

Four Corners TB and HIV Conference
November 3, 2015
Durango, CO

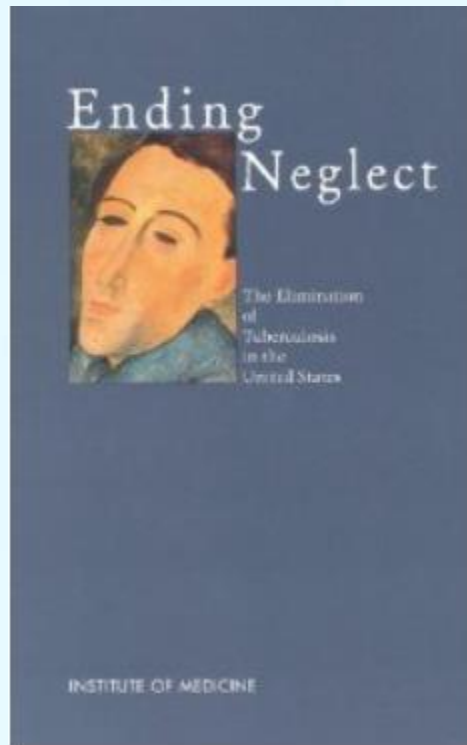
**The Tip of the Iceberg:
Addressing Latent Tuberculosis Infection to
Accelerate Tuberculosis Elimination**

Philip LoBue, MD

Outline

- ❑ **Role of latent tuberculosis infection (LTBI) testing and treatment in US TB elimination strategy**
- ❑ **Modeling of LTBI testing and treatment**
- ❑ **New opportunities**
- ❑ **Challenges**
- ❑ **What is needed to address LTBI**

Elements of National Elimination Strategy



- ❑ **Ending Neglect: The Elimination of Tuberculosis in the U.S.**
- ❑ **Institute of Medicine Report published in 2000**
- ❑ **CDC response includes 6 goals that are elements of elimination strategy in United States**

6 Goals

- ❑ Main control of TB
- ❑ **Accelerate the decline**
- ❑ Develop new tools
- ❑ Reduce the global TB burden
- ❑ Mobilize and sustain support
- ❑ Track Progress



Goal II: Accelerate the decline

Advance toward TB elimination through targeted testing and treatment of persons with latent TB infection, appropriate regionalization of TB control activities, rapid recognition of TB transmission using DNA fingerprinting methods, and rapid outbreak response.



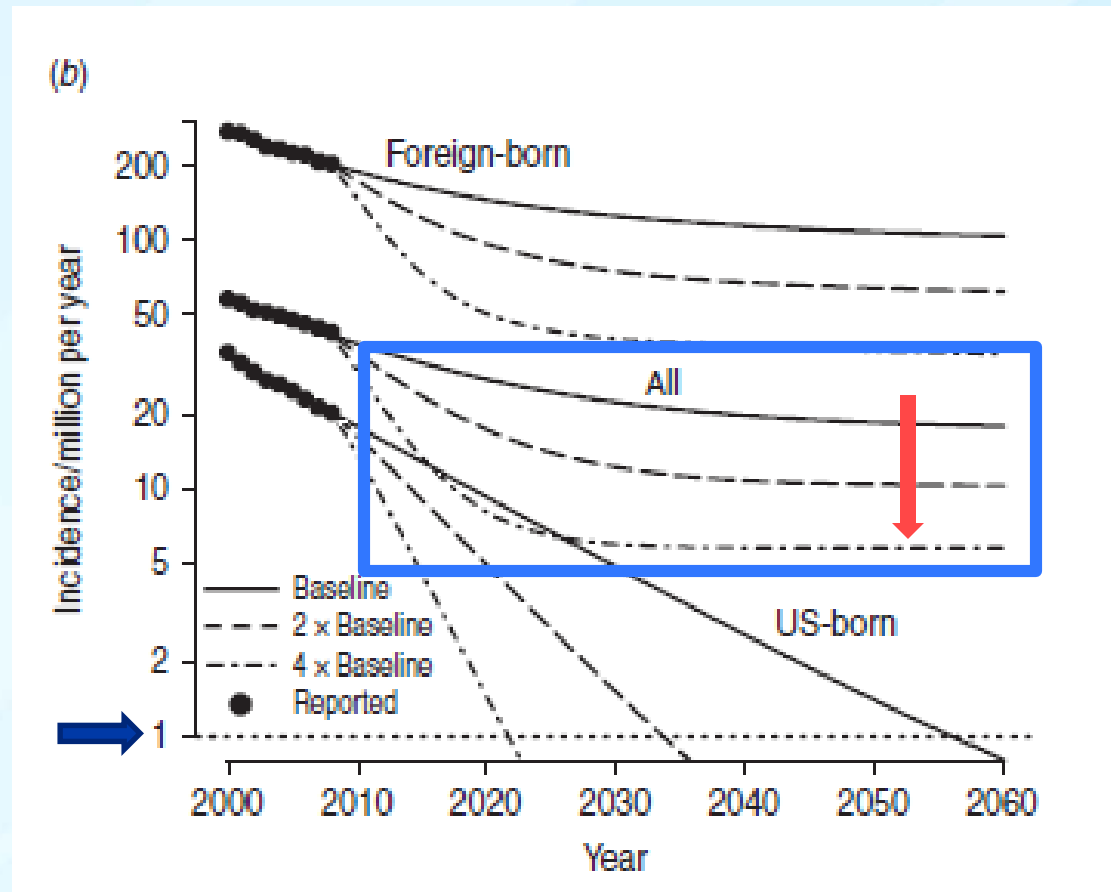
Why Focus on Latent TB Infection?

- ❑ **Modeling**
- ❑ **New Opportunities**



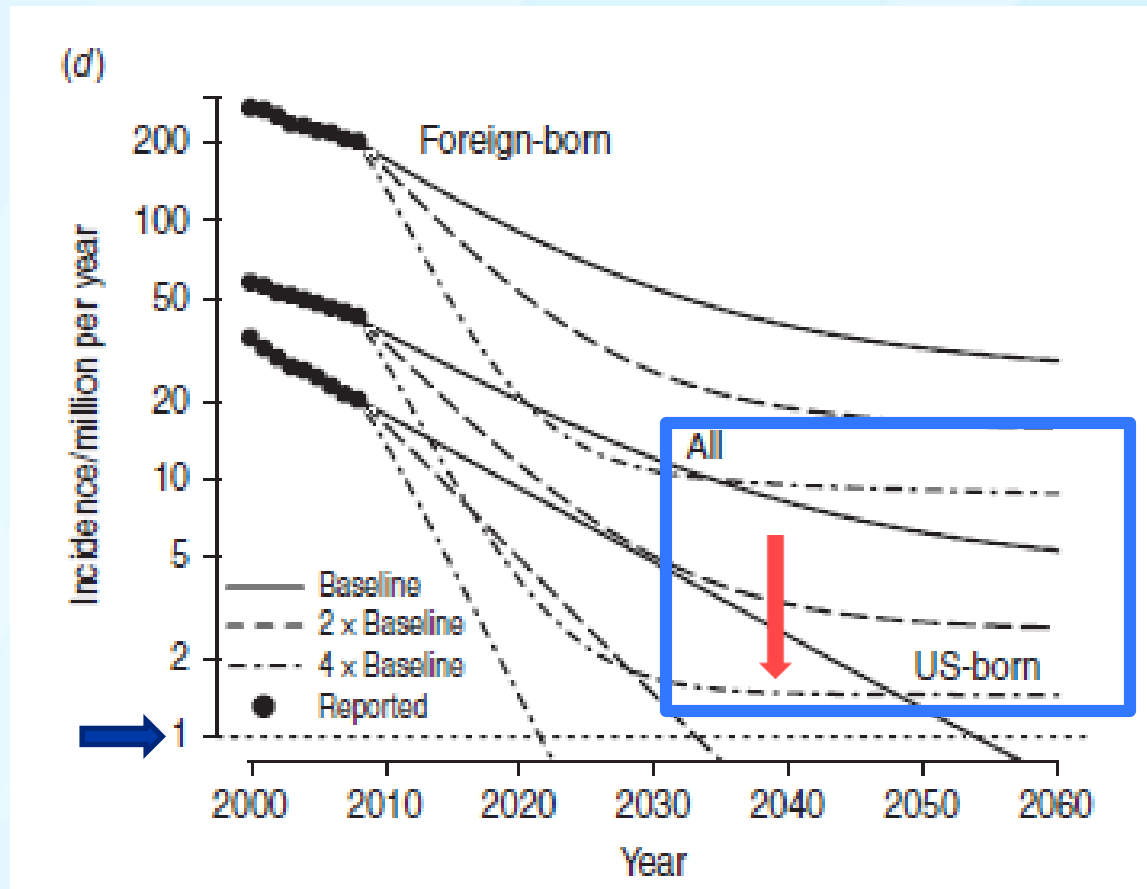
Reaching TB Elimination (<1 case per 1 million population)

Hill et al. Modelling tuberculosis trends in the USA



2 x = doubling rate of LTBI treatment; 4 x = quadrupling rate of LTBI treatment

Decrease LTBI Among Foreign-Born Persons to 25% of Current Level



2 x = doubling rate of LTBI treatment; 4 x = quadrupling rate of LTBI treatment

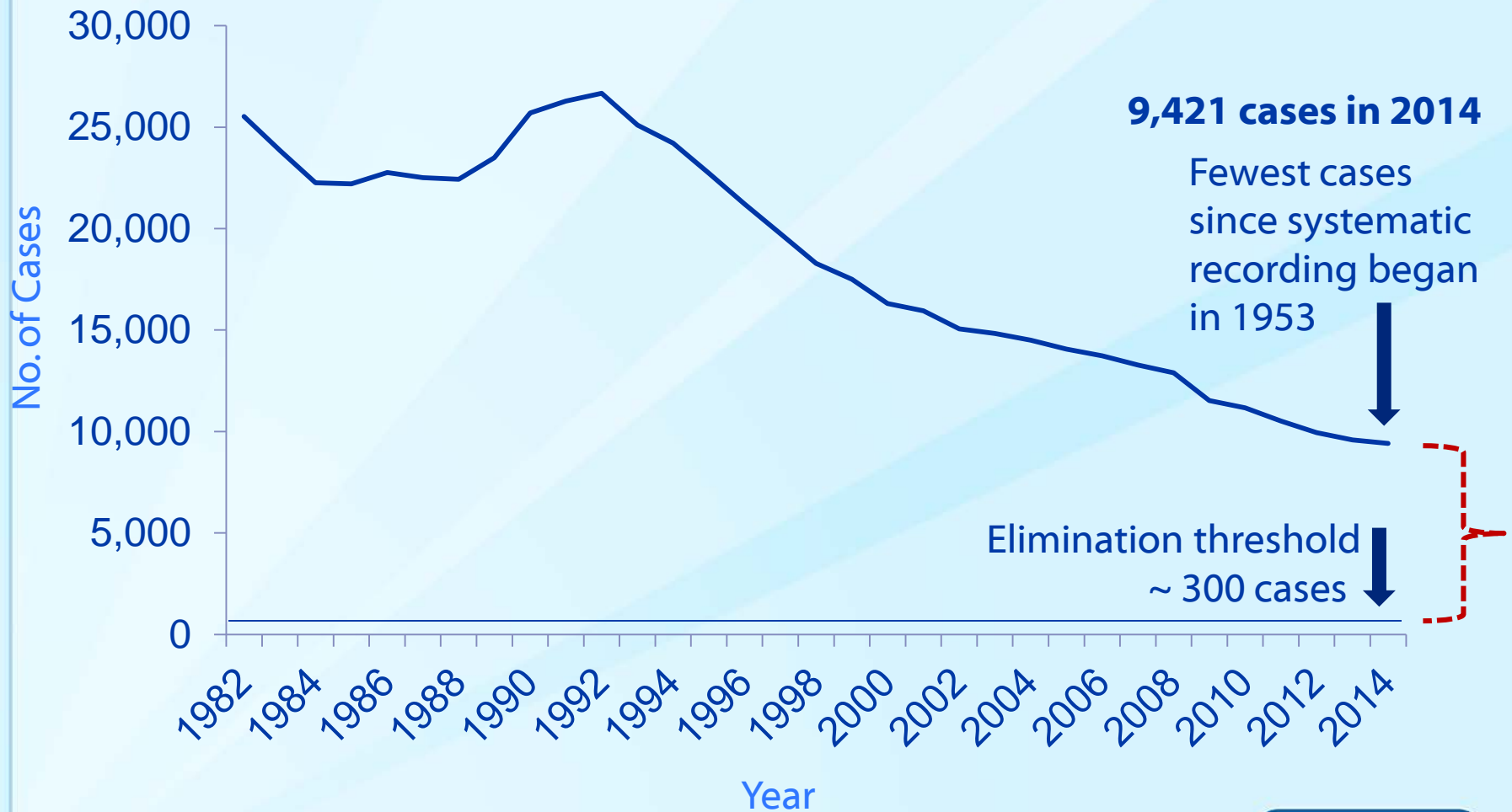
Opportunities to Better Address LTBI

- ❑ **Lowest burden of TB disease in the US since systematic national reporting began**
 - Very high treatment completion rates; not much room for improvement
 - Can we reduce diagnostic delays? No easy answer
- ❑ **Most TB cases in the US result from reactivation of LTBI**
- ❑ **Newer tests that have advantages in key populations**
- ❑ **Newer and better treatment regimens**
- ❑ **Increased insurance coverage through Affordable Care Act**
 - Possible recommendation by US Preventive Services Task Force

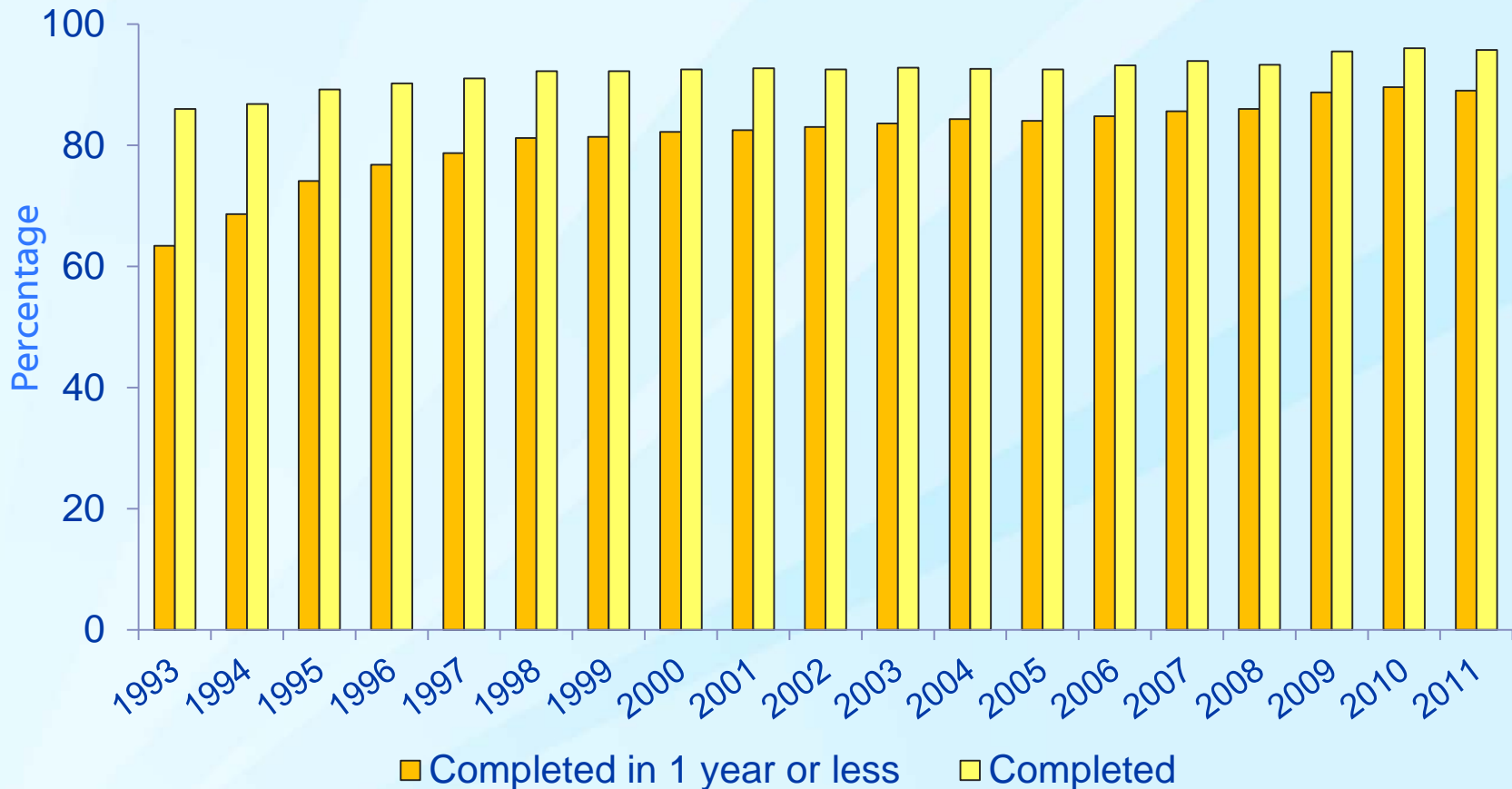


Where are we? Where do we have to go?

Reported TB Cases, United States, 1982–2014



Completion of TB Therapy, United States, 1993 – 2011*



* Updated as of June 11, 2014. Data available through 2011 only.

Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die during therapy. Excludes persons with initial isolate rifampin resistant, or patient with meningeal disease, or pediatric patient (aged <15) with miliary disease or positive blood culture.



Recent Transmission Versus Reactivation of Latent Infection

- ❑ **Analysis of US genotyping data from 2005-2009 found only 23% of cases were clustered by genotype, time and location**
 - Cases that represent recent transmission
- ❑ **More than $\frac{3}{4}$ cases are not the result of recent transmission**
 - Cases that represent reactivation of latent TB infection

Moonan PK, Ghosh S, Oeltmann JE, Kammerer JS, Cowan LS, Navin TR. Emerg Infect Dis. 2012;18(3):458-65.



LTBI Testing and Key Risk Groups



Key Risk Groups for TB in the United States

- ❑ **Foreign-born: 67% of cases; case rate 13 times higher than US-born**
 - Mexico, Philippines, Vietnam, China, India top 5 countries
- ❑ **Racial/ethnic minorities: ~85% of cases; case rates 7-28 times higher than whites**
- ❑ **HIV infected: ~ 7% of cases**
- ❑ **Homeless: ~ 6% of cases**
- ❑ **Incarcerated: ~ 4% of cases**
- ❑ **Substance abuse: 7-12% of cases**



LTBI Testing: Advantages of Interferon-gamma Release Assays (IGRAs) in Key Populations

- ❑ **Foreign-born persons with BCG vaccination**
 - No cross-reaction with BCG so no false positive tests due to BCG
- ❑ **One visit for blood draw**
 - Do not have to re-test persons who miss TST reading
 - Advantage in groups that are particularly unlikely to follow up for second visit (e.g., homeless)
 - Only have to track down persons with positive test results



Prevalence of Positive Test Results in Highly BCG Vaccinated Populations

	NHANES (2011-2012)	TBESC II
Percent in study who were foreign-born	100%	80%
TST-positive	20%	39%
IGRA-positive	16%	19-24%

Fewer positive IGRA tests means fewer chest radiographs and fewer persons to treat, but is this because of fewer false positive TSTs due to BCG or could the IGRA negative, TST positive results be false negative IGRA results?



IGRAs in BCG Vaccinated Persons

- ❑ Study from Germany of 1033 contacts of persons with infectious TB, more than 50% BCG vaccinated, with up to 5 years of follow up
- ❑ 63% were TST positive (5 mm); 20% were IGRA positive
- ❑ Only IGRA positive patients were offered LTBI treatment; only 51 of 209 completed LTBI treatment
- ❑ 19/158 untreated patients developed TB disease
- ❑ All were IGRA positive; 17/19 were TST positive
- ❑ Progression rates were 12.9% for IGRA positive versus 3.1% for TST positive (5 mm)
- ❑ Suggests fewer false positive tests due to BCG

Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. Am J Respir Crit Care Med. 2011 Jan 1;183(1):88-95



Better Treatment for LTBI

- ❑ 12-dose, once-weekly isoniazid and rifapentine (3HP)
- ❑ 4 months of daily rifampin (4R)



9 Months Isoniazid (9H) Versus 3HP

	9H completion	3HP completion	Efficacy/Liver toxicity
TBTC Study 26*	69%	82%	3HP as good as 9H with less liver toxicity
TBTC Study 33 (unpublished data)	n/a	DOT: 87% SAT: 74%	Not designed to measure efficacy; less liver toxicity
Program data	50-60%	> 80%	Not available yet

*Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, Weis SE, Weiner M, Wing D, Conde MB, Bozeman L, Horsburgh CR Jr, Chaisson RE; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med.* 2011;365(23):2155-66



9H Versus 4R

	9H completion	4R completion	9H liver toxicity	4R liver toxicity
Aspler et al.	60%	78%	3.8%	0.7%
Lardizabal et al.	53%	80%	1.4%	0.0%
Menzies et al.	62%	86%	5.0%	0.0%

Aspler A, Long R, Trajman A, Dion MJ, Khan K, Schwartzman K, Menzies D. Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. *Thorax*. 2010 Jul;65(7):582-7.

Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. *Chest* 2006; 130: 1712-7.

Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. *Am. J. Respir. Crit Care Med*. 2004; 170: 445-9.



Efficacy of 4R?

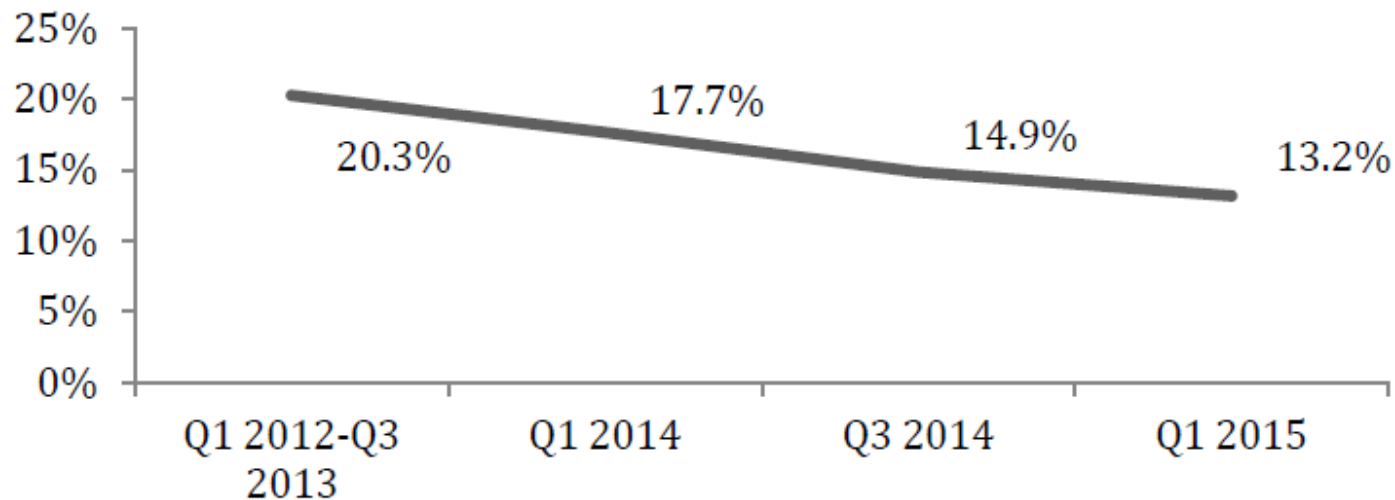
- ❑ **No direct published studies**
 - Large ongoing randomized clinical trial
- ❑ **Extrapolated from studies of 3R and 4HR, which suggested these regimens are as good as 9H**

The Affordable Care Act (ACA) and Insurance Coverage

- ❑ **More people are insured since implementation of ACA**
- ❑ **Increases in coverage are greater in low-income groups and in racial/ethnic minorities**
 - Groups at higher risk for TB



Quarterly estimates of the Uninsured Rate Gallup-Healthways Well-Being Index, 2012-2015



	Q1 2014	Q3 2014	Q1 2015
Number gained coverage since baseline (Q1 2012-Q3 2013)	5,200,000	10,700,000	14,100,000

Source: Office of the Assistant Secretary for Planning and Evaluation (ASPE) analysis of Gallup-Healthways Well-Being Index survey data through 3/4/15.



Insurance Coverage Under ACA by Medicaid Expansion and Federal Poverty Level (FPL)

	Baseline Uninsured Rate	Q1 2014	Q3 2014	Q1 2015
		Change in Percentage Points from Baseline Trend		
Non-expansion	23.4	-2.5	-4.5	-6.9
<138% of FPL	61.8	2.7	-0.9	-7
139-400% of FPL	22.2	-4.7	-7.3	-10.1
>400% of FPL	1.9	0.4	-0.6	-1.1
Expansion	18.2	-2.8	-6.2	-7.4
<138% of FPL	55.0	-2.7	-5.5	-13
139-400% of FPL	18.1	-4.1	-8.3	-9.5
>400% of FPL	1.8	-0.4	-1.3	-1.3



Insurance Coverage Under ACA by Race/Ethnicity

	Baseline Uninsured Rate	Q1 2014	Q3 2014	Q1 2015
Change in Percentage Points from Baseline Trend				
Whites	14.3	-1.7	-4.7	-5.3
African Americans	22.4	-4.5	-7.2	-9.2
Latinos	41.8	-4.1	-5.9	-12.3

ACA and US Preventive Services Task Force (USPSTF)

- ❑ ACA mandates that USPSTF recommendations with grade A or B be covered by insurance with no co-pay**
- ❑ LTBI testing for high-risk groups is currently under review by USPSTF**
- ❑ If USPSTF recommends that LTBI testing should be done with grade A or B, LTBI testing must be covered by insurance with no co-pay**
- ❑ Recommendation is expected by end of 2015**



Main Challenges to TB Elimination

❑ Political commitment

- As cases continue to decrease, seems less of a priority to general public and policymakers
- Resources at risk

❑ Loss of expertise and experience

- Clinical, laboratory, program

❑ Drug and biologic shortages because of lack of market

- Regulatory requirements limit access to GDF or other mechanisms that can access larger global market

❑ Concentration of remaining cases and outbreaks in more difficult-to-reach populations

- Foreign-born, homeless, etc.

❑ How to address the large pool of persons with latent tuberculosis infection (LTBI)

- <10 thousand TB cases; millions of persons with LTBI



Tuberculosis (TB) Disease: Only the Tip of the Iceberg

There are **two** types of TB conditions:
TB disease and **latent TB infection**.

People with **TB disease** are sick from active TB germs. They usually have symptoms and may spread TB germs to others.

People with **latent TB infection** do not feel sick, do not have symptoms, and cannot spread TB germs to others.

But, if their TB germs become active, they can develop **TB disease**.

Millions of people in the U.S. have **latent TB infection**. Without treatment, they are at risk for developing **TB disease**.



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention



To learn more about TB, visit
www.cdc.gov/tb

Estimating LTBI: NHANES

- ❑ **NHANES is a series of sequentially run cross-sectional studies, implemented in 2-year cycles that assess the health of the civilian, non-institutionalized U.S. population**
- ❑ **To obtain a nationally representative sample of the civilian, non-institutionalized U.S. population, NHANES employs a complex, stratified, multistage probability cluster sampling design**
- ❑ **Approximately 5,000 persons participate in the survey in approximately 15 counties per year**
- ❑ **In 2011-2012, NHANES included a TB component with TST and Quantiferon testing**

How Much LTBI Is There in the United States?

	Prevalence	Number of people
TST positive	4.7%	13.1 million
Quantiferon positive	5.0%	13.9 million
Both positive	2.1%	5.9 million

Estimates from National Health and Nutrition Examination Survey, 2011-2012, manuscript submitted

How Much LTBI Is There in the United States in Foreign-born Persons?

	Prevalence	Number of people
TST positive	20.5%	8.2 million
Quantiferon positive	15.9%	6.4 million
Both positive	9.3%	3.7 million

Estimates from National Health and Nutrition Examination Survey, 2011-2012, manuscript submitted

Targeted Testing and Treatment of Latent Tuberculosis

- ❑ **Primary focus on foreign-born from medium- and high-incidence countries**
- ❑ **Highest priority to foreign-born with conditions that increase risk of progression (e.g., HIV, smoking , diabetes, TNF-a antagonists)**
- ❑ **IGRAs have an advantage in BCG-vaccinated persons**
- ❑ **Short-course regimens can increase completion**
- ❑ **Expansion of testing and treatment beyond health department**
 - How can we leverage Affordable Care Act?
 - USPSTF considering recommendation for LTBI testing
 - Who serves targeted populations in the community and how can we engage them?

LTBI: What Needs to Be Done Using Existing Tools?

- ❑ **Major initiative with 5 parts**
 - Requires substantial additional resources
- ❑ **1) Registry/surveillance system**
- ❑ **2) Scale up of testing to targeted populations**
 - More focused guidance on who to target
 - Eliminate wasteful testing of low-risk persons
 - Specific funding for IGRAs, especially for foreign-born
- ❑ **3) Scale up of short course LTBI treatment**
 - 3HP and 4R
- ❑ **4) Communication, outreach**
 - Engagement of affected communities and their medical providers
 - Reach beyond health department
- ❑ **5) Increased public health staffing for implementation and oversight**

TB-FREE USA Tuberculosis Prevention

- ❑ **Developed in collaboration with NTCA leadership**
 - Jenny Flood, John Bernardo, Donna Wegener, NTCA board, Ann Cronin
- ❑ **Requests \$40 million per year for 5 years**
- ❑ **Funds would support annual screening of 550,000 persons at risk for LTBI (primarily focusing on foreign-born persons), treatment of approximately 70,400 persons with LTBI, and prevention of 3,520 future cases of TB disease**
- ❑ **Favorable technical review, but did not make 2017 Presidential budget**
- ❑ **Will continue to pursue for future budget**

What New Tools Are Needed?

- ❑ **A test that is much more predictive of progression from LTBI to TB disease than TST or IGRAs**
 - IGRAs are better in BCG vaccinated persons, but are still poor
- ❑ **Even shorter LTBI treatment**
 - Next aim should be for 4-6 weeks

Thank You !

Questions?