We “know” it works…so why doesn’t it work?

The limits of screening and treatment for latent TB as a TB control strategy

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- I work part-time for the Fonds de la Recherche du Québec—Santé [Quebec Health Research Funds]

Objectives

- To briefly review data illustrating the promise and limits of screening and treatment for latent tuberculosis infection (LTBI) as a TB control strategy
- To indicate potential reasons for its limited performance in this regard
- To highlight key areas for improvement

Comstock in Alaska

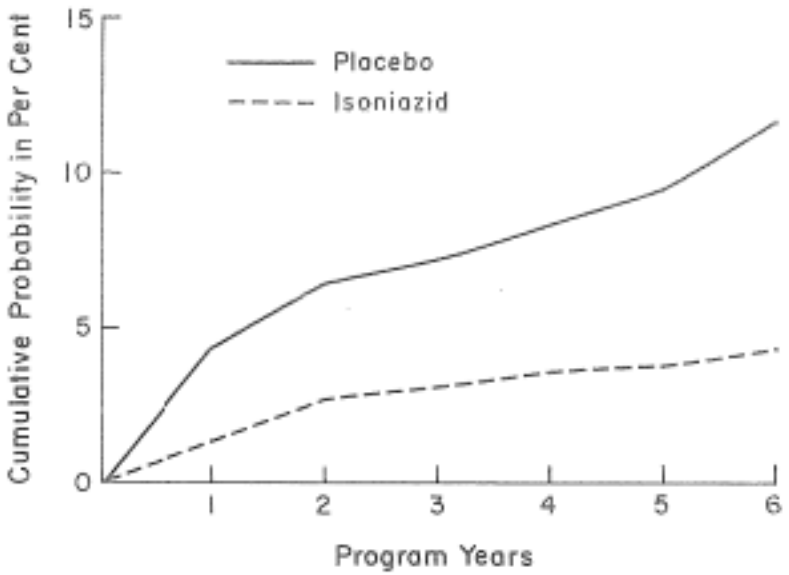


Fig 1.—Cumulative probability of developing active tuberculosis among persons with UNT during six years after start of controlled trial, by program year and medication prescribed.

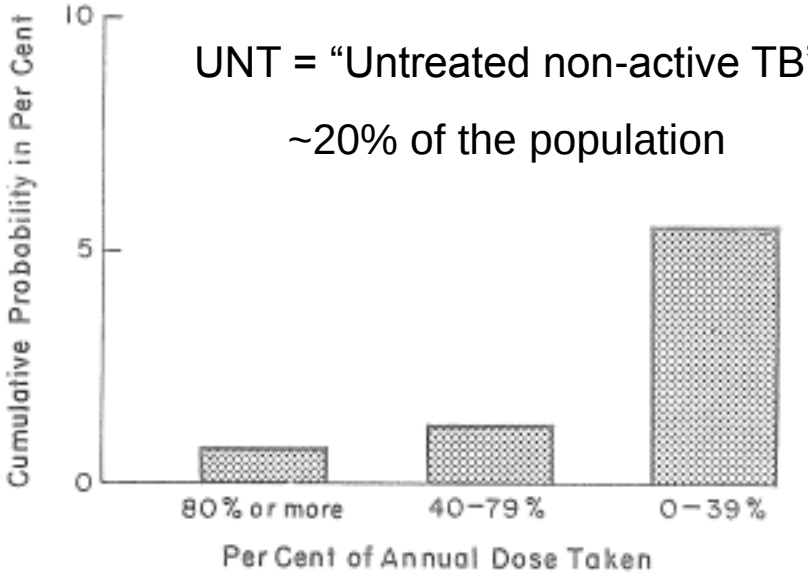


Fig 3.—Cumulative probability of developing active tuberculosis among persons with UNT during six years after start of demonstration project, among persons for whom isoniazid was prescribed, by percent of annual dose taken.

UNT = "Untreated non-active TB"

~20% of the population

- These studies involved isoniazid for one year, in Inuit communities
- In the RCT, one-third of subjects took >80% of doses, and half took 40-80%
- In the demonstration project, 80% of subjects took >40% of doses; average was 65%
- Comstock estimated that with similar adherence, and provision of treatment to all with "untreated non-active TB," the incidence of active TB would fall by 30%

Comstock and Woolpert, *Arch Environ Health* 1972

TB in Alaskan Inuit—A closer look

- The magnitude of the problem, and the impact of public health interventions, were unprecedented
- In 1949-51, the estimated annual risk of TB infection was 25%
- This fell to 1% by 1960
- The randomized trial of isoniazid began in winter 1957-58
- Treatment of LTBI could only have been a minor player

Comstock and Woolpert, *Arch Environ Health* 1972

Flash forward…TBTC Study 26

Table 2. Number of Subjects with Tuberculosis and Event Rates.*

Population and Study Group	No. of Subjects	Subjects with Tuberculosis			Difference in Cumulative Rate†	Upper Limit of 95% CI for Difference in Cumulative Rate
		no.	*no. per patient-yr*	*cumulative rate*	*percentage points*	
Modified intention-to-treat analysis						
Isoniazid only	3745	15	0.16	0.43	−0.24	0.01
Combination therapy	3986	7	0.07	0.19		
Per-protocol analysis						
Isoniazid only	2585	8	0.11	0.32	−0.19	0.06
Combination therapy	3273	4	0.05	0.13		

* Combination therapy consisted of 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg). Isoniazid-only therapy consisted of 9 months of self-administered daily isoniazid (300 mg). Data are shown for a period up to 33 months after study enrollment.

† The difference is the rate in the combination-therapy group minus the rate in the isoniazid-only group.

69% of eligible subjects assigned to 9INH completed it, versus 82% for 3HP

Sterling et al, *NEJM* 2011

A great advance, but…

- Under **clinical trial conditions**, 69% of subjects completed the 9INH regimen (>240/270 doses)
- Results from the 3HP arm reflected directly observed treatment, which can have a very significant impact on TB control resources
  - Estimated incremental cost to health care system of $21,500 per additional active TB case prevented, vs. 9INH—using data from the clinical trial
    - Shepardson et al, *IJTLD* 2013
  - This refers to persons already in care
- The reality “on the ground” is quite different…

42 Studies, N=63,604 Immigrants		
	Percent	Number
Total number eligible for screening		1000
Proportion Completing Screening	77%	770
LTBI Prevalence	40%	308
Proportion Offered Treatment	76%	234
Proportion Started Treatment of Offered	88%	205
Proportion Completed Treatment of Started	59%	121

Program Effectiveness		
Proportion completed treatment of TST positive	121/400	30%
Proportion completed treatment of eligible for screening	121/1000	12%

Trung 1997, Adair 1999, Sutherland 1983, Parenti 1987, Lifson 2002, Varkey 2007, Sariaya 2002, Saiman 2001, Brassard, Minodier 2010, Levesque, 2004, Pottie 2007, Doering 1999, Scolari 1999, El-Hamad 2001, Carvalho 2005, Hurega 2002, Manzardo 2008, Garcia de Oalla 2003

Bettache et al, **Effectiveness of post-arrival LTBI screening programs in migrants** [Slide courtesy of Dr. C. Greenaway; very similar findings for post-arrival surveillance programs]

Limited uptake and completion

- In North America, studies in other population groups e.g. contacts have shown similar or worse numbers
  - Health care workers often the worst—why?

- Note the substantial impact of non-attendance at screening, and of non-prescription by clinicians
  - Will direct observation and/or shorter regimens fix this?
  - Accuracy of diagnostic tools
  - Drug intolerance and toxicity
  - Limits of the hypertension analogy
    - No marker of successful LTBI treatment (≠ widespread BP cuffs)
    - Many treatment alternatives for hypertension
    - We have challenges even with symptomatic disease e.g. asthma

What about a totally different setting?

Table 2. Overall Effect of Community-wide Isoniazid Preventive Therapy: Tuberculosis Incidence and Prevalence.

Outcome	Control Clusters		Intervention Clusters		Rate Ratio (95% CI)*			
	Cases	Rate	Cases	Rate	Unadjusted	P Value	Adjusted†	P Value
	no./no. of person-yr	*per 100 person-yr‡*	*no./no. of person-yr*	*per 100 person-yr‡*				
Primary outcome: tuberculosis incidence§								
Any	856/29,014	2.95	887/29,352	3.02	1.00 (0.75–1.34)	0.98	0.96 (0.76–1.21)	0.71
Definite or probable	656/29,014	2.26	703/29,352	2.40	1.07 (0.70–1.64)	0.72	1.04 (0.73–1.48)	0.80

- Cluster-randomized trial involving nearly 79,000 South African gold miners in total
- ~14% prevalence of HIV infection, based on self-report so likely a marked underestimate
- Those in intervention clusters were offered TB screening and then 9 INH, in the absence of active TB disease
- Among miners who in fact took INH, there was a nearly 60% reduction in active TB during the 9-month treatment period, but this rapidly rebounded afterward

Churchyard et al, *NEJM* 2014

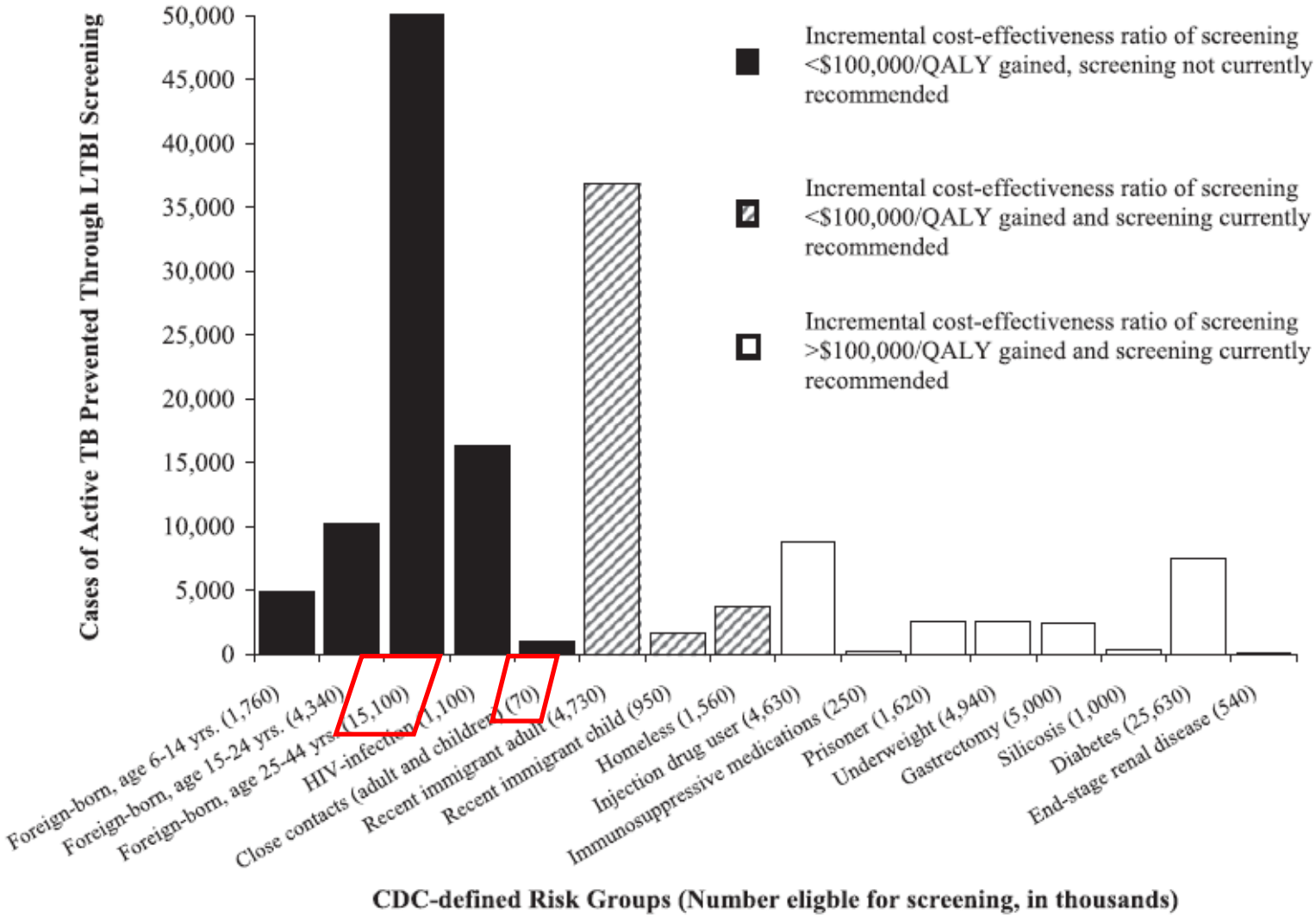
How efficient and cost-effective might mass screening and treatment be in the US?

TABLE 3. BASE CASE RESULTS OF AN ANALYSIS OF SCREENING FOR LTBI IN THE UNITED STATES

Risk-group	Number Needed to Screen	Incremental Cost-Effectiveness Ratio ($/QALY)
Close-contact child		
No screen	—	—
Screen TST	110	6,200
Screen IGRA	104	21,100
Close-contact adult		
No screen	—	—
Screen TST	73	8,900
Screen IGRA	69	21,500
HIV-infected		
No screen	—	—
Screen TST	71	12,800
Screen IGRA	67	23,800
Recent immigrant adult		
No screen	—	—
Screen TST	136	Dominated
Screen IGRA	128	35,200
Foreign-born living in the US >5 yr age 6–14 yr		
No screen	—	—
Screen IGRA	358	52,900
Screen TST	380	Dominated
Foreign-born living in the US >5 yr age 25–44 yr		
No screen	—	—
Screen IGRA	301	57,400
Screen TST	319	Dominated
Foreign-born living in the US >5 yr age 15–24 yr		
No screen	—	—
Screen IGRA	424	63,200
Screen TST	450	Dominated

Linas et al, *AJRCCM* 2011

What kind of scale-up?



Linas et al, *AJRCCM* 2011

The bottom line (1)

- Treatment of LTBI is highly efficacious in clinical trial settings
- Real-world effectiveness is very different
  - 1950s-60s Alaska may have been a “best case” setting for impact of treatment, and many other factors were clearly at work
  - Current processes of screening and treatment leave many important gaps
- Impact of HIV, reinfection, drug resistance depending on setting

The bottom line (2)

- Huge logistical and cost challenges in North America and elsewhere, e.g. massive screening and treatment of foreign-born
  - Human resource needs
  - Could the necessary $ be better spent?
- In the US and Canada, TB incidence is decreasing **without** broader-based LTBI treatment

What we need (1)

- Better diagnostics
  - Limits of TST and IGRAs well known
  - We need to be able to identify the small group most likely to yield both individual and population benefit from treatment of LTBI, so as to focus efforts
  - We need a marker for successful treatment
  - Targeted screening and treatment, for the 21st century

What we need (2)

- Better drug regimens
  - Much of the foregoing would become moot
- Better preventive tools e.g. vaccines
- Better engagement and mobilization
  - With our patients, their families and communities, providers, advocates and funders

- Thank you!