Mortality hazard and survival after tuberculosis treatment

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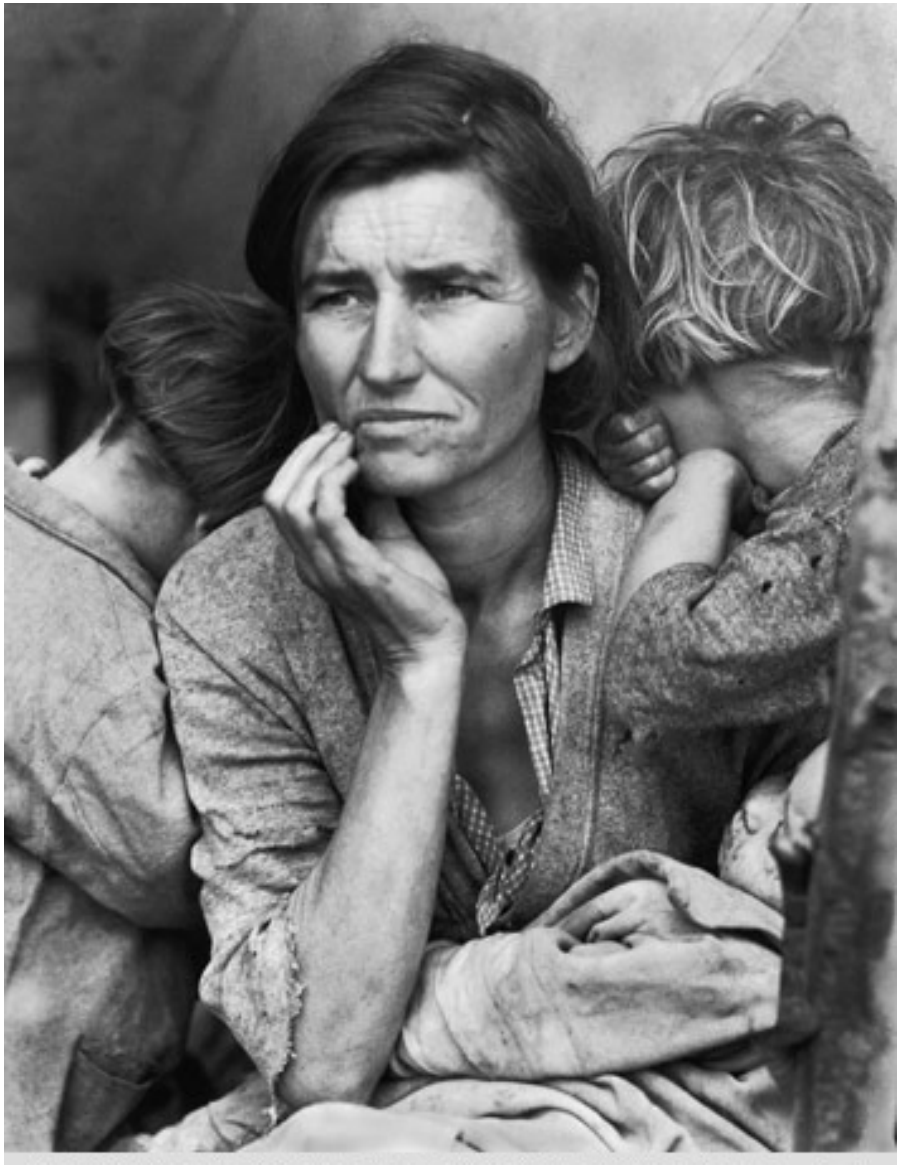
Health and survival after TB cure

- Why talk about TB research? To illustrate how PHSSR as a tool to identify modifiable health risks then enhance practice and policy
- Health outcomes after TB treatment completion remain incompletely studied
  - Can we assume prevention and cure equivalent?
  - Does treatment completion restore health?
  - Is prevention correctly valued?
- Perhaps not
  - Evidence suggests TB "cure" may simply mark a transition from acute to chronic health losses
    - chronic pulmonary impairment among 60% of fully treated pulmonary TB patients; extra pulmonary TB can leave a range of damage
- Such sequellae may compromise health or survival, but often may be preventable
- Diagnosis and treatment of TB infection during a latent stage is a safe, cheap, well understood, and effective means to prevent active TB

Some background

Dorthea Lange's "Migrant Mother," was left a widow by TB…



An enemy old as civilization

- Consumption, white plague, scrofula (the King's Evil)
- TB found in samples from 4000 year old Egyptian mummies
- "Phthisis" (consumption) noted in Greek literature
  - Around 460 BCE, Hippocrates noted TB to be widespread and almost always fatal
- Fine line between past and present danger…

TB and US health policy

- Population protection under public health authority
- Goal of domestic elimination by 2010 made policy in 1989
  - Much progress, but goals remain unmet
  - We now recognize need to emphasize prevention as well as cure
- Challenges are daunting
  - Public investments subjectively prioritized, require political will
  - Benefits of prevention often unseen
  - Resurgence, antibiotic resistance lurking
  - Diagnostic and treatment limitations
  - Population reservoirs of latent infection
  - Imported TB via immigration

Research and advocacy

- Health authorities are entrusted with stewardship of public "blood and treasure"
  - Must advocate for best use of these among many competing alternatives
  - Well meant and "gut" decisions are insufficient--clear and credible evidence of relative value is essential
- Failure to sustain vital health protections brings real and direct damage
  - In NY in late 1980s, program cuts led to TB resurgence that resulted in over $1 billion in excess costs , outbreaks are not infrequent and can consume vast energies and resources
  - Substantial money costs are associated with the presence of TB in our communities. Health and life lost to TB can never be recovered
- TB is preventable but lacks priority and consistent support
  - Value of TB prevention is poorly described and difficult to discern and communicate
  - Opportunity costs can be an intuitive way to illustrate value
- We sought to identify and measure disproportionate mortality hazard among individuals with a history of cured active TB
  - Such evidence would suggest greater value for prevention or other activities that modify the hazard

Methods

- Retrospective analysis of mortality
  - 3,853 case subjects completing treatment for active TB
  - 7,282 comparison subjects diagnosed with latent TB infection (LTBI)
- Public health records used to select subjects
  - TX, MA, and Seattle/King County
  - Identifiable subjects recorded in registries between 1993 and 2002 eligible
  - Standardized identifying and clinical data included in a research database
- Vital status determined via CDC's National Death Index
  - Vital status ascertained as of 12/31/2008, a minimum 6 years post enrollment
  - Identifiers/match probability strengthened using LexisNexis® Accurint® database prior to NDI match
- Mortality rates, hazard, and associations were identified using Cox regression
- This study was authorized by CDC's central IRB and those of each participating agency

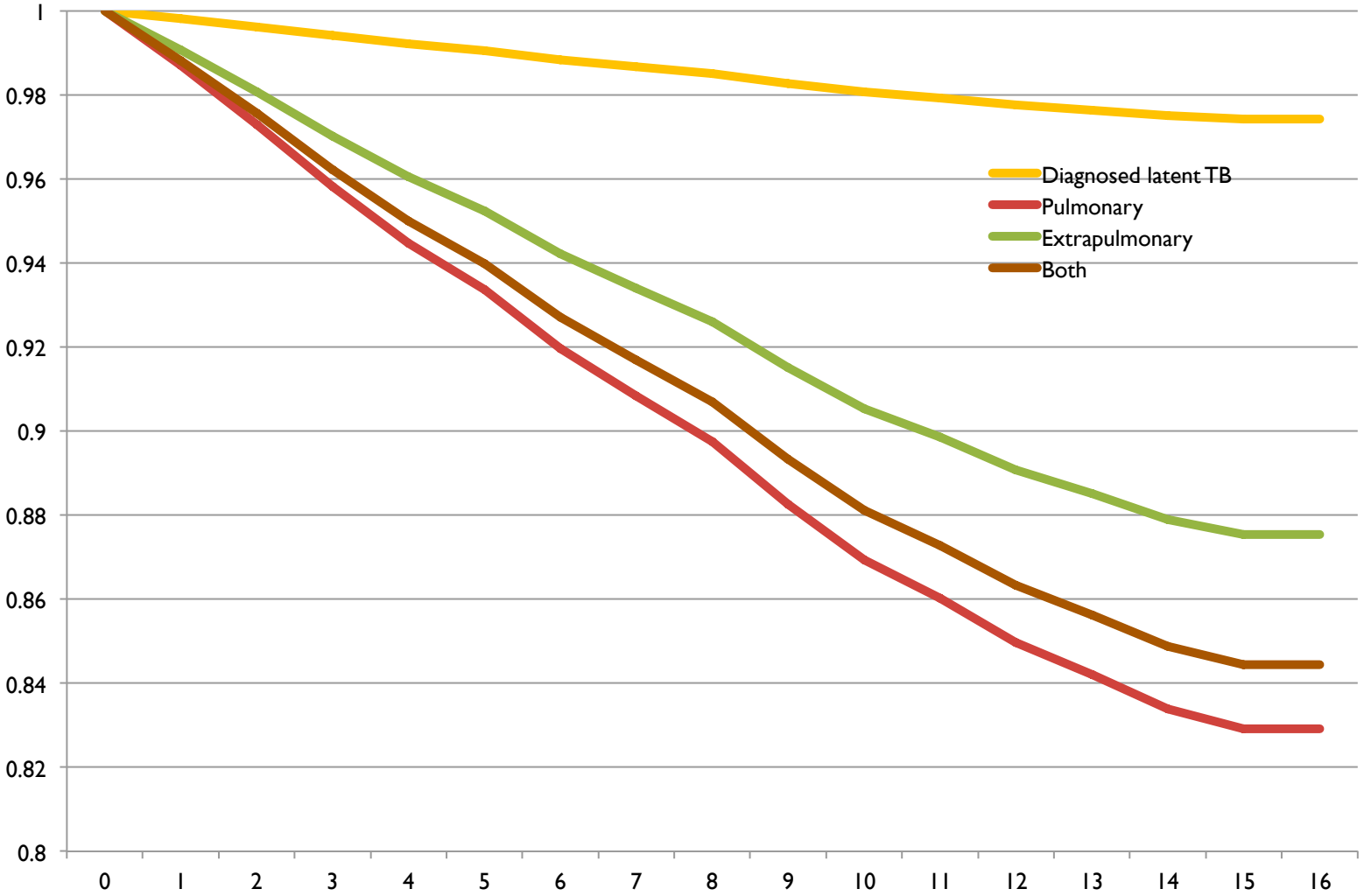
Cohort description and distribution of age, gender, race/ethnicity, HIV status, nativity, and vital status, N = 11,135. Significant differences of proportion indicated by * and ** (p of chi2 significant at 0.05 and 0.01 levels, respectively)

	Fully treated TB survivors- N (%)				LTBI comparison - N (%)			
	All TB survivors	Living	Dead	% dead	All LTBI	Living	Dead	% dead
Overall	3853 (100)	3054 (79.3)**	799 (20.7)**	20.7**	7282	7057 (96.9)**	225 (3.1)**	3.1**
				Time observed				
<5 years	386 (10.0)**	0	386 (48.3)**	100.0	60 (.8)**	0	60 (26.7)**	100.0
5-9 years	1613 (41.9)**	1312 (43.0)**	301 (37.7)*	18.7*	1763 (24.2)**	1656 (23.5)**	107 (47.6)**	6.1*
>=10 years	1854 (48.1)**	1742 (57.0)**	112 (14.0)**	6.0**	5459 (75.0)**	5401 (76.5)**	58 (25.8)*	1.1**
Unadj obs duration, years	9.2	10.3	5.3		11.6	11.7	7.1	
				Selected descriptives				
18-39	823 (21.4)**	758 (24.8)*	65 (8.1)*	7.9**	2480 (34.1)**	2446 (34.7)*	34 (15.1)*	1.4**
40-64	1917 (49.8)	1610 (52.7)	307 (38.4)**	16.0**	4185 (57.5)	4051 (57.4)	134 (59.6)**	3.2**
>=65	1113 (28.9)**	686 (22.5)**	427 (53.4)**	38.4**	617 (8.5)**	560 (7.9)**	57 (25.3)**	9.3**
Male	2399 (62.3)	1817 (59.5)	582 (72.8)	24.3**	4157 (57.1)	3990 (56.5)	167 (74.2)	4.0**
Female	1454 (37.7)	1237 (40.5)	217 (27.2)	14.9**	3125 (42.9)	3067 (43.5)	58 (25.8)	1.9**
White	895 (23.2)	547 (17.9)	348 (43.6)**	38.9**	1590 (21.8)	1520 (21.5)	70 (31.1)**	4.4**
Hispanic	945 (24.5)	768 (25.2)	177 (22.2)	18.7**	2354 (32.3)	2304 (32.7)	50 (22.2)	2.1**
Black	933 (24.2)	763 (25.0)	170 (21.3)*	18.2**	1652 (22.7)	1581 (22.4)	71 (31.6)*	4.3**
Other race	1080 (28.3)	976 (32.0)*	104 (13.0)	9.6**	1686 (23.2)	1652 (23.4)*	34 (15.1)	2.0**
HIV Positive	334 (8.7)	222 (7.3)	112 (14.0)*	33.5**	384 (5.3)	367 (5.2)	17 (7.6)*	4.4**
HIV Unknown	3519 (91.3)	2832 (92.7)	687 (86.0)*	19.5**	6898 (94.7)	6690 (94.8)	208 (92.4)*	3.0**
Foreign born	2257 (58.6)	2051 (67.2)	206 (25.8)	9.1**	4252 (58.4)	4203 (59.6)	49 (21.8)	1.2**
US born	1596 (41.4)	1003 (32.8)	593 (74.2)	37.2**	3030 (41.6)	2854 (40.4)	176 (78.2)	5.8**

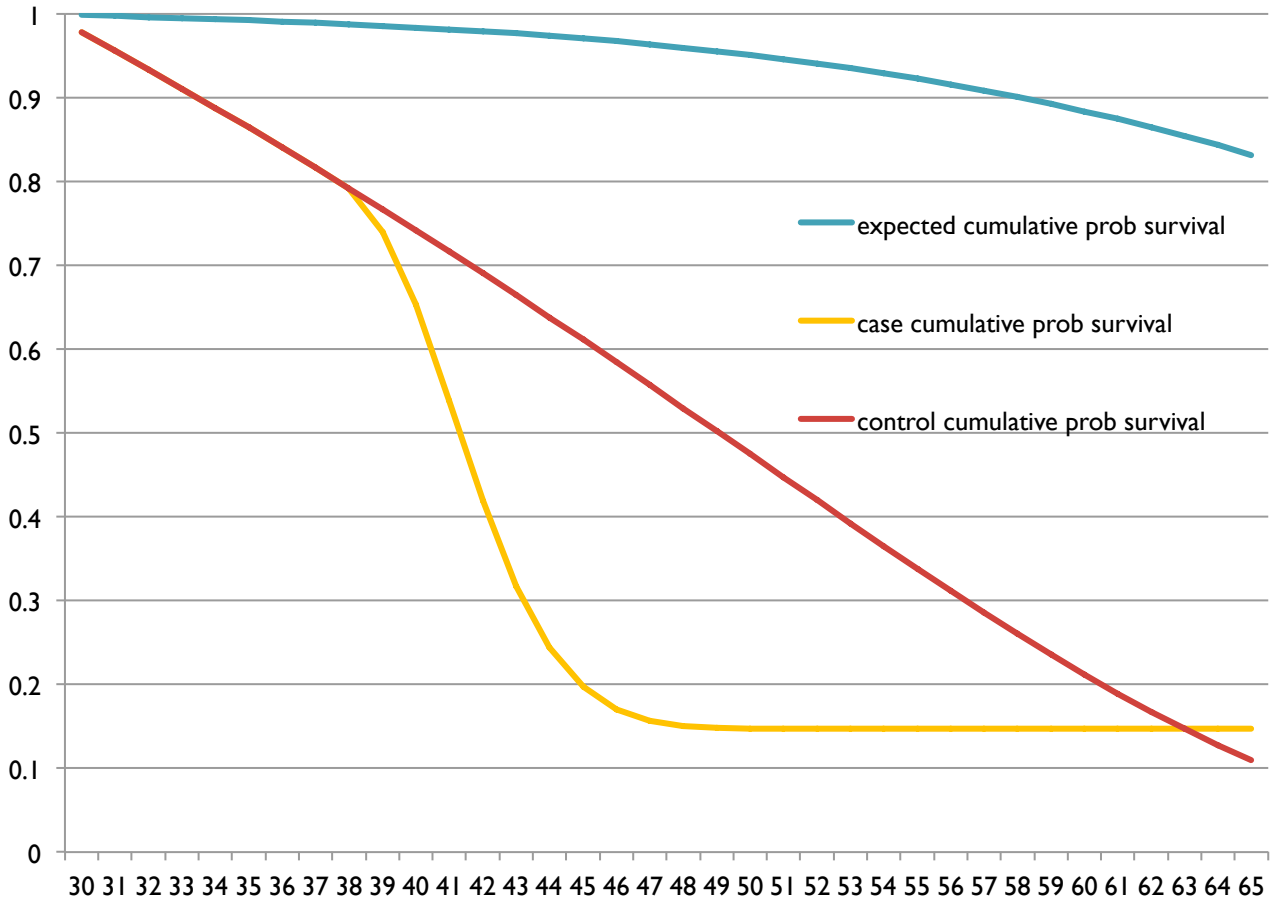
Results

- 11,135 individuals over 119,772 person years of observation included in analysis
- TB survivors more frequently dead at vital status ascertainment than LTBI comparison subjects (20% vs. 3.1%)
- Subjects with a history of fully treated TB suffered an adjusted excess mortality averaging 7.6 deaths/1,000 person years relative to the comparison group (8.8 vs. 1.2 p-value<.001).
- Mortality hazard among TB survivors is not evenly distributed
  - Markers of frailty include extra-pulmonary site of disease, known HIV, and US nativity
- The adjusted average survival after cure among TB survivor decedents was 4.1 years
  - 1.6 years less than decedent comparison subjects (4.1 vs. 5.7 years, respectively).

Cox-regression probability of survival by number of years post-diagnosis/treatment and site of disease, adjusted for age, gender, race/ethnicity, HIV, and nativity

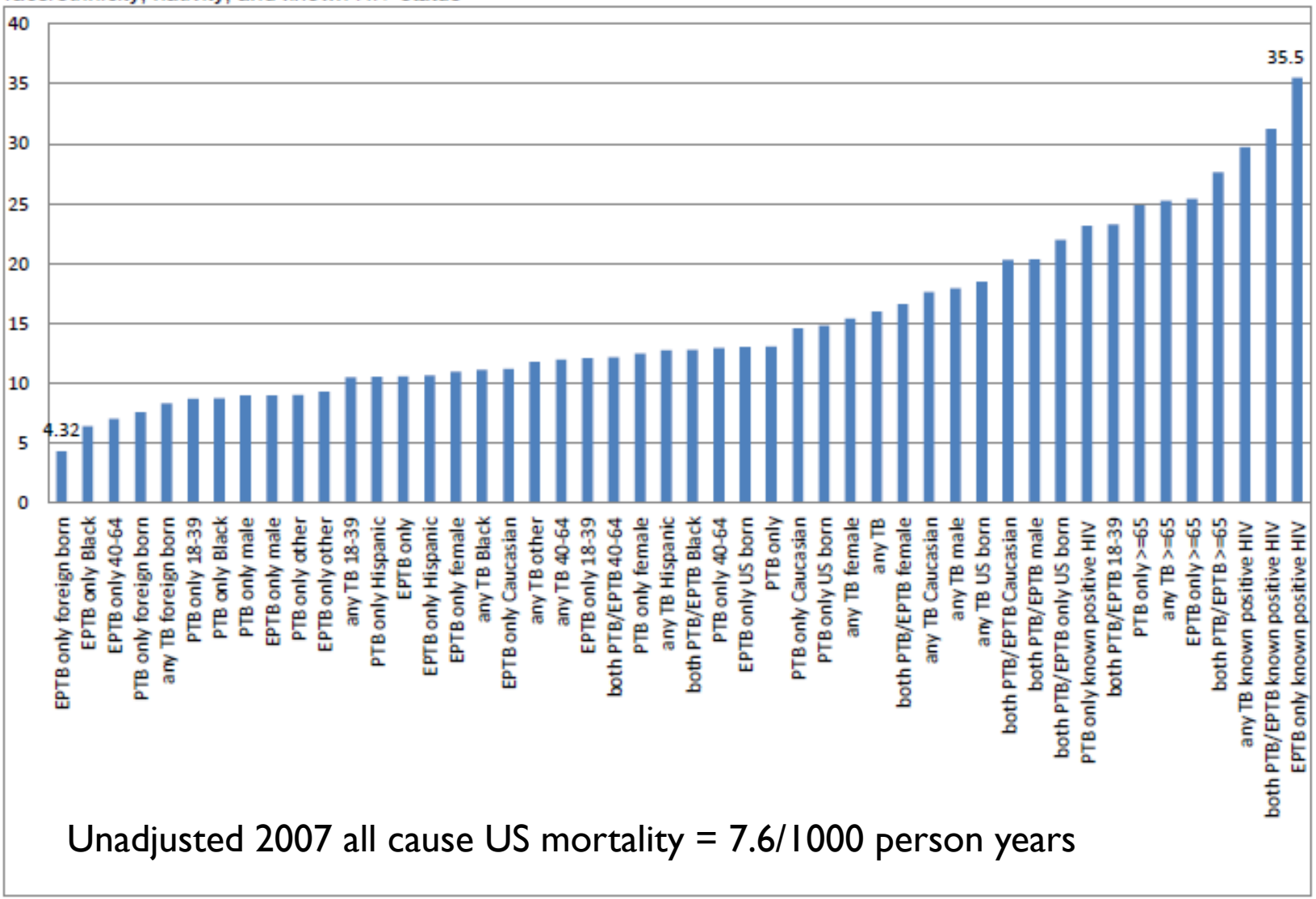


Survival by age for gender adjusted US all population (from CDC Life Tables), TB survivors, and LTBI comparison subjects (predicted by adjusted Cox regression)



Post cure mortality risk distribution

Figure 1: Mortality after TB treatment: Cox regression adjusted incidence/1000 person years by site of infection, age, gender, race/ethnicity, nativity, and known HIV status



Unadjusted 2007 all cause US mortality = 7.6/1000 person years

Limitations

- Preliminary study, using available data
  - Retrospective design
  - Administrative data
  - Non-linearities for age
  - Potential ascertainment bias
- Limitations do not compromise findings
  - Direction, significance, and magnitude unchanged in alternate analyses
  - Testing indicated no confounding or systematic sample bias
  - Underestimates of mortality due to emigration or other factors would suggest our findings are conservative

Conclusions/Outcomes

- Fully treated TB survivors have 7 times expected mortality
  - 1 in 5 had died an average of 4.1 years after treatment completion
- Clinical practice enhancement
  - Targets testing/care toward TB survivors at most risk;
  - Targets priority prevention activities toward populations at most risk
- Resource allocation and advocacy
  - Data helps inform economic models
  - Used by TXDSHS in current legislative session
- Policy enhancement
  - Full value of TB prevention greater than often understood
  - TB "cure" is insufficient protection; prevention likely best to modify risk

Acknowledgments

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Questions?

Cox regression adjusted mortality/1000 person-years and 95% confidence interval among study cohort by TB history, site, and selected characteristics.

	LTBI comparison	Any TB	PTB only	EPTB only	Both PTB/EPTB
Overall	1.23 (.72, 1.74)	8.79 (4.94, 12.64)**	8.31 (5.17, 11.44)**	6.02 (3.34, 8.70)**	7.55 (3.89, 11.21)**
Age					
18-39	.86 (.59, 1.13)	5.89 (3.30, 8.47)**	5.23 (2.74, 7.71)**	6.22 (2.64, 9.81)**	9.74 (4.67, 14.81)**
40-64	1.60 (.82, 2.37)	7.27 (4.43, 10.11)**	8.22 (5.06, 11.37)**	4.28 (2.04, 6.53)*	5.34 (2.16, 8.51)*
>=65	5.09 (2.56, 7.62)	18.33 (13.26, 23.41)**	18.94 (13.77, 24.11)**	17.21 (11.46, 22.95)**	15.05 (8.16, 21.94)**
Gender					
Male	2.04 (1.12, 2.97)	9.69 (5.53, 13.85)**	9.32 (5.87, 12.76)**	5.92 (3.13, 8.72)**	8.50 (4.32, 12.68)**
Female	1.14 (.68, 1.60)	7.63 (4.12, 11.14)**	7.03 (4.18, 9.89)**	6.16 (3.19, 9.13)**	6.36 (2.60, 10.11)**
White	1.72 (1.05, 2.39)	11.73 (6.85, 16.61)**	11.24 (7.13, 15.36)**	6.96 (3.34, 10.58)**	12.48 (6.25, 18.71)**
Hispanic	1.25 (.61, 1.89)	8.30 (4.51, 12.09)**	7.99 (4.81, 11.17)**	6.40 (2.89, 9.91)**	4.42 (1.17, 7.68)
Black	1.69 (.84, 2.54)	7.64 (4.07, 11.21)**	7.17 (4.19, 10.16)**	4.37 (1.79, 6.95)	8.0 (3.23, 12.77)*
Other race	1.96 (1.01, 2.92)	8.28 (4.43, 12.13)**	7.60 (4.38, 10.81)**	6.14 (2.76, 9.52)*	7.76 (2.23, 13.29)*
HIV Positive	2.01 (.80, 3.22)	16.95 (10.69, 23.21)**	14.61 (9.36, 19.87)**	20.87 (13.24, 28.50)**	14.41 (7.10, 21.72)**
HIV unknown	1.59 (.94, 2.24)	8.42 (4.69, 12.14)**	8.0 (4.95, 11.05)**	5.53 (3.0, 8.06)**	7.24 (3.66, 10.81)**
Foreign born	.92 (.46, 1.37)	5.95 (3.08, 8.82)**	5.95 (3.46, 8.44)**	3.63 (1.74, 5.53)**	4.18 (1.38, 6.98)*
US born	3.48 (2.24, 4.73)	14.75 (9.27, 20.22)**	12.98 (8.60, 17.35)**	11.80 (6.97, 16.63)**	16.38 (9.87, 22.89)**

N = 11,135. Cox regression predicted mortality incidence/1000 person-years. Cox regression adjusts for all variables listed in table and location.

* Denotes difference between tuberculosis survivors and diagnosed LTBI is statistically significant at the 5% level; ** denotes significance at the 1% level.

Relative mortality hazard among tuberculosis survivors by site of disease and selected characteristics.

	Any TB	PTB only	EPTB only	Both PTB/EPTB
Overall	7.63 (2.32, 12.94)*	7.18 (2.64, 11.72)**	5.10 (1.68, 8.52)*	6.48 (1.78, 11.19)*
18-39	9.40 (3.74, 15.05)**	8.30 (3.08, 13.53)**	9.97 (2.53, 17.41)*	16.10 (4.11, 28.08)*
40-64	6.28 (1.95, 10.60)*	7.16 (2.20, 12.11)*	3.60 (.83, 6.38)	4.53 (.70, 8.37)
>=65	5.37 (1.43, 9.32)*	5.59 (1.48, 9.70)*	4.98 (1.08, 8.89)*	4.26 (.45, 8.08)
Male	6.66 (1.81, 11.51)*	6.38 (2.11, 10.64)*	3.93 (1.08, 6.79)*	5.77 (1.30, 10.25)*
Female	9.29 (2.84, 15.75)	8.52 (3.10, 13.94)**	7.40 (2.23, 12.57)*	7.66 (1.48, 13.83)*
White	9.79 (2.94, 16.64)*	9.34 (3.36, 15.31)**	5.56 (1.43, 9.69)*	10.49 (2.0, 18.97)*
Hispanic	9.25 (2.10, 16.40)*	8.88 (2.50, 15.26)*	7.01 (1.17, 12.85)*	4.77 (.11, 9.42)
Black	6.25 (1.41, 11.09)*	5.84 (1.61, 10.08)*	3.48 (.55, 6.40)	6.56 (.65, 12.48)
Other race	5.85 (1.35, 10.35)*	5.34 (1.47, 9.20)*	4.26 (.76, 7.76)	5.46 (0, 10.96)
HIV Positive	12.70 (1.68, 23.72)*	10.69 (1.83, 19.55)*	16.31 (1.21, 31.40)*	10.52 (.18, 20.87)
Unknown HIV	7.39 (2.24, 12.53)*	7.0 (2.57, 11.44)**	4.73 (1.53, 7.94)*	6.29 (1.69, 10.88)*
Foreign born	8.90 (2.15, 15.66)*	8.91 (2.63, 15.18)*	5.33 (1.25, 9.41)*	6.15 (.60, 11.71)
US born	6.17 (1.97, 10.36)*	5.33 (2.04, 8.63)*	4.80 (1.52, 8.07)*	6.97 (1.81, 12.12)*

Ratio of comparison:case hazard rate from multivariate Cox regression * Denotes statistical significance at the 5% level; ** denotes significance at the 1% level.