

Latent *M. tuberculosis* Infection

Screening and Treatment as Population-Based Control Strategies in Low TB Incidence Settings

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Disclosures

- **Grant funding:** National Institutes of Health
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- **Relevant financial relationships with a commercial interest:**
 - Sanofi aventis one-day consultation at FDA in 2012
 - Otsuka data safety monitoring board—trial

Treatment of latent *M. tuberculosis* infection and TB elimination

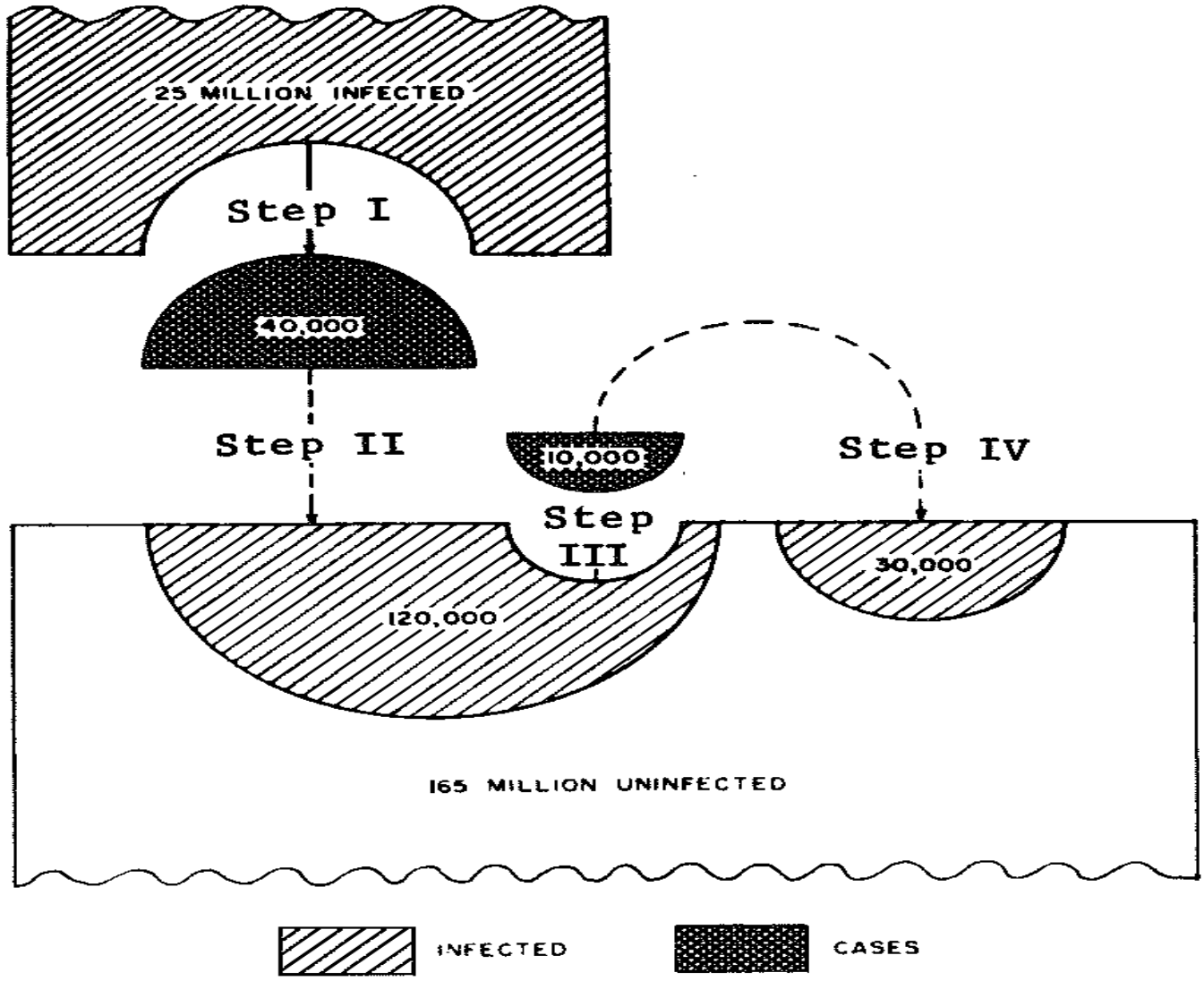
Global; United States and Canada

- **Epidemiology of *M. tuberculosis* infection**
 - Contribution of latent infection to TB disease burden
- **TB elimination**
 - Target and projections
- **Current treatment regimens**
- **Screening and treatment strategies**
 - Whom to target

Latent *M. tuberculosis* infection and contribution to TB burden

- The global burden of latent *M. tuberculosis* infection is enormous.
 - More than 2 billion people (33%) infected
 - Raviglione MD. JAMA 1995;273:220-6. Dye C et al. JAMA 1999;282:677-86
- From this reservoir, millions of people will develop active TB
 - 100-200 million cases
- In the U.S., 10 million people (4%) infected
 - 500,000-1,000,000 potential TB cases
 - Khan K. AJRCCM 2008;177:455-60. Bennett DE. AJRCCM 2008;177:348-55.

Schematic: development of TB infection and disease, United States—1963



Ferebee SH. Bull Nat Tuberc Assoc 1967;53:4-7.

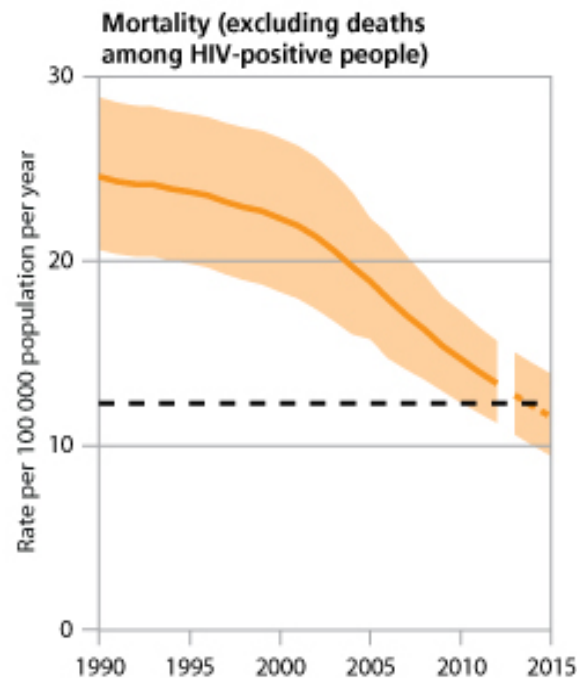
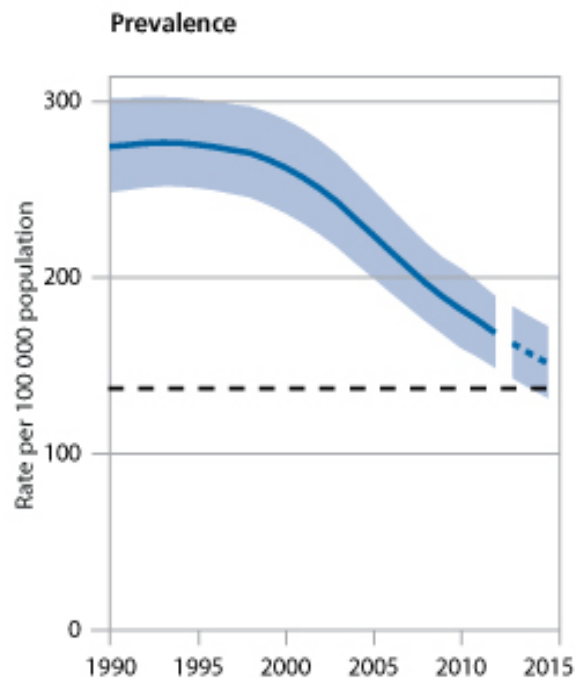
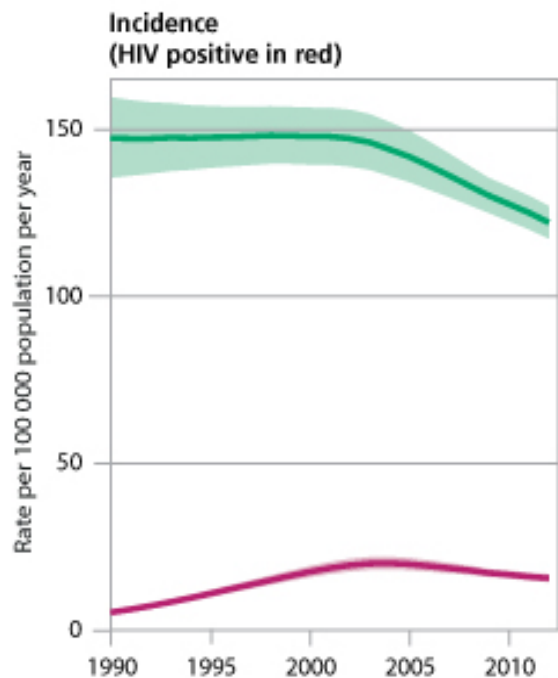
Rationale for treatment of latent *M. tuberculosis* infection: U.S.

- Of the 39,920 TB cases reported in the U.S. during 2006-2008, 80% were attributed to reactivation (NHANES, CDC-universal genotyping)
 - Shea KM. Am J Epidemiol 2014;179:216-25.
- U.S. TB case rate in 2012 lowest ever recorded:
 - 9,945 cases
 - Approximately 32 cases per 1,000,000 population
 - CDC. June 10, 2013
- As TB case rate declines, TB elimination in the U.S. will increasingly depend on treatment of the large pool of persons with latent TB infection—particularly those at increased risk of progression to active TB

Targets for TB Control and Elimination

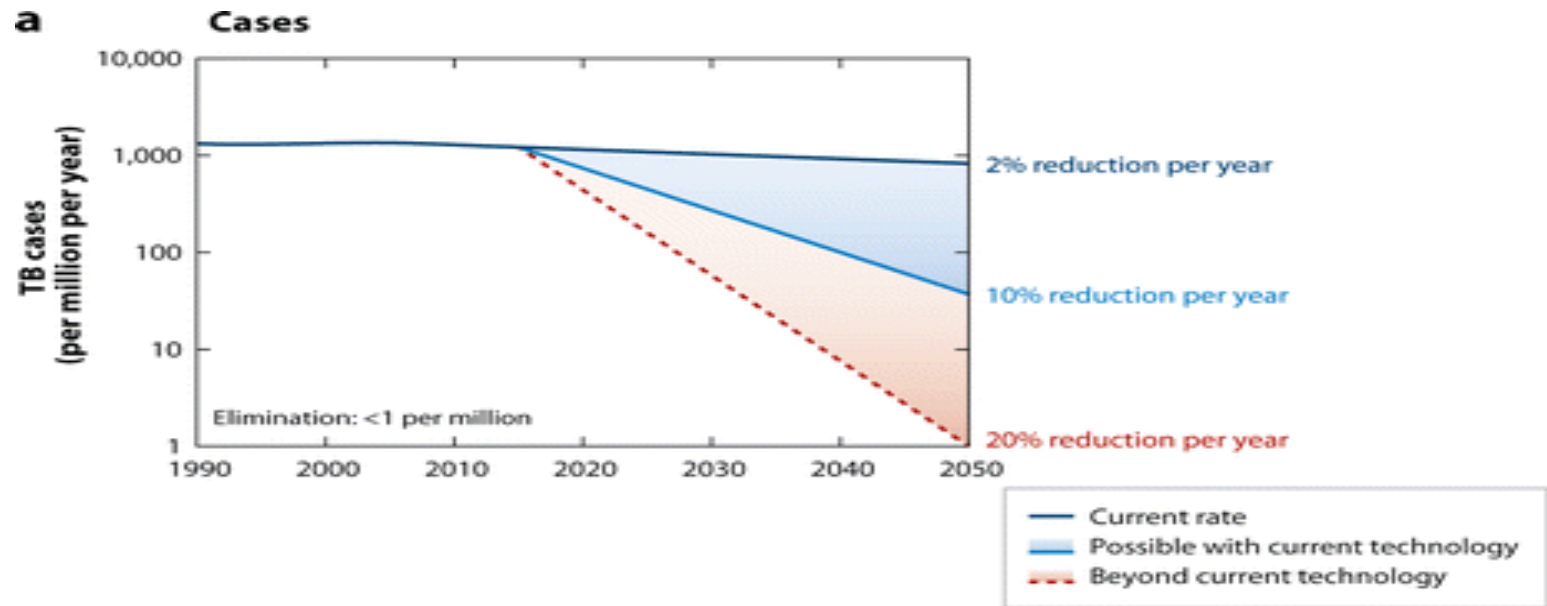
Global

- The Stop TB Strategy:
 - Halt and reverse TB incidence by 2015
 - By 2015: decrease the prevalence and deaths due to TB by 50% compared to 1990
 - Prevalence < 155 per 100,000 population
 - TB deaths < 14 per 100,000 population
 - By 2050: eliminate TB
 - < 1 case per million population



Source: Global Tuberculosis Report 2013, WHO

Projected Trends in TB Incidence Rates, 2020 - 2050



Dye C, et al. 2013.

Annu. Rev. Public Health. 34:271–86

Screening for and Treating LTBI

Effect on TB incidence

- Identify persons with *M. tuberculosis* infection
 - TB risk if IGRA+ vs. IGRA-: pooled IRR: 2.11
 - TB risk if TST+ vs. TST-: pooled IRR: 1.60
 - Rangaka MX. Lancet Infect Dis 2012;12:44-55.
 - Implies 44-51% of TB patients would be IGRA or TST+
 - If treatment of LTBI is 65% effective, there would be 29-33% ↓ in TB incidence if complete coverage
 - Dowdy DW, Golub JE. Lancet Infect Dis 2012;12:827-8.
 - Similar to Bethel, Alaska (30% ↓)
 - Comstock GW. ARRD 1967;95:935-43.
- Household contact tracing
 - If performed contact tracing of all household contacts for 5 years and treated LTBI: 17-27% ↓ in TB incidence
 - Kassaue P. Am J Respir Crit Care Med 2014. Epub ahead of print

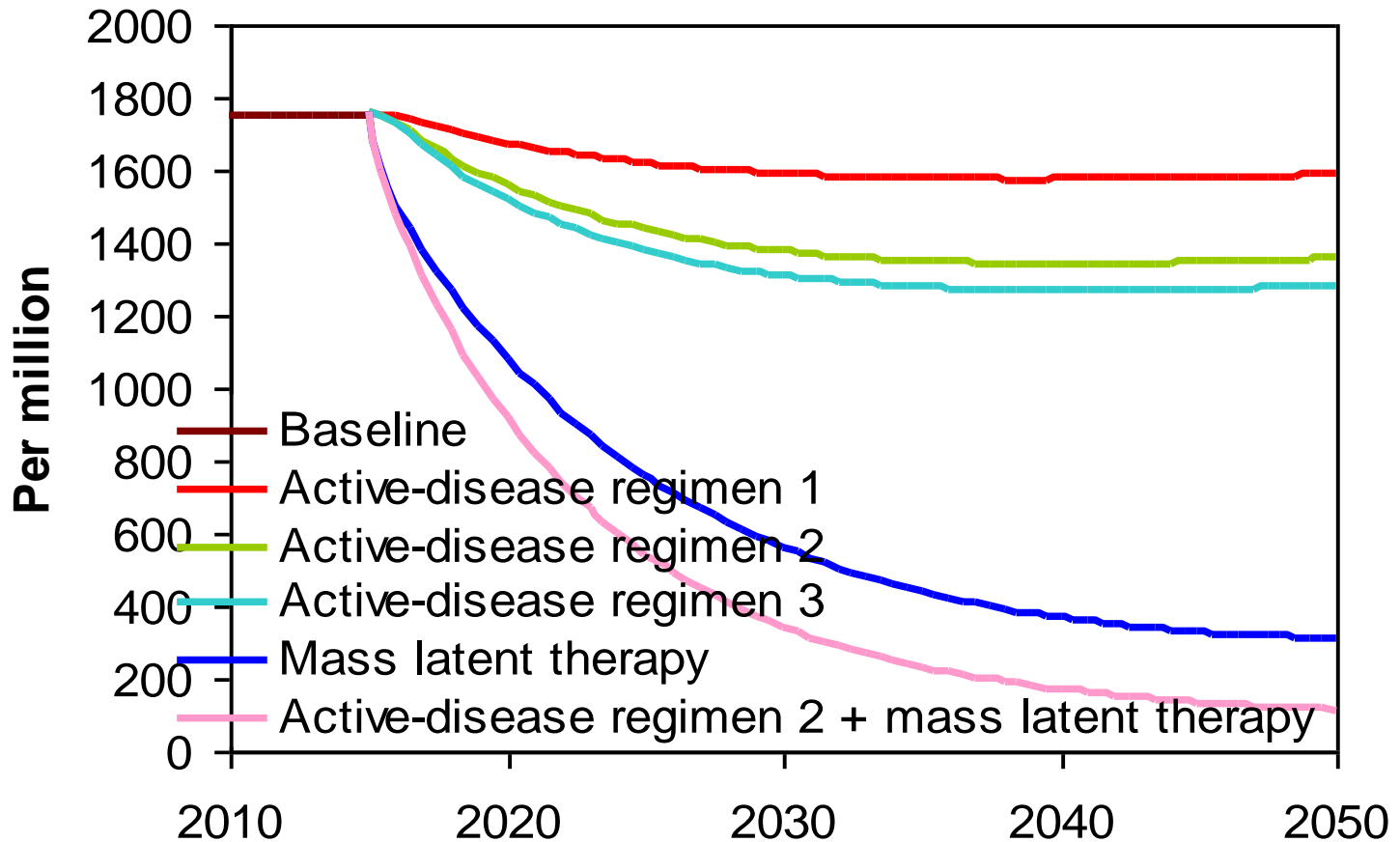
Effect by year up to 2050 of interventions and strategies begun in 2015 on TB incidence per million population

E

2-month
TB Rx:
23% ↓

Mass
latent
therapy:
82% ↓

2-month
TB Rx +
mass
latent
therapy:
94% ↓



Treatment of *M. tuberculosis* Infection

Current Regimens

Regimen	Efficacy / Effectiveness	Tolerability Drug d/c AE Hepatotoxicity	Comments
9 INH (9H) Daily	90% 25-88% median:60%	0-31% 0.1-3.8%	6 and 12 months well-studied; 30-60% completion
3 INH + rifapentine (3HP) once-weekly	90% (estimated) 90% (estimated)	4.9% 0.4%	82% completion Directly-observed
3 INH + rifampin daily	--- 41-59%	0-5.1% 0-5.1%	Not ATS guideline An alternative Hepatotoxicity
4 rifampin daily	--- 46-50% (3 months)	1.9-14% 0-0.7%	Never studied. When INH R, intolerance Not in HIV+

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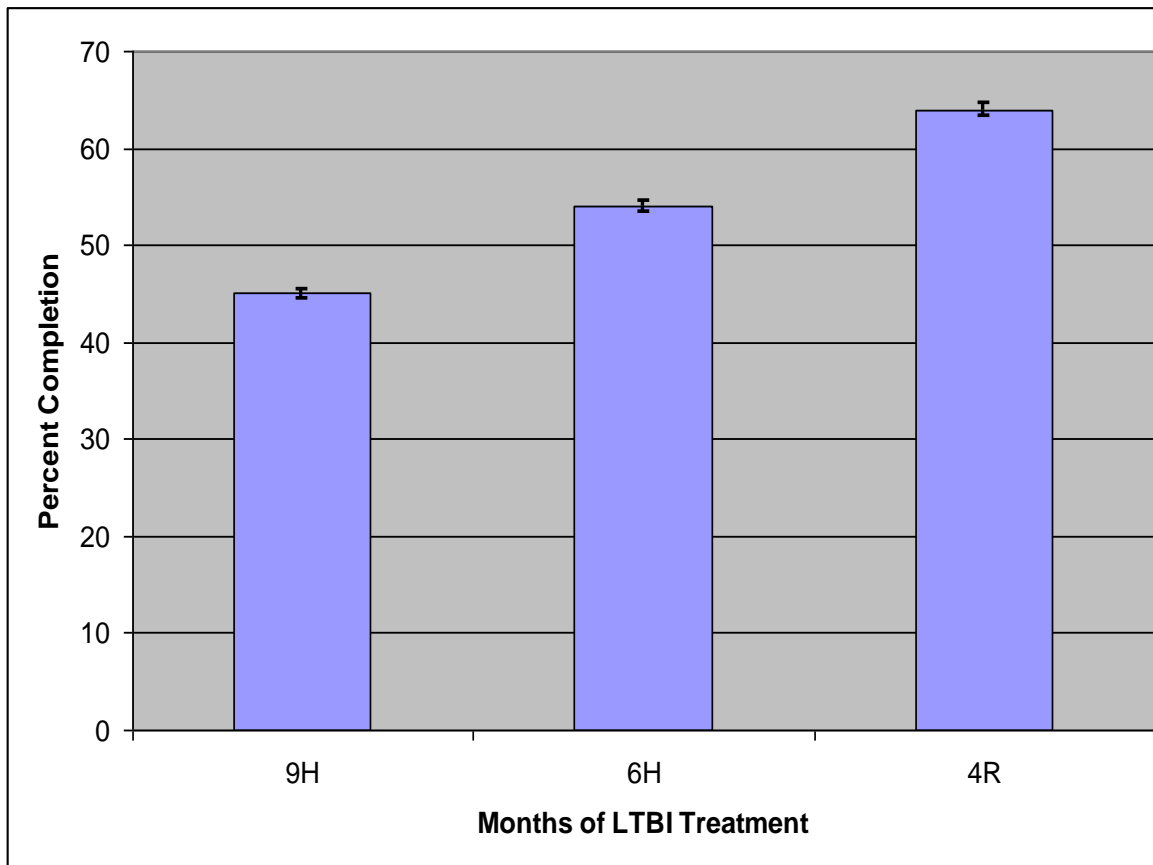
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Overall treatment completion rate: 47%

Completion rate increased as regimen duration decreased



Cost-Effectiveness

Treatment of latent tuberculosis infection

- **INH highly cost-effective in young adult close contacts**
 - Diel R. Eur Respir J 2005;26:465-73.
- **Incentives + peer counseling cost-effective in adolescents receiving INH due to ↑ completion rates**
 - Kominski G. J Adolescent Health 2007;40:61-8.
- **Cost-effectiveness of screening immigrants to low-prevalence countries would be ↑ by improved adherence to treatment of latent infection**
 - Schwartzman K. AJRCCM 2000. Dasgupta Eur Respir J 2005.
- **Risk-based targeted testing programs cost-effective**
 - Miller TL. AEP 2006;16:305-12.
- **3HP cost-effective alternative to 9H**
 - More so if cost of RPT ↓, and focus treatment on those at high TB risk
 - Shephardson D. IJTLD 2013;17:1531-7.

Persons with LTBI who are at high risk of developing TB

Risk Factor TST-positive and:	TB/100 person-years
No other risk factor	0.1 (approx)
Infection < 1 year	1.29
HIV-infected	3.5-16.2
IDU	
HIV-infected	7.6
HIV-uninfected	1.0
Silicosis	6.8
Prior TB on CXR	0.2 – 1.36
< 85% ideal body weight	0.26

Am J Respir Crit Care Med 2000; 161:S221-S243.

Persons with LTBI who are at high risk of developing TB

Characteristic	TB reactivation rate per 100 p-y With co-factor	TB reactivation rate per 100 p-y Without co-factor
HIV-infection	1.82	0.073
Foreign-born	0.098	0.082

Shea KM. Am J Epidemiol 2014;179:216-225

TB in the foreign-born in the United States:

- TB within 1 year of pre-immigration evaluation: 85% imported (active on immigration)
- TB in years 2-9 after arrival: 76% due to reactivation
0.32 per 100 p-y, and rate did not ↓ with time

Walter ND. Am J Respir Crit Care Med 2014;189:88-95

Scope of Treatment of *M. tuberculosis* Infection

United States, 2002

- **TB Epidemiologic Studies Consortium**
- **19 sites in the United States, 2 in Canada**
 - Represented 8.6% of U.S. population
 - 12.7% of U.S. TB cases
- **Survey among clinics that initiated treatment for ≥ 10 patients**
- **37,857 persons initiated treatment**
 - 37,145 in U.S. clinics

Scope of Treatment of *M. tuberculosis* Infection

TB risk groups receiving treatment

Risk population	# LTBI patients	%
TB contacts	4,694	13.5
Drug users	3,458	10.0
HIV-infected	717	2.1
Homeless	1,657	4.8
Incarcerated	4,266	12.3
Migrant farmworker	1,479	4.3
Native American	215	0.6
Foreign born	19,479	56.2

Key Questions

- Do we need to identify all 10 million infected persons in the United States?
- Of the 10 million people with *M. tuberculosis* infection, how many are in the key high risk groups?
 - HIV-infected
 - 1,000,000 HIV+ x 0.04 M. tb prevalence = **40,000**
 - Shea KM. AJE 2014. Khan K. AJRCCM 2008. Bennett DE. AJRCCM 2008.
 - Recently infected
 - 10,000 TB cases x 3 contacts infected/case = **30,000**
 - Jereb J. Int J Tuberc Lung Dis 2003;7:S384-90.
 - Foreign born
 - 36,416,000 x 0.187 M. tb prevalence = **6,800,000**
 - Shea KM. AJE 2014.
- How many persons are treated for LTBI in the United States?
 - 300,000 per year
 - Sterling AJRCCM 2006

Conclusions

- Most TB disease is due to reactivation of latent *M. tuberculosis* infection
- Preventing reactivation is critical for achieving TB elimination
- Treatment of latent *M. tuberculosis* infection can have a profound effect on decreasing TB incidence

Conclusions

- For logistical feasibility, must:
 - target high-risk populations
 - use effective treatment that will be completed
- The extent to which latent *M. tuberculosis* infection should be treated is dictated by the objective.
- If goal is TB elimination, must treat latent *M. tuberculosis* infection