Supplementary Material

What is the health impact of identifying a person with tuberculosis through systematic screening?

Kendall EA and Dowdy DW

Table of Contents

Text S1: Description of DALY model

The full model code is published at https://github.com/eakendall/ACF-impact-Rshiny. Primary DALY estimation functions are located in the file daly_estimator.R, and parameter estimates are in file define_params and in Table S1 below.

Step 1: Total DALYs per average TB case

- TB morbidity DALYs are estimated as
  Morbidity_average_case = (TB disability weight) * (TB symptom duration)
- TB mortality DALYs are estimated as
  Mortality_average_case = (TB case fatality ratio) *
  $\sum_{y=0}^{\text{Years of life lost per TB death}-1}(1 - \text{Annual discounting rate})^y$
- Post-TB sequelae DALYs are estimated as
  Sequelae_average_case =
  (Post-TB disability weight) * $\sum_{y=0}^{\text{Post-TB duration}-1}(1 - \text{Annual discounting rate})^y$ + (Post-TB case fatality ratio) * $\sum_{y=0}^{\text{Years of life lost per post-TB death}-1}(1 - \text{Annual discounting rate})^y$.
- TB transmission-related DALYs are estimated as:
  Transmission_average_case =
  (Downstream cases) *
  (Morbidity_average_case + Mortality_average_case + Sequelae_average_case) *
  (1 – Annual discounting_rate)$^{(\text{Downstream case timing})}$

Step 2: Differences between detected and non-detected cases

This component of the model is kept simple by parametrizing the relationship between duration and other disease outcomes as a covariance.

Across all TB episodes, we represent the distribution of duration as D, of mortality risk as M, and of cumulative transmission as T. We define these on relative scales, such that the means or expected values E[D] = E[M] = E[T] = 1. And because they are distribution functions, $\int dT = \int dM = \int dD = 1$,
We then represent joint distributions of duration and transmission as f[D, T], and of duration and mortality as f[D, M].
By definition, the covariance cov(D, T) = $\int dD\, dT\, (D - E[D])(T - E[T])\, f[D,T] =$
$\int dD\, dT\, (f[D,T]D\,T - f[D,T]D - f[D,T]DT + f[D,T])) =$
$\int dD\, dT\, (f[D,T]D\,T) - \int dT\, (\int dD\, D\, f[D,T]) - \int dD\, (\int dT\, T\, f[D,T]) + \int dT\, dD\, f[D,T] =$
$\int dD\, dT\, (f[D,T]D\,T) - \int dT\, E[D] - \int dD\, E[T] + 1 =$
$\int dD\, dT\, (f[D,T]D\,T) - \int dT - \int dD + 1 =$
$\int dD\, dT\, (f[D,T]D\,T) - 1 - 1 + 1 =$
$\int dD\, dT\, (f[D,T]D\,T) - 1$
And similarly, cov(D, M) = $\int dD\, dM\, (f[D,M]D\,M) - 1$.

For estimating the relative DALYs associated with detected cases versus the average case, we are interested in the expected value of T when weighted by D, i.e.,
Avertible_transmission_multiplier_if_detected =
$\int dD\, dT\, (D\,T\, f[D,T])$ = (Transmission-duration covariance) + 1

And similarly,
Avertible_mortality_multiplier_if_detected = (Mortality-duration covariance) + 1.

(Note that for illustrative purposes in the Shiny app, we must also specify coefficients of variation (cv) for duration, mortality, and transmission, such that covariance = correlation * duration_cv * mortality_cv or covariance = correlation * transmission_cv * transmission_cv. However these are not necessary for the model itself.)

Step 3: Proportion of DALYs that are averted by early detection

We first parametrize the timing of DALY accrual within the screen-detectable window as:

- a fraction *f* of DALYS that accrue during the first half of the period, and
- a power *p* that describes how the rate of DALY accrual changes over the course of the screen-detectable window, i.e. DALY accrual rate $r(t) = r0 + r1\ t^p$, where $t \in [0,1]$ is the proportion of the screen-detectable window that has elapsed.

Simultaneously solving $\int_0^1 r0 + r1\ t^p dt\ = 1$ and $\int_0^{1/2} r0 + r1\ t^p\ dt = f$, we obtain the following:
$r0 = \frac{-1+2^{1+p}f}{-1+2^p}$, $r1 = \frac{-2^p(-1+2f)(1+p)}{-1+2^p}$.

And assuming that detection by screening is equally likely to occur at any time in the screen-detectable window $t \in [0,1]$, the proportion of DALYs averted by screening is equal to:
Averted_average_proportion(f, p) =

$$\int_0^1 t\ r(t)\ dt = \int_0^1 r0\ t + r1\ t^{p+1}\ dt = \frac{-1+2^{1+p}f}{2(-1+2^p)} + \frac{2^p(-1+2f)(1+p)}{(2+p)(-1+2^p)}.$$

We apply this function to estimate the average proportion of all transmission (and associated DALYs) averted when a case is detected early:

Average_proportion_avertible_transmission =
(1 – (Pre-detectability transmission) – (Post-diagnosis transmission)) *
Averted_average_proportion(
f = Early-detectable-period transmission,
p = Timing power relationship, transmission within screen-detectable window),

And similarly, we estimate the average proportion of personal-health DALYs averted when a TB case is detected early as:

Average_proportion_avertible_personal =
(1 – (Pre-detectability morbidity and mortality accrual) – (Post-diagnosis transmission morbidity and mortality accrual)) *
Averted_average_proportion(
f = Early-detectable-period morbidity and mortality accrual,
p = Timing power relationship, morbidity/mortality accrual within screen-detectable window).

Text S2: Estimation of specific parameters

Code for estimating these parameters can be found at https://github.com/eakendall/ACF-impact-Rshiny, in the file Parameter estimates.R and accompanying data files.

Average age of TB survivors:

Using WHO TB incidence estimates disaggregated by age group, sex and risk factor,[1] we considered data for year 2022 and aggregated data across all risk groups and countries to count the estimated number of cases in each of the age groups "0-4", "5-14", "15-24", "25-34", "35-44", "45-54", "55-64", and "65plus". Using these data, we determined that the median age of incident TB is estimated to be in the 35-44 year old age group, and by estimating the mean ages within age groups as 2, 9.5, 19.5, 29.5, 39.5, 49.5, 59.5, and 69.5 years, respectively, we used a weighted mean to estimate the average age of a person with TB as ~39.

Estimated rate of TB incidence decline by country:

Using WHO's TB burden estimates by country for years 2015 through 2023,[1] limited to countries with estimated TB incidence > 100 per 100,000 population in at least one year, we fit a linear trend to incidence for each country and estimated the rate of change as of 2021. The interquartile range of this rate across countries was 0-4%.

Covariance estimation, mortality vs duration:

First, to estimate TB case fatality ratio by HIV status, we extracted HIV-stratified estimates of global TB incidence and TB deaths in people with and without HIV from the 2022 WHO Global TB Report. We then estimated case fatality ratios (CFRs: deaths/incident cases), stratified by HIV status. The estimated CFR was 1.9x greater for HIV-associated TB than for HIV-negative TB.

The, we simulated a cohort of 10,000 people with TB, with a latent "immune status" variable that is associated with their HIV status, disease duration, and TB mortality risk. We arbitrarily represent immune status as normally distributed with mean of 0 and sd of 5, and HIV status is assigned to be positive with probability 0.4*inv.logit(-immune_status). This gives an HIV prevalence of 20% among TB cases, and a moderate correlation (r = -0.4) of HIV status and immune status.
We then model TB duration as gamma distributed with mean and sd of 1, and we assign sampled durations to the cohort in roughly the rank-order of the latent immune status, with some error: duration[order(duration + rnorm(10000, 0, 1))]. This results in a mean duration that is 0.5x as large for HIV-positive as for HIV-negative people with TB.
We model a correlation of mortality with immune status that results in approximately 20% overall case fatality and a 2x higher mortality in those with versus without HIV coinfection: mortality = rbinom(10000, 1, 0.4*inv.logit(-0.5*immune_status -0.5)).
Finally, we normalize both the duration and the mortality and estimate their covariance, with a result of approximately -0.4.

Text S3: Estimation of downstream cases avertable through preventing one episode of TB

To estimate the secondary cases attributable to one case, we used a published TB transmission model,[2] removed one active case in the present day, and ran the model for 30 years. We compared the outcomes pairwise to no-intervention models with the same parameters and starting states.

Across all data-consistent parameter sets considered in the published analysis, the cumulative incidence averted was median 0.8 cases (95% uncertainty range 0.4 – 1.3) when the removed case was asymptomatic and 1.0 (0.5 – 1.8) when the removed case had TB symptoms. Half of the averted incidence occurred within the first 8 years (range 7-10 across calibrated models; uncertainty extended to account for model structural uncertainty).

Table S1: Parameter estimates

Parameter	Description/notes	Estimate (range)	Sources/Justification
Personal Health Consequences			
TB disability weight	Relative reduction in quality of life during time with symptomatic TB	0.35 (0.2—0.6)	IHME estimates[3]: 0.33 for HIV-negative; 0.41 for HIV+ (based on "has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss")
TB symptom duration	Average cumulative time with TB symptoms (years)	0.25 (0.083 – 0.42)	81 (70-92) + 30 (26-33) day delay in systematic review, among those eventually diagnosed.[4] Patients may not fully recall time with milder symptoms (resulting in higher total severity-weighted duration),[5] but some recalled symptoms may be milder than the disability weight above represents, and people whose TB spontaneously resolves may experience fewer symptoms (both reflected in lower-bound estimate).
TB case fatality ratio	Proportion of incident TB that ends in death under current care	0.12 (0.05—0.20)	WHO Global TB Report 2023 mortality:incidence[6]
Years of life lost per TB death	Remaining healthy life expectancy in the absence of TB, for people who die of TB (years)	15 (5—25)	Average age at TB death ~55 (but left skew);[7] healthy life expectancy ranges 10-20 years at age 60 globally,[8] so 10-25 at age 55, but lower in people who develop TB.
Post-TB disability weight	Relative reduction in quality of life caused by TB, averaged over all post-TB survival	0.035 (0.01—0.10)	Point estimate from Menzies et al.[7] (corresponding to, for example, 20% prevalence of mild (DW 0.02), 10% of moderate (DW 0.2), and 3% of severe (DW 0.4)[3] causally-mediated COPD among TB survivors), with wide uncertainty
Post-TB duration	Total average post-TB survival (years)	25 (10—35)	Average TB survivor age ~40 ([9] and Supplement Text S2), and remaining life expectancy less than global average of ~35[8] due to underlying TB risk factors and male predominance.
Post-TB cumulative mortality	Proportion of TB survivors who die prematurely from TB sequelae	0.05 (0.02—0.15)	Earlier modeling analysis[9] estimated 1.14x relative mortality globally ==> ~.14/1.14=12% of deaths attributable to TB. This was taken as a high-end estimate (with wide uncertainty) given likely recall bias, inability to differentiate TB-caused versus TB-predisposing lung disease apart from matching by smoking history, and the earlier model's assumption that TB survivors would have had the average life expectancy for their age and HIV status, had they not developed TB.
Years of life lost per post-TB death	Remaining healthy life expectancy in the absence of TB, for people who die of post-TB sequelae (years)	10 (5—20)	Excess post-TB mortality is greater for older TB patients (like TB mortality) and mostly occurs within 10 years of TB (estimated as ~5 years into post-TB life expectancy)[10]
Post-TB death timing	Mean years to death, for those who die early of post-TB sequelae (relevant to discounting only)	5 (1-10)	In large Danish cohort with long follow-up, TB patient and control mortality rates are similar after ~10 years[10]
Transmission			
Downstream cases	Average downstream cases avertable if one TB case were prevented	0.9 (0.4—2.0)	Estimated using Shrestha et al model[2] as described above
Downstream case timing	Median time to preventable downstream cases (years)	8 (5—15)	Estimated using Shrestha et al model[2] as described above
Annual discounting rate	Applied to morbidity/mortality/sequelae and transmission outcomes	0.03 (0—0.07)	Assumed for consistency with other analyses and explored in sensitivity analysis[11]
Timing			
Pre-detectability transmission	Proportion of transmission that occurs before TB becomes detectable by screening	0.05 (0—0.1)	For chest X-ray screening and pathogen-directed confirmatory testing, sensitivity for sputum-culture-positive prevalent TB may be 60-70%,[12] but those who aren't detectable have low bacterial and/or radiographic disease burden and much lower expected infectivity[13]
Pre-detectability morbidity and mortality accrual	Proportion of TB-attributable personal health consequences that accrue before TB becomes detectable by screening	0.1 (0—0.3)	The <40% of culture-positive TB missed by chest X-ray and molecular sputum confirmatory testing[12] has limited pulmonary disease extent, as well as lower inflammatory burden[14,15] and fewer symptoms,[16] reducing the accrued TB and post-TB

			morbidity. Extrapulmonary TB with high morbidity and mortality may be missed but is a small proportion of prevalent TB person-time.
Post-diagnosis transmission	Proportion of transmission that occurs after TB has been diagnosed through routine care	0.1 (0.05—0.3)	Limited to transmission that occurs during the brief window between diagnosis and effective treatment,[17] plus a proportion of cumulative transmission from the ~20% with pretreatment loss to follow-up, treatment failure, or recurrence[6,18]
Post-diagnosis morbidity and mortality accrual	Proportion of TB-attributable personal health consequences that remain avertable after diagnosis through routine care	0.2 (0.1—0.5)	Greater than for transmission, due to strong temporal association between severe symptoms and passive diagnosis. But excludes the majority of total TB mortality that occurs before routine diagnosis (11.5% total case fatality, of which [3.8% fatality]*[77% case detection] is death during treatment plus some proportion are death after unsuccessful treatment [~10% unsuccessful * 11.5% case fatality])[19]. Also excludes the large proportion of symptomatic TB person-time that occurs before routine diagnosis, and the considerable proportion of morbidity and mortality that occur despite prompt and effective treatment once patients seek care for symtoms.[20,21]
Early-detectable-period transmission	Of transmission during the screen-detectable window, proportion that occurs during the first half (used for fitting exponential increase)	0.33 (0.1—0.5)	Point estimate corresponds to 2x more infectious at diagnosis than at onset of detectability, with linear increase. Upper bound corresponds to uniform infectiousness over the disease course (e.g. if increased bacterial burden later in the disease course is fully offset by a reduced contact rate).
Early-detectable-period morbidity and mortality accrual	Of personal health consequences that accrue during the screen-detectable window, proportion that accrues during the first half	0.25 (0 —0.5)	Lower than for transmission because clinical severity often leads to passive diagnosis, but same theoretical upper bound.
Timing power relationship, transmission within screen-detectable window	Power p in relationship between transmission rate and time t within screen-detectable window [0,1]: rate = $a + b\,t^p$	1.5 (1—2)	Weak correlation of bacillary burden (and likely transmission) with symptoms that could lead to passive diagnosis
Timing power relationship, morbidity/mortality accrual within screen-detectable window	Power p in relationship between mortality/mortality accrual rate and time t within screen-detectable window [0,1]: rate = $a + b\,t^p$	3 (2—4)	The most substantial symptoms and pathology change are likely to occur close to passive diagnosis or death.
Heterogeneity			
Transmission-duration covariance	Covariance of the duration of a TB episode's screen-detectable window with the cumulative transmission the case would generate, when each is estimated on a relative scale with mean of 1	1 (0.5—1.5)	Point estimate of 1.0 assumes that x times longer disease duration translates to x times greater cumulative transmission (as would occur if all TB has the same transmission rate); range considers that longer disease courses may also have higher (if higher bacillary burdens are more persistent[22]) or lower (if milder disease progresses more slowly but without resolving[23]) transmission rates that augment or offset the time-based correlation.
Mortality-duration covariance	Covariance of the duration of a TB episode's screen-detectable window (in absence of screening) with expected mortality-related DALYs, when each is estimated on a relative scale with mean of 1	-0.4 (-1—0)	Point estimate of -0.4 is based on simulated HIV-stratified data (see supplement, Text S2) with 0.5x duration and 2x mortality risk among those with HIV.[9,24]

Figure S1: Estimates of TB (and post-TB) morbidity should use the same symptom criteria for estimating the degree and the duration of morbidity. For example, a disability weight that corresponds to severe symptoms (persistent cough, fever, weakness, weight loss[3]) should be applied to only the duration of those symptoms, while time with milder symptoms should be down-weighted and time with asymptomatic TB ignored. Prevalence survey data suggest that approximately half of time spent with undiagnosed TB has minimal or no symptoms.[25,26] Thus, cumulative disability may be more accurately estimated by limiting the estimated duration over which disability weights are applied (for example, patients retrospectively estimate approximately 3 months of recognizable symptoms, some of which may not have been severe[4]).

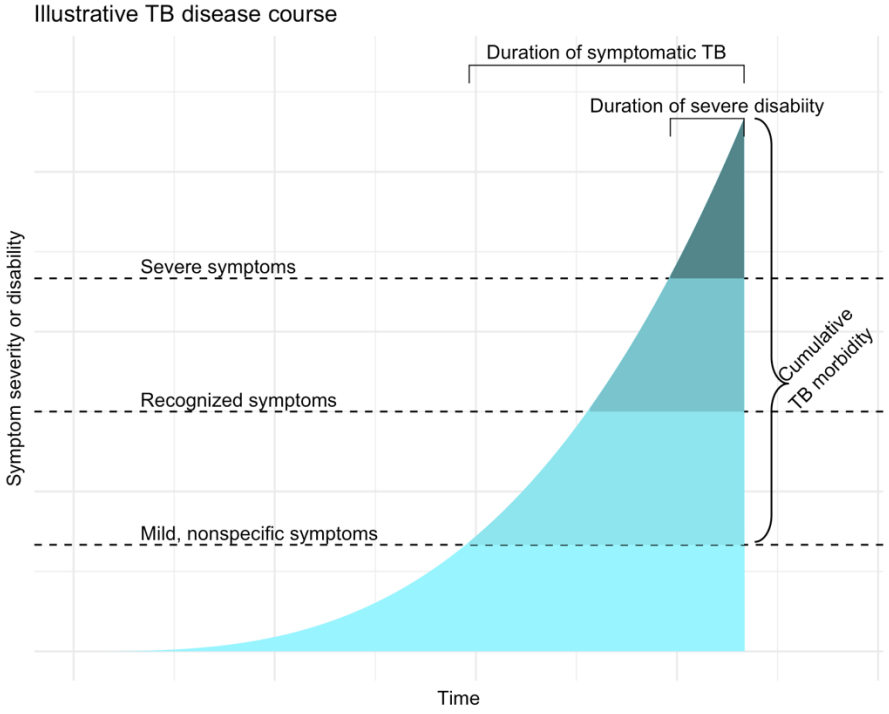
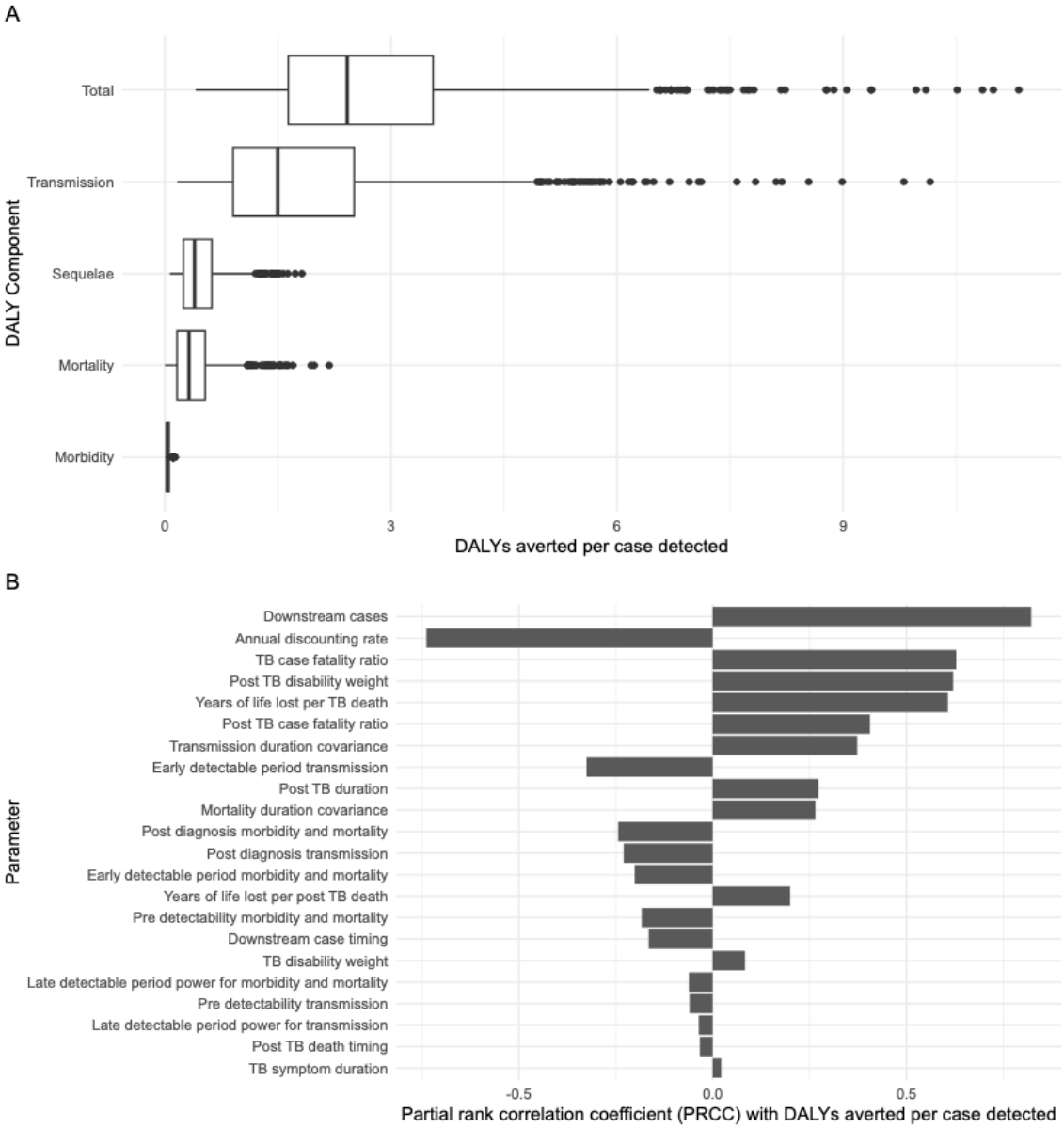


Figure S2: DALY estimate and one-way sensitivity analysis. Panel A shows the distribution of estimated DALYs averted per case detected, overall and by component, for 1000 probabilistically sampled parameter sets. The boxes extend from the 25th to the 75th percentile with a line at the median; the whisker lines extend to the largest value that lies no further than 1.5 times the interquartile range from the box ends in each direction; and estimates beyond the whisker lines are plotted as individual points. Panel B shows the extent to which each model parameter is correlated with the outcome of total DALYs averted per case detected by screening, after adjusting for all other model parameters.



References

1 World Health Organization Global TB Programme. Tuberculosis Data. https://www.who.int/teams/global-tuberculosis-programme/data (accessed Jan 2, 2025).

2 Shrestha S, Kendall EA, Chang R, *et al.* Achieving a 'step change' in the tuberculosis epidemic through comprehensive community-wide intervention: a model-based analysis. *BMC Med* 2021; **19**: 244.

3 Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Disability Weights. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2024 https://ghdx.healthdata.org/record/ihme-data/gbd-2021-disability-weights (accessed July 12, 2024).

4 Bello S, Afolabi RF, Ajayi DT, *et al.* Empirical evidence of delays in diagnosis and treatment of pulmonary tuberculosis: systematic review and meta-regression analysis. *BMC Public Health* 2019; **19**: 820.

5 Ku C-C, MacPherson P, Khundi M, *et al.* Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data. *BMC Medicine* 2021; **19**: 298.

6 World Health Organization. Global Tuberculosis Report 2023. Geneva, 2023 https://www.who.int/teams/global-tuberculosis-programme/data (accessed Nov 25, 2023).

7 Menzies NA, Quaife M, Allwood BW, *et al.* Lifetime burden of disease due to incident tuberculosis: a global reappraisal including post-tuberculosis sequelae. *Lancet Glob Health* 2021; **9**: e1679–87.

8 WHO Global Health Observatory. GHE: Life expectancy and healthy life expectancy. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-life-expectancy-and-healthy-life-expectancy (accessed July 12, 2024).

9 Global Tuberculosis Programme. Tuberculosis data. Data provided by countries to WHO and estimates of tuberculosis burden generated by WHO for the Global Tuberculosis Report. https://www.who.int/teams/global-tuberculosis-programme/data (accessed July 12, 2024).

10 Christensen A-SH, Roed C, Andersen PH, Andersen ÅB, Obel N. Long-term mortality in patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study. *Clin Epidemiol* 2014; **6**: 405–21.

11 Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. *Health Policy and Planning* 2020; **35**: 107–14.

12 World Health Organization. WHO Consolidated Guidelines on Tuberculosis, Module 2: Screening Systematic screening for tuberculosis disease, Annex C. GRADE Evidence to Decision Tables. 2021. https://www.who.int/publications/i/item/9789240022676 (accessed May 21, 2024).

13 Garcia LS, Costa AG, Araújo-Pereira M, *et al.* The Xpert® MTB/RIF cycle threshold value predicts M. tuberculosis transmission to close contacts in a Brazilian prospective multicenter cohort. *Clin Infect Dis* 2024; : ciad794.

14 Cox SR, Erisa KC, Kitonsa PJ, *et al.* Accuracy of C-Reactive Protein for Tuberculosis Detection in General-Population Screening and Ambulatory-Care Triage in Uganda. *Ann Am Thorac Soc* 2024; **21**: 875–83.

15 Ruperez M, Shanaube K, Mureithi L, *et al.* Use of point-of-care C-reactive protein testing for screening of tuberculosis in the community in high-burden settings: a prospective, cross-sectional study in Zambia and South Africa. *Lancet Glob Health* 2023; **11**: e704–14.

16 Stuck L, Klinkenberg E, Abdelgadir Ali N, *et al.* Prevalence of subclinical pulmonary tuberculosis in adults in community settings: an individual participant data meta-analysis. *Lancet Infect Dis* 2024; **24**: 726–36.

17 Shah M, Dansky Z, Nathavitharana R, *et al.* NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings. *Clin Infect Dis* 2024; : ciae199.

18 MacPherson P, Houben RM, Glynn JR, *et al.* Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bull World Health Organ* 2014; **92**: 126–38.

19 World Health Organization. Global Tuberculosis Report 2024. Geneva, Switzerland, 2024 https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024 (accessed Oct 30, 2024).

20 Burke RM, Nyirenda SK, Mtenga T, *et al.* Enhanced tuberculosis diagnosis with computer-aided chest X-ray and urine LAM in adults with HIV admitted to hospital (CASTLE study): A cluster randomised trial. *Clin Infect Dis* 2024; : ciae273.

21 Haraka F, Kakolwa M, Schumacher SG, *et al.* Impact of the diagnostic test Xpert MTB/RIF on patient outcomes for tuberculosis. *Cochrane Database Syst Rev* 2021; **5**: CD012972.

22 Ryckman TS, Dowdy DW, Kendall EA. Infectious and clinical tuberculosis trajectories: Bayesian modeling with case finding implications. *Proc Natl Acad Sci U S A* 2022; **119**: e2211045119.

23 Ragonnet R, Flegg JA, Brilleman SL, *et al.* Revisiting the Natural History of Pulmonary Tuberculosis: a Bayesian Estimation of Natural Recovery and Mortality rates. *Clin Infect Dis* 2020; published online Aug 7. DOI:10.1093/cid/ciaa602.

24 Law I, Floyd K, African TB Prevalence Survey Group. National tuberculosis prevalence surveys in Africa, 2008-2016: an overview of results and lessons learned. *Trop Med Int Health* 2020; **25**: 1308–27.

25 Frascella B, Richards AS, Sossen B, *et al.* Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. *Clin Infect Dis* 2020; published online Sept 16. DOI:10.1093/cid/ciaa1402.

26 Stuck L, van Haaster AC, Kapata-Chanda P, Klinkenberg E, Kapata N, Cobelens F. How “Subclinical” is Subclinical Tuberculosis? An Analysis of National Prevalence Survey Data from Zambia. *Clin Infect Dis* 2022; **75**: 842–8.