
Soborg et al., 2007 (40)	0.66 (0.58–0.74)

Pooled specificity = 0.59 (0.46–0.73)
Chi-square = 55.69; $P < 0.001$
Inconsistency $I^2 = 91.0\%$

BCG-vaccinated
Pooled specificity **59%**←←

Pai M et al Annals Intern Med 2008

Discordant Results
What do they mean? What should one do?

- Discordant results = IGRA+/TST- or IGRA-/TST+
- Consider positive result of *either* IGRA or TST as evidence of TB infection when
  - Clinically suspect active TB
  - Risks for infection, progression, and poor outcome are increased (HIV infection, children <5 yrs)
- In BCG-vaccinated persons (not at risk for poor outcome), can discount TST result <15 mm when IGRA is negative

Cost effectiveness of IGRAs

IGRAs was cost saving compared to TST

*Linas B, et al. AJRCCM 2011; 184(**5**):590-601*

- Evaluated CDC-defined risk-groups referenced in current U.S. LTBI screening guidelines
  - Contacts
  - HIV
  - Immigrants – regardless of time living in the US
  - Base case cost used: IGRA - $52 and TST- $22

QFT-GIT more cost-effective for individuals referred to public health clinic for a positive TST

*Shah M, et al. BMC Infect Dis 2012; **12**:360*

- Additional QFT-GIT testing of individuals referred
- Conclusion: LTBI screening with TST in low-prevalence settings may lead to overtreatment and increased costs
  - Base case cost used: QFT-GIT - $43.5


DO NOT
FLUSH
PAPER TOWELS,
NEWSPAPER,
WRAPPING PAPER
RAGS, DISPOSABLE
DIAPERS, SANITARY
NAPKINS,
TAMPONS
PLASTIC, STICKS,
ETC., DOWN
TOILET.

TB testing: How good are our tests?

Facts:

- TST and IGRAs are indirect methods and are dependent on a healthy immune system
- Do not distinguish latent infection from active disease
- Do not provide any direct evidence of the presence of viable bacilli
- No gold standard to compare for LTBI
- Accuracy of tests depends on the prevalence of infection
- The published literature of IGRAs is massive and continues to grow

New Recommendation on IGRAs in Children*

- Age: Strong consensus **(NEW 2018 REDBOOK RECOMMENDATION)** on their use in children **> 2 years**. Many experts do IGRAs in children down to 1 years of age. *

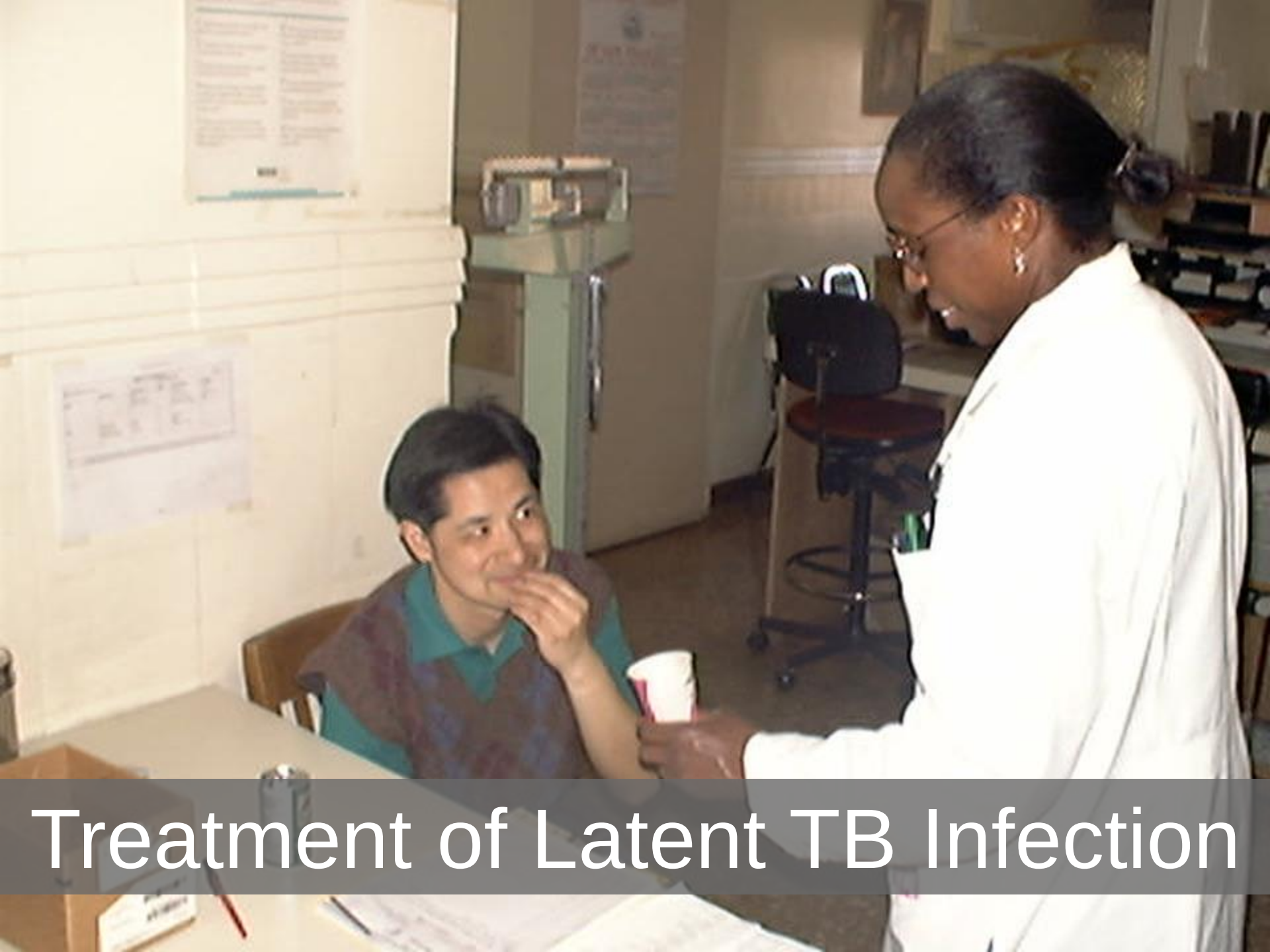
Jeff Starke IUATLD Feb 2018*

Hot Off the Press: **QFT-GIT PLUS**

- This version became available **(June 2018)**
- Four tubes instead of three
- Measures not only CD4 but also CD8
- CD8 counts higher with active TB or untreated LTBI
- If both tubes are + 99% sensitivity (1% false +)
- CD8 cells “might” help to determine who will go on to active disease (ie. Proxy of recent infection)

Summary

- IGRAs are a significant advance because of their high specificity and operational advantages over the TST
- Findings among high risk groups show consistent performance: higher sensitivity and specificity of IGRAs
- Cost effective studies have demonstrated savings and effectiveness using QFT compared to TST and Tspot. among the most important TB risk groups
- New knowledge from IGRAs are being used to advance screening policies that will benefit individuals, communities and their providers

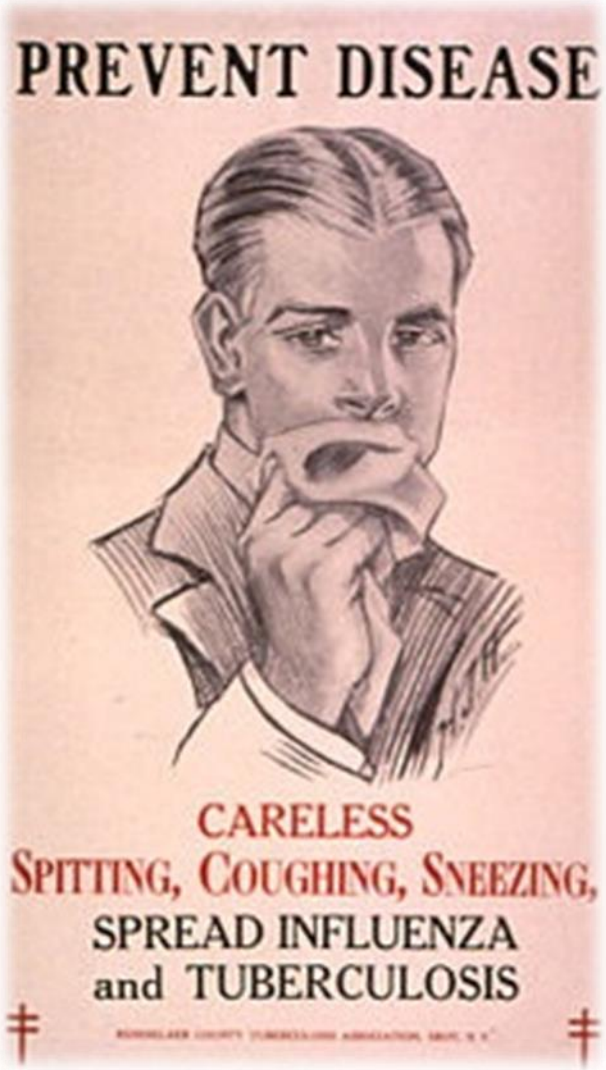


Treatment of Latent TB Infection

Pre-treatment Evaluation

Before initiating treatment for LTBI:

- Medical History
  - History of TB or HIV treatment
  - TB exposure
- Rule out TB disease
  - CXR
  - Assess/evaluate for symptoms
  - 3 sputum samples for AFB smear, culture, & sensitivities if TB symptoms or CXR findings
- Assess risks and benefits of treatment
  - Active liver disease; alcoholism etc
  - Complete medication list
- Laboratory tests
  - CBC and LFTs, if indicated



Initiating Treatment: Patient Education

- Counsel and educate patient
  - Discuss patient's risk for progressing to TB disease
  - Emphasize benefits of treatment
  - Assess whether patient willing to be treated for full treatment period
- Review common side effects
- Establish treatment plan

Treatment Regimens for LTBI

Drugs	Months of Duration	Interval	Minimum Doses	Rating/ Evidence
INH	9*	Daily	270	AII
		2x wkly**	76	BII
INH	6	Daily	180	BI
		2x wkly**	52	Avoid: HIV infected, children (CII)
RIF	4	Daily	120	BII

Preferred ** Intermittent treatment only with DOT

INH=isoniazid; RIF=rifampin

New Option for LTBI Treatment

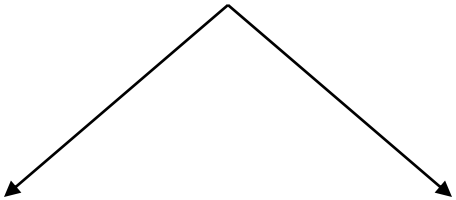
- 12 weekly doses of Isoniazid/Rifapentine (INH/RPT) with directly observed therapy (DOT)
- Based on review of randomized clinical trial and two other studies:
  - As effective as INH for 9 months
  - More likely to be completed

- CDC Recommendations in December 9, 2011

MMWR 2011; Vol 60 No. 48

TBTC Study 26, PREVENT-TB: A randomized, controlled trial of two regimens for treatment of LTBI

Patients with LTBI at high risk for reactivation
(mainly close contacts of active cases)



randomization
by household

9 months of daily INH, self-administered (270 doses)

3 months of once weekly INH and rifapentine by DOT (12 doses)

Study endpoint: development of active TB at 2 years

TBTC Study 26, PREVENT-TB: Outcomes

Population and Study Group	No. of Subjects	Subjects with Tuberculosis		
		no.	*no. per patient-yr*	*cumulative rate*
Modified intention-to-treat analysis				
Isoniazid only	3745	15	0.16	0.43
Combination therapy	3986	7	0.07	0.19
Per-protocol analysis				
Isoniazid only	2585	8	0.11	0.32
Combination therapy	3273	4	0.05	0.13

N Engl J Med 2011; 365:2155-2166

TBTC Study 26, PREVENT-TB : Adherence to therapy

Outcome	Isoniazid Only (N=3759)	Combination Therapy (N=4040)	P Value[†]
Permanent drug discontinuation — no./total no. (%)			
For any reason	1160/3745 (31.0)	713/3986 (17.9)	<0.001
Because of an adverse event	139/3745 (3.7)	196/3986 (4.9)	0.009

↓ 69 % completion

↓ 82 % completion

N Engl J Med 2011; 365:2155-2166

Hepatotoxicity

Among persons receiving ≥ 1 dose
During treatment or within 60 days of the last dose

Toxicity	9H N=3,759	INH-RPT N=4,040	P-value
All hepatotoxicity	**113 (3.0)**	**24 (0.6)**	**<0.0001**
Related to drug	**103 (2.7)**	**18 (0.5)**	**<0.0001**
Not related	**13 (0.4)**	**6 (0.2)**	**0.08**

TBTC Study 26, PREVENT-TB Conclusions

- INH-RPT was at least as effective as 9H
  - The INH-RPT TB rate was approximately half that of 9H
- INH-RPT completion rate was significantly higher than 9H
  - 82% vs. 69%
- INH-RPT was safe relative to 9H
  - Lower rates of:
    - Any adverse event
    - Hepatotoxicity attributable to study drug

3HP Post Marketing Surveillance Project and iAdhere Study 33

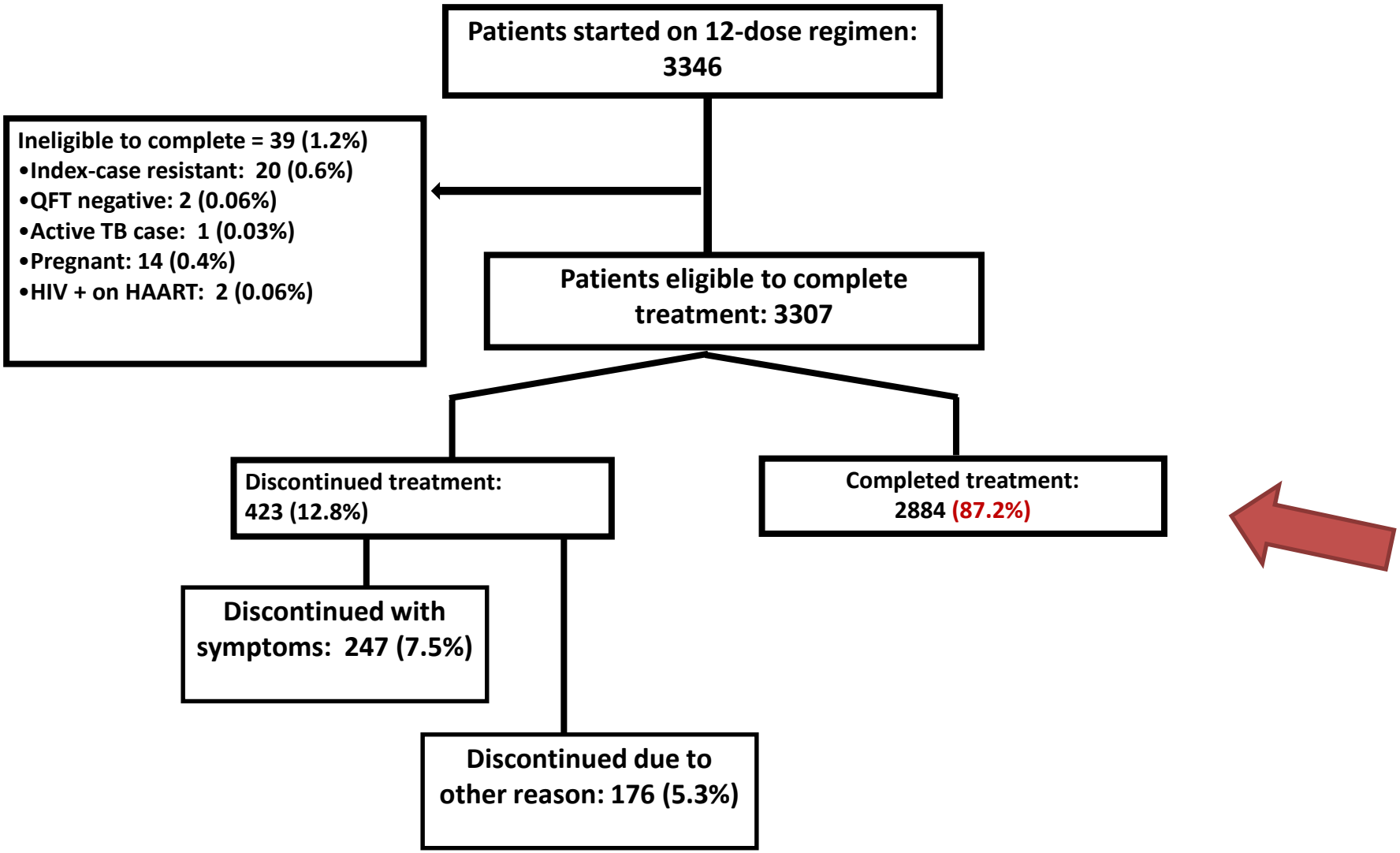
- Determine treatment completion rates
- Evaluate factors affecting treatment completion
- Evaluate rates of Adverse Events (AE)
- Assess ease of programmatic use of 3HP in a non-research setting
- Assess impact of the 3HP regimen on program
- Staffing
- Costs
- Conduct a two-year passive surveillance for TB
- TB registry match

Project sites and participants

- 22 volunteer sites participated in project design
- 16 sites contributed data
  - State Health Departments
  - County TB Programs
  - Community Providers

- Sites differed in the type of patients treated ranging from
  - Contacts
  - Health care workers
  - Converters
  - Class B immigrants
  - Refugees
  - Homeless
  - Immunosuppressed
  - Foreign-born persons
  - University students
  - ≥ 12 years
  - Correctional inmates/workers

Patient flow- chart



Conclusions

- Treatment completion rate was high
  - Similar to treatment in study 26 trial (87.2% vs. 82.1%)
  - Significantly higher than daily INH (87.2% vs. 67%)
  - High completion rate across programmatic settings, even in difficult to treat populations

- The regimen was safe
  - No deaths (or severe organ damage)
  - ~65% of patients did not report any symptoms
  - ~ 7.5% stopped due to AE
  - Nausea was the most commonly reported symptom and reason for stopping
  - Headache was an unsolicited symptom but ranked 4th among the symptoms reported

I-Adhere Update
(TBTC Study 33)

3HP regimen

DOT versus SAT

I-Adhere: Protocol Synopsis

Primary Objective:

Evaluate treatment completion by DOT vs SAT with or without text reminders

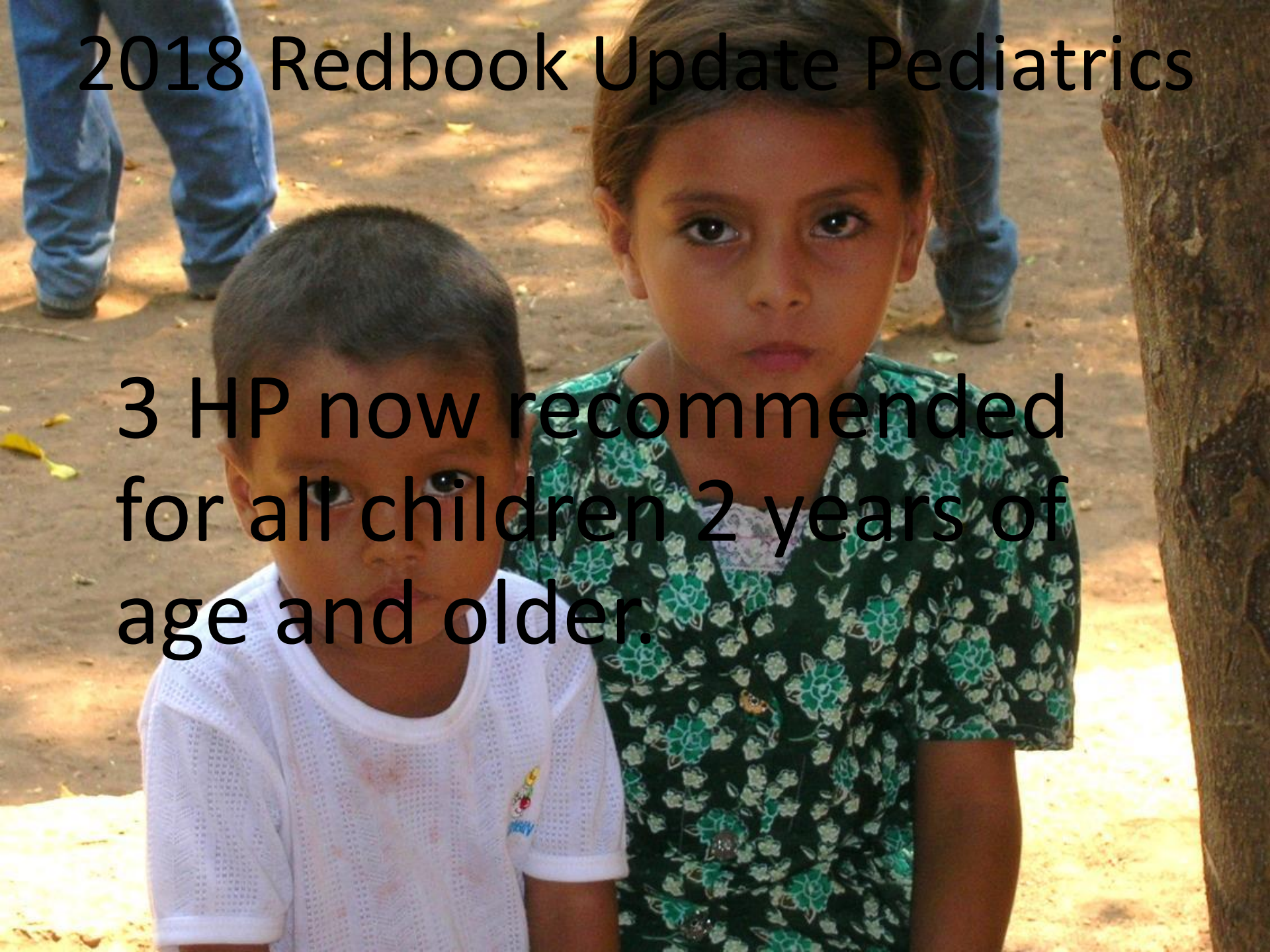
- Phase 4 open label, randomized design
- Target Population: Adults with LTBI
- All patients received 3HP
  1. DOT (control)
  2. Standard SAT
  3. SAT with weekly SMS reminders

Treatment Completion

	DOT	SAT	SAT w/ texts
All Participants	87%	74%	76%
U.S. Only	85%	78%	77%

- DOT completion was higher than in Study 26
- SAT completion varied by country of enrollment

2018 Redbook Update Pediatrics



3 HP now recommended for all children 2 years of age and older.

Completion Rates for Treatment of LTBI

Drugs	Duration (months)	Interval	Completion Rate
INH/Rifapentine	**3**	**Once a week (DOT) or (SAT)**	**90%+**
Rifampin	**4**	**Daily**	**80%**
Isoniazid	9	Daily Twice weekly	43-46%
Isoniazid	6	Daily Twice weekly	60%+

Drug Regimen for Treatment of LTBI 2018

Drugs	Duration (months)	Interval	Minimum doses
INH/Rifapentine	**3**	**Once a week (DOT) or (SAT)**	**12**
Rifampin	**4**	**Daily**	**120**
Isoniazid	9	Daily Twice weekly	270 76
Isoniazid	6	Daily	180

Increasing Risks for All

1. Failure to develop measures to prevent and treat TB everywhere threatens our ability to control the disease anywhere
2. The elimination of TB in the U.S. will depend increasingly on the elimination of TB among the non-US-born

TB ANYWHERE IS TB EVERYWHERE!

Ed Zuroweste, MD 814-571-7395
ezuroweste@migrantclinician.org