**Online Data Supplement: “The health and economic benefits of tests that predict future progression to TB disease.”**

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# Detailed model descriptions

## Harvard Model

The Harvard model is a deterministic compartmental model of TB1, developed to simulate long-term TB trends in the United States. The model subdivides the population into discrete strata describing important mechanisms of TB transmission, natural history, and treatment. The model is further stratified into additional dimensions describing (i) TB drug resistance patterns, (ii) prior TB and LTBI treatment, (iii) the impact of HIV on TB epidemiology, (iv) heterogeneity in TB risks between US-born and non-US-born populations, and (v) age-based differences in disease mechanisms and risk factor prevalence.

In the model, *Mycobacterium tuberculosis* infection is assumed to confer a small risk of immediate progression to TB disease, with all other infected individuals entering a set of LTBI states that allow for declining reactivation risk over time2,3, and reduced IGRA and TST positivity for individuals with distant infection. LTBI is also assumed to confer partial immunity to superinfection. Treatment of LTBI is assumed to reduce but not eliminate reactivation risk4,5, and treated individuals may also be re-infected in the future. The model allows for international immigration (entering individuals assumed to have higher TB burden than current residents), emigration of non-US-born residents, and inter-state net migration (entering/exiting individuals assumed to have same TB burden as current residents, by age and other TB risk factors). The model allows for international immigration (entering individuals assumed to have higher TB burden than current residents), emigration of non-US-born residents, and inter-state net migration (entering/exiting individuals assumed to have same TB burden as current residents, conditional on age and other individual covariates). Future immigration volume is assumed to increase at 0.8% per year from 2017 levels, based on US Census projections of net international migration6, and TB burden among entering residents is assumed to decline at 1.5% per year. Future rates of inter-state migration and international emigration are held at 2017 levels.

TB transmission risks are calculated dynamically based on disease prevalence and mixing patterns. Bayesian evidence synthesis7,8 is used to combine data sources and calibrate the model to evidence on population demography, TB epidemiology, and receipt of TB prevention and treatment services. A sample of 1,000 simulated epidemic trajectories is used to understand the possible distribution of future outcomes.

## Johns Hopkins Model

The Johns Hopkins model uses an individual-based modeling framework to model natural history, state-level transmission, TB epidemiology, and the impact of TB prevention9,10. To capture natural history of TB, the model classifies individuals as being in one of four TB states: (i) uninfected; (ii) LTBI; (iii) TB disease, or (iv) successfully treated. Rates of transmission of TB infection were modeled as proportional to the fraction of individuals with TB disease (under a homogeneous mixing assumption) and time-dependent to capture secular trends in TB. LTBI was conceptualized as a permanent state that confers partial protection against superinfection and that can be exited (to the uninfected state) through successful treatment, with treatment efficacy defined as the proportion of treated individuals who make this transition.

In the model, TB disease was modeled as resulting from reactivation of LTBI, and the rate of reactivation was assumed to be dependent on age and time since exposure. Rates of transmission and LTBI reactivation were calibrated: the model uses a likelihood-based framework for model calibration, with calibration process aimed to capture the temporal trends in TB incidence between 1993-2015 and the cross-sectional distribution of TB incidence by nativity, age, and select high-risk populations (diabetic, HIV-positive, homeless and incarcerated) in 2015. The model allows for reinfection, diagnosis, and successful treatment (modeled as an instantaneous transition).

Birth, death and international immigration rates were calibrated to reflect each state’s population distributions, by age and nativity. LTBI prevalence in newly arriving non-US-born were modeled to reflect TB prevalence in the sender countries/region. The model did not explicitly consider immigration of US-born individuals (from other states), or distinguish domestic or international immigration of non-US-born. (See Shrestha, et al, 20179, and Cherng, et al, 201911 for further details on calibration, and data sources).

For future population projections, non-US-born population was assumed to represent a fixed fraction of the total population, and the distributions of non-US-born population by age and countries/region of origin were also held fixed in the future, all calibrated to 2015 levels. Model estimates and projections were generated via 1,000 repeated simulations of the maximum-likelihood model; point estimates represent median values in the simulations, and 95% ranges represent 2.5th and 97.5th percentiles.

## UCSF Model

The University of California San Francisco (UCSF) model is an individual-based, stochastic model of 1% of the Californian population age 15 and older. Cycles are one month long. The model is a locally-interacting Markov model, where each individual in the model occupies states on multiple Markov chains, and position on one chain affects transition probabilities on other chains. The model incorporates differential mixing as a function of race and nativity; infectious TB cases transmit 80% of infections within their own race-nativity strata. Risk of progression to TB disease follows an exponential decay function with time since infection according to the formula $R\_{t}=R\_{0}e^{-λt}$, where *t* is the number of months since infection, *Rt* is the risk of progression at month *t*, and *R0* is the risk of progression in the first month after infection. Methods for determining the values of *R0* and *λ* are described elsewhere12. The decline in reactivation risk plateaus at 9 years post-infection. LTBI is assumed to be a lifelong state that can only be exited via death or progression to TB disease. Persons who have received a full course of LTBI treatment have a reduced but non-zero risk of progression. Individuals previously infected with *Mycobacterium tuberculosis* face no risk of reinfection or superinfection. The model is calibrated to reported cases in California from 2005 to 2017. Medical risk factors affecting risk of progression are diabetes, HIV infection, end-stage renal disease, organ transplant, smoking, and TNF-α antagonist use. Future immigration projections were fixed at the mean of the number of entrants for the last three years with available data, stratified by age, race, sex, country or region of birth, and years residing in the United States. New individuals entered the UCSF model by aging in at age 18, and via both international and domestic migration, and exited via death and emigration. Data from the American Community Survey were used to estimate the California population in 2000, and estimate the numbers of persons turning 18 and immigrating to California each cycle. LTBI prevalence trends for US natives and long-term (>5 years) US residents present in January 2000, aging into the model, or moving to California from another state were estimated from IGRA positivity rates in 2011-2012 National Health and Nutrition Examination Survey NHANES13, stratified by age, race, and sex. Comparison to 1999-2000 NHANES was used to estimate time trends in LTBI prevalence. For international migrants and non-US-born internal migrants and 18 year-olds who had less than five years residence in the United States, we used prevalence rates and recent infection rates estimated by Houben and Dodd14 and compared these with estimates from an earlier paper15 to estimate trends in LTBI prevalence. Further details are provided in other publications12. Data from the World Health Organization were used to estimate prevalence of TB disease in all new model entrants.

# Analysis of test performance for a new test

## Definitions

N = No prevalent LTBI

L = Prevalent LTBI, **will not** progress to TB disease in future as a result of current infection

T = Prevalent LTBI, **will** progress to TB disease in future as a result of current infection

I+ = Positive on IGRA

Z+ = Positive on new test

SeLTBI = Sensitivity of IGRA for LTBI = P(I+ | L ∪ T)

SpLTBI = Specificity of IGRA for LTBI = P(I- | N)

SeFTB = Sensitivity of IGRA for future TB = P(I+ | T)

SpFTB = Specificity of IGRA for future TB = P(I- | N ∪ L)

pN = fraction of screened population in class N

pL = fraction of screened population in class L

pT = fraction of screened population in class T

## Outcomes of testing with IGRA

We assume:

* N, L, and T are mutually exclusive ($N∩L= N∩T= L∩T=∅$)
* N, L, and T are collectively exhaustive ($\left(N∪L∪T\right)^{C}=∅$). This ignores individuals with TB disease. It is assumed that these individuals will be identified for TB treatment before LTBI treatment is initiated.
* *pN* + *pL* + *pT* = 1
* L and T have same probability of testing positive with IGRA, which is therefore equal to sensitivity (P(I+ | L) = P(I+ | T) = SeLTBI).
* The new test and IGRA have the same sensitivity for future TB: Pr( Z+ | T ) = Pr( I+ | T ) = SeLTBI

One can create the following contingency table for IGRA:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | N | L | T | Sum |
| I+ | $$p\_{N}\left(1-Sp^{LTBI}\right)$$ | $$p\_{L}Se^{LTBI}$$ | $$p\_{T}Se^{LTBI}$$ | $$p\_{N}\left(1-Sp^{LTBI}\right)+ \left(p\_{L}+p\_{T}\right)Se^{LTBI}$$ |
| I- | $$p\_{N}Sp^{LTBI}$$ | $$p\_{L}\left(1-Se^{LTBI}\right)$$ | $$p\_{T}\left(1-Se^{LTBI}\right)$$ | $$p\_{N}Sp^{LTBI}+ \left(p\_{L}+p\_{T}\right)\left(1-Se^{LTBI}\right)$$ |
| Sum | $$p\_{N}$$ | $$p\_{L}$$ | $$p\_{T}$$ | $$1$$ |

Where the PPV for future TB = P(T|I+) = $\frac{p\_{T}Se^{LTBI}}{\left(p\_{N}\left(1-Sp^{LTBI}\right)+ \left(p\_{L}+p\_{T}\right)Se^{LTBI}\right)}$. By assumption, the sensitivity of IGRA for future TB is the same as the sensitivity for LTBI: SeFTB = SeLTBI. We can also define the sensitivity and specificity of IGRA for future TB: SpFTB = P(I- | $N∪L$) = $\frac{p\_{N}Sp^{LTBI} + p\_{L}\left(1-Se^{LTBI}\right)}{p\_{N}+ p\_{L}}$

## Outcomes of testing with a more specific test for future TB

We define $RR\_{FP}$ as the ratio of the false positive fraction (1 - specificity) for the new test as compared to IGRA, this $RR\_{FP}=\frac{P(Z+| N∪L)}{P(I+ | N∪L)}$. Since we model a hypothetically more specific test Z, it is assumed that this value is less than 1. We assume that the number of N and L testing positive is reduced proportionally ($\frac{P(Z+| L)}{P(I+ | L)}=\frac{P(Z+| N)}{P(I+ | N)}=RR\_{FP}$). It is further assumed that the increased specificity of test Z for future TB is produced by some N and L individuals being I+ and Z-, but that there are no N and L individuals who test I- and Z+.

Based on these assumptions one can create the following contingency table for the new test:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | N | L | T | Sum |
| Z+ | $p\_{N}\left(1-Sp^{LTBI}\right)RR\_{FP}$  | $$p\_{L}Se^{LTBI}RR\_{FP}$$ | $$p\_{T}Se^{LTBI}$$ | $\left(p\_{N}\left(1-Sp^{LTBI}\right)+p\_{L}Se^{LTBI}\right)RR\_{FP}+p\_{T}Se^{LT}$  |
| Z- | $$p\_{N}\left(1-\left(1-Sp^{LTBI}\right)RR\_{FP}\right)$$ | $$p\_{L}\left(1-Se^{LTBI}RR\_{FP}\right)$$ | $$p\_{T}\left(1-Se^{LTBI}\right)$$ | $p\_{N}\left(1-\left(1-Sp^{LTBI}\right)RR\_{FP}\right)+p\_{L}\left(1-Se^{LTBI}RR\_{FP}\right)+p\_{T}\left(1-Se^{\begin{array}{c}LTBI\\\end{array}}\right)$  |
| Sum | $$p\_{N}$$ | $$p\_{L}$$ | $$p\_{T}$$ | $$1$$ |

These formulae allow the estimation of LTBI treatment volume for a scenario where individuals are tested with Z using model results for a test with the sensitivity of Z (producing the correct TB health effects) but the specificity of IGRA. Based on tables above we would multiply modelled treatment volume by the ratio: $R=\frac{P(Z+)}{P(I+)}= \frac{\left(p\_{N}\left(1-Sp^{LTBI}\right)+p\_{L}Se^{LTBI}\right)RR\_{FP}+p\_{T}Se^{LTBI}}{p\_{N}\left(1-Sp^{LTBI}\right)+ \left(p\_{L}+p\_{T}\right)Se^{LTBI}}$. This is the ratio of the test positive rows of both tables.

We can calculate specificity and PPV of the new test for future TB (SpZFTB, and PPVZFTB) with sensitivity same as IGRA:

SpZFTB = P(Z- | N $∪$ L) = $\frac{p\_{N}\left(1-\left(1-Sp^{LTBI}\right)RR\_{FP}\right) + p\_{L}\left(1-Se^{LTBI}RR\_{FP}\right)}{p\_{N}+ p\_{L}}$

PPVZFTB = P(T|Z+) = $\frac{p\_{T}Se^{LTBI}}{\left(p\_{N}\left(1-Sp^{LTBI}\right)+p\_{L}Se^{LTBI}\right)RR\_{FP}+p\_{T}Se^{LTBI}}$

# Additional details on cost calculations

TB hospitalization costs, which make up most of TB treatment costs, were from Aslam et al.16 for a drug susceptible-TB hospitalization, adjusted for hospitalization characteristics, at $20,323 per episode (updated to 2018 dollars using the Bureau of Economic Analysis Personal Consumption Expenditures (PCE) separate indices for inpatient healthcare services17), plus $2,421 in physician fees estimated from Peterson et al.18 in 2014 dollars), or $1,303 per day for an average 15.6 days per episode, multiplied by an estimated 24 days per TB patient hospitalized over multiple episodes from Shepardson et al.19 ($31,266). The estimated percentage of non-MDR-TB patients who are hospitalized (49%) comes from Taylor et al.20 Estimates from Shepardson et al.19 were used for outpatient cost estimates and updated to 2018 dollars using the outpatient PCE index.17 Multidrug-resistant (MDR) TB and extensively drug resistant (XDR) TB morbidity cost estimates derived from Marks et al.21 and were updated to 2018 dollars using the PCE index.17 Non-mortality productivity losses for MDR- or XDR-TB were also estimated by Marks et al.21 Using the approach described above, the average direct cost in 2018 dollars of non-MDR TB was estimated at $18,527, of MDR TB at $174,939, and of XDR TB at $544,182. Weighted by the number of reported non-MDR, MDR, and XDR TB patients in the United States in 2018,22 the average direct cost of TB treatment was $20,267 in 2018 dollars.

The Medicare reimbursement for the IGRA lab test was used to estimate the cost of LTBI testing using an IGRA.23 LTBI treatment costs for 3 months of self-administered weekly doses of isoniazid and rifapentine (3HP), inclusive of testing to rule out TB disease, were extrapolated from Shepardson et al.19 by removing costs of direct observation and updated to 2018 dollars using the outpatient PCE index.17 From Shepardson et al,19 costs reported in 2010 dollars were: $110.94 for an initial clinic visit, $24.37 for a follow-up clinic visit, $54.90 for supplies at the initial clinic visit and $3.56 per follow-up visit. The direct medical costs of treating adverse events, averaged over all patients taking the regimen, were $30.89. LTBI medication costs were estimated from those reported by the Veterans’ Administration.24 Costs per dose were estimated at $11.12. Total direct costs in 2018 dollars of self-administered 3HP were $405.

Estimates of remaining lifetime labor productivity—used to value the economic losses due to TB deaths—were derived from Grosse et al.25, adjusted for the age distribution of TB deaths,26 and inflated to 2018 values using the Employment Cost Index from the Bureau of Labor Statistics27 to account for price inflation and increases in real income.

# One-way sensitivity analyses

We conducted a set of one-way sensitivity analyses to assess the robustness of our results to different assumptions in several key parameters. To do so we varied each parameter between extreme values while holding other parameters at their point estimate, and report the impact of these changes on the costs and QALYs produced by targeted testing and treatment with a more specific test (PPV 10%). Results are shown in Figure E3.

# Table E1: Definition of test performance outcomes

|  |  |
| --- | --- |
| Outcome | Definitions\* |
| Sensitivity for LTBI (SensitivityLTBI) | Fraction of individuals in *‘LTBI, won’t progress’* and *‘LTBI, will progress’* categories that test positive. |
| Specificity for LTBI (SpecificityLTBI) | Fraction of individuals in *‘No LTBI’* category that test negative. |
| Positive predictive value for LTBI (PPVLTBI) | Fraction of individuals testing positive who are in the *‘LTBI, won’t progress’* and *‘LTBI, will progress’* categories. |
| Sensitivity for LTBI that will progress to TB disease in the future (SensitivityFTB) | Fraction of individuals in *‘LTBI, will progress’* category that test positive. |
| Specificity for LTBI that will progress to TB disease in the future SpecificityFTB) | Fraction of individuals in *‘No LTBI’* and *‘LTBI, won’t progress’* categories that test negative. |
| Positive predictive value for LTBI that will progress to TB disease in the future (PPVFTB) | Fraction of individuals testing positive who are in the *‘LTBI, will progress’* category. |

\*‘No LTBI’ represents individuals without LTBI. ‘LTBI, won’t progress’ represents individuals with LTBI will not progress to TB disease. ‘LTBI, will progress’ represents individuals with LTBI who will progress to TB disease in their remaining lifetime. LTBI = latent TB infection.

# Table E2: Categorization of hypothetical tested cohort in 2020 and 2035 according to IGRA result and future risk of TB for individuals with LTBI.

|  |  |
| --- | --- |
| Model, setting | Performance of IGRA for identifying individuals who will develop TB in the future due to current LTBI\* |
| True positive (%) | False positive (%) | False negative (%) | True negative (%) |
| Outcomes in **2020** Harvard, US | 0.14 | 8.68 | 0.04 | 91.14 |
|  Johns Hopkins, CA | 0.12 | 7.08 | 0.03 | 92.77 |
|  Johns Hopkins, FL | 0.06 | 5.00 | 0.02 | 94.92 |
|  Johns Hopkins, NY | 0.06 | 5.39 | 0.02 | 94.53 |
|  Johns Hopkins, TX | 0.07 | 4.05 | 0.02 | 95.86 |
|  UCSF, CA | 0.02 | 3.11 | 0.01 | 96.86 |
|  Mean value | 0.08 | 5.55 | 0.02 | 94.35 |
| Outcomes in **2035** Harvard, US | 0.08 | 6.05 | 0.02 | 93.85 |
|  Johns Hopkins, CA | 0.09 | 5.74 | 0.03 | 94.14 |
|  Johns Hopkins, FL | 0.04 | 4.13 | 0.01 | 95.81 |
|  Johns Hopkins, NY | 0.04 | 4.33 | 0.01 | 95.61 |
|  Johns Hopkins, TX | 0.05 | 3.43 | 0.01 | 96.5 |
|  UCSF, CA | 0.02 | 3.06 | 0.01 | 96.91 |
|  Mean value | 0.05 | 4.46 | 0.02 | 95.47 |

\* Results in table relate to the outcome of future TB resulting from current LTBI. Table S1 provides definitions of sensitivity and specificity for future TB. LTBI = latent TB infection. IGRA = interferon-gamma release assays.

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# Figure E1: Relationship between the positive predictive value for future TB, LTBI prevalence, and the probability of future TB among individuals with LTBI, for modelled cohorts in 2020 tested with IGRA\*.



\*LTBI = latent TB infection. IGRA = interferon-gamma release assays. PPV = positive predictive value.

# Figure E2: Reduction in societal costs resulting from improved test positive predictive value for future TB, as compared to IGRA.\*



\* Assumes all other features of LTBI testing and treatment are held constant. Results reported per person screened. PPV = positive predictive value. IGRA = interferon-gamma release assays.

# Figure E3: One-way sensitivity analyses for several key parameters, showing the changes in costs and QALYs produced by LTBI testing and treatment with a test with PPV=10%.\*



\* Each sensitivity analysis (row of the figure) assumes all other parameters are held constant. Values in parentheses represent the point estimate and bounds tested in sensitivity analysis (bounds shown in square brackets). Panel A: incremental costs produced by LTBI testing and treatment in a cohort of 10,000. Panel B: incremental QALYs produced by LTBI testing and treatment in a cohort of 10,000.

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