Implications of progressive lung damage and post-tuberculosis sequelae for the health benefits of prompt tuberculosis treatment in high HIV prevalence settings: a mathematical modelling analysis

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Summary

Background Untreated pulmonary tuberculosis causes ongoing lung damage, which can persist after treatment. Conventional modelling approaches for assessing tuberculosis health effects might not fully capture these mechanisms. We evaluated how tuberculosis-associated lung damage and post-tuberculosis sequelae affect the lifetime health consequences of tuberculosis in high HIV prevalence settings.

Methods We developed a microsimulation model (computer simulations that reproduce disease natural history and intervention effects for sampled individuals) representing dynamic changes in lung function for individuals evaluated for tuberculosis in routine clinical settings. We parametrised the model with data (from a previously published study) for three African countries with a high burden of tuberculosis and HIV: Uganda, Kenya, and South Africa, and estimated lifetime health outcomes under prompt, delayed, and no tuberculosis treatment scenarios. We compared results to earlier modelling approaches that omit progressive lung damage and post-tuberculosis sequelae.

Findings We estimated a 5·1 years (95% uncertainty interval 3·8–6·4) reduction in life expectancy due to tuberculosis with prompt treatment, 7·7 years (5·5–10·1) with delayed treatment, and 18·5 years (15·5–20·6) with no treatment. Estimated per-person disability-adjusted life-years (DALYs) from tuberculosis were 11·4 years (8·9–14·2) with prompt treatment, 17·1 years (13·1–22·1) with delayed treatment, and 37·7 years (34·3–40·3) with no treatment. Compared with individuals without HIV, individuals with HIV had a greater proportion of tuberculosis-attributable deaths, but fewer life-years lost to tuberculosis. Post-tuberculosis DALYs represented 52·5% of total DALYs with prompt treatment, 42·7% with delayed treatment, and 9·1% with no treatment. Modelling approaches that omit progressive lung damage and post-tuberculosis sequelae underestimated lifetime health losses of tuberculosis by 48–57% and underestimated the benefits of prompt treatment by 45–64%.

Interpretation Delayed initiation of tuberculosis treatment causes greater lung damage and higher mortality risks during and after the disease episode than prompt treatment. In settings with coprevalent tuberculosis and HIV, accounting for these factors substantially increased estimates of the lifetime disease burden and life expectancy loss caused by tuberculosis. These findings imply greater health effects and cost-effectiveness for interventions to prevent tuberculosis and achieve earlier treatment initiation than indicated in previous analytical approaches.

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Introduction

In 2022, more than 10·6 (95% uncertainty interval 9·9–11·4) million people developed tuberculosis, with 1·3 (1·1–1·5) million people dying with the disease.[1] Although tuberculosis can affect multiple organ systems, it most commonly affects the lungs, with pulmonary tuberculosis (with or without extrapulmonary involvement) representing most global tuberculosis cases.

Pulmonary tuberculosis progresses through several disease stages, although this process can differ widely between individuals.[2] After initial infection, *Mycobacterium tuberculosis* replicates inside a granuloma (aggregation of immune cells) within the lungs. An individual progresses to infectious disease when bacteria escape this granuloma, which can happen soon after infection or decades later, with this risk declining with increasing time since infection.[3] This disease progression is marked by damage to local lung tissue due to both bacterial infection and the immune response. Initially, individuals might not feel sick, and some will develop chronic subclinical tuberculosis or self-cure.[2] However, many will eventually develop symptoms traditionally associated with tuberculosis, including cough, fever, and

Research in context

Evidence before this study

Research on long-term sequelae among tuberculosis survivors has focused on describing the prevalence and nature of these post-tuberculosis sequelae and quantifying their contribution to the overall burden of tuberculosis disease. There is little evidence describing how improvements in tuberculosis diagnosis and prompt treatment initiation could affect the overall health losses associated with tuberculosis, including post-tuberculosis sequelae. We searched PubMed from database inception until July 19, 2024, with no language restrictions for studies reporting how tuberculosis diagnosis and treatment affect post-tuberculosis sequelae and lifetime health losses, with the search terms "(tuberculosis OR TB) AND (post-TB OR post-tuberculosis) AND (diagnos*) AND (treat*) AND (model*)". We found 21 publications based on this search. Of these, one study reported a mathematical modelling approach for estimating lifetime health outcomes and costs, stratified by HIV status, by considering the delay in diagnosis, post-tuberculosis sequelae, and treatment discontinuation among tuberculosis patients in Brazil, but did not simulate changes in lung function during the tuberculosis episode.

Added value of this study

To our knowledge, this is the first study to investigate the effects of timeliness of tuberculosis diagnosis on progressive lung damage and lifetime health outcomes for individuals with tuberculosis in high HIV burden settings. To do so, we constructed a mathematical model simulating changes in lung function before, during, and after tuberculosis treatment, and simulated multiple counterfactual scenarios for a cohort of individuals presenting to primary health services with undiagnosed tuberculosis disease in Uganda, Kenya, and South Africa, three African countries with a high burden of tuberculosis and HIV. We compared the results of this analysis to the estimates produced by earlier modelling approaches that do not represent tuberculosis-associated lung damage or post-tuberculosis sequelae.

Implications of all the available evidence

The results of this analysis showed that post-tuberculosis sequelae represent a substantial share of the overall health losses associated with tuberculosis, and that better post-tuberculosis lung function (resulting from a shorter duration of untreated tuberculosis disease) is a major contributor to the overall health benefits of prompt tuberculosis diagnosis and treatment. The health outcomes were also compared based on HIV diagnosis to understand the effect of HIV on the lifetime health outcomes during and after tuberculosis episode. These results are not accurately captured by earlier modelling approaches that did not consider tuberculosis-associated lung damage or post-tuberculosis sequelae. The findings of this analysis contribute to the evidence base describing how tuberculosis interventions can influence lung function dynamics during and after tuberculosis disease, and the resulting changes in disability and mortality due to tuberculosis.

weight loss. Individuals with symptomatic disease are also likely to have progressive lung damage, including cavitation (lung cavities formed by the destruction of healthy tissue) and consolidated areas, and involvement of other organs. Although the tuberculosis disease will clear in some individuals without intervention, the case-fatality rate is approximately 50% without treatment.[4] For individuals with impaired immunity (eg, those with HIV), disease progression is faster and survival poorer.[5]

Effective tuberculosis treatment can stop the disease process, with symptoms ameliorating during treatment.[6] However, for many individuals the lungs do not fully heal, particularly if lung damage was extensive before treatment was started. This damage can lead to persistent respiratory impairment and elevated risks of conditions such as bronchiectasis, aspergillosis, and lung cancer. Multiple meta-analyses have documented a high prevalence of respiratory impairment among people cured of tuberculosis, with poorer spirometry results and functional lung health compared with healthy controls.[7,8] Individuals cured of multidrug resistant tuberculosis have been found to have worse lung function measures compared with those with previous drug-susceptible tuberculosis.[8] Studies that have adopted quasi-experimental designs to assess the causal effects of tuberculosis on subsequent health outcomes have also estimated elevated health-care use and mortality rates among people cured of tuberculosis compared with matched controls.[9–11] This collection of persistent sequelae—collectively known as post-tuberculosis lung disease—has drawn increasing scientific and policy attention.[12,13]

Mathematical modelling is commonly used to extrapolate from clinical studies to estimate long-term population-level outcomes,[14] with these analyses reproducing key features of tuberculosis epidemiology and natural history.[15,16] In many published tuberculosis models, active disease is represented by a single disease state, sometimes stratified to capture differences in diagnostic test results (eg, sputum-smear positivity). Moreover, most published models assume complete recovery after tuberculosis cure. Although simplifications are needed to render analyses tractable, if they produce a biased representation of underlying disease mechanisms it could produce incorrect policy conclusions (eg, misestimating intervention health effects or omitting important costs).[17] The potential biases produced by overly simplified modelling approaches have been shown previously for *M tuberculosis* infection.[16,18] It is unclear whether simplified models of

tuberculosis disease progression and post-tuberculosis sequelae affect the findings of these analyses.

In this study, we developed a novel model of tuberculosis progression, treatment, and long-term health outcomes among individuals with symptomatic tuberculosis disease, explicitly modelling the progressive lung damage caused by tuberculosis, the recovery of lung function during and after treatment, and how these processes are modified by the presence of comorbid HIV. We used this model to assess the long-term outcomes of tuberculosis diagnosis and treatment with detailed data on primary care attendees evaluated for tuberculosis in Uganda, Kenya, and South Africa—three settings with high rates of tuberculosis and HIV infection. We compared these results to those produced by traditional modelling representations of tuberculosis disease, to understand whether the different modelling approaches produce substantively different results.

Methods

Data sources

We constructed a study cohort representing individuals with symptomatic pulmonary tuberculosis presenting at routine health-care settings. This scenario represents the way most individuals with tuberculosis access treatment in low-income and middle-income settings. To do so, we obtained data on individuals evaluated for tuberculosis in a multicentre diagnostic accuracy study in Uganda, Kenya, and South Africa,[19] with this sample chosen to be representative of settings with a high burden of tuberculosis and HIV. This sample included primary health-care attendees aged 18 years or older who were evaluated for tuberculosis based on clinical suspicion. For participants determined to have tuberculosis via sputum culture, we extracted data on age, sex, and HIV status, and CD4 cell count if HIV positive. We used forced expiratory volume in 1 s (FEV_1; expressed as a percentage of mean values in the population) to quantify the extent of tuberculosis-related lung damage among individuals presenting for care.[8,20,21] As study data did not include FEV_1 values, we assigned FEV_1 values to participants based on published studies describing the distribution of FEV_1 among individuals with diagnosed tuberculosis. We reweighted trial data to match national tuberculosis notification data by age, sex, and HIV status,[22] and created an analytical cohort of 10 000 individuals per country (appendix p 5). This study was approved by the Institutional Review Board of the Harvard T H Chan School of Public Health.

Model design

We developed a Markov microsimulation model that tracks individuals in the analytical cohort over time to evaluate long-term health outcomes under multiple tuberculosis diagnosis and treatment scenarios (appendix p 2). The model was parametrised to represent each individual in the analytical cohort, and updated with a weekly timestep from model initiation until death. The appendix (pp 3–4) reports parameter values and sources, and full model details are given in the appendix (pp 17–26).

For lung function dynamics, we used changes in FEV_1 to track the evolution of tuberculosis-attributable lung damage for individuals with untreated tuberculosis disease, during tuberculosis treatment, and among individuals surviving the disease episode. In the model, FEV_1 was represented as an individual-level characteristic updated weekly for the remainder of the individual's lifetime. Changes in FEV_1 depended on tuberculosis disease status. For individuals with untreated tuberculosis disease, FEV_1 was assumed to decline linearly to a minimum value of 20%. FEV_1 was assumed to rebound for individuals starting tuberculosis treatment and then increase at a slower rate after the completion of treatment, to reach a final value calculated as a function of their minimum pre-treatment FEV_1 (appendix pp 15–16, 21–23). As a marker of tuberculosis disease severity, FEV_1 was assumed to affect multiple other health risks and outcomes, with lower FEV_1 associated with elevated tuberculosis and post-tuberculosis mortality rates, lower self-cure rates, and higher disability weights (indicating lower quality of life during tuberculosis infection and post-tuberculosis). In sensitivity analyses, we examined alternative assumptions regarding the proportion of pre-treatment FEV_1 decline attributable to tuberculosis.

We assumed some individuals with tuberculosis disease would self-cure in the absence of treatment. The self-cure rate was calculated as a function of HIV status, CD4 cell count, and FEV_1.

Individuals with untreated tuberculosis disease were assumed to seek diagnosis and treatment at a fixed rate, differentiated by antiretroviral therapy (ART) status. Individuals receiving tuberculosis treatment could complete the regimen (assumed to be the standard 6-month first-line regimen),[23] die during treatment, or be lost to follow-up before completion. For individuals lost to follow-up, we assumed that the probability of cure would depend on the timing of discontinuation, with a cure probability of 0% for individuals completing less than 8 weeks of the regimen.

For HIV natural history and treatment, the analytical cohort was subdivided by HIV status and receipt of ART. We assumed that individuals with undiagnosed HIV would be diagnosed as part of tuberculosis assessment and start ART. Individuals receiving ART were assumed to discontinue ART at a fixed rate, based on published rates of loss to follow-up for routine ART programmes. We used CD4 cell count as a marker of HIV-related immune function and modelled time-changes in CD4 cell count (differentiated by ART status) through approaches developed in previous modelling.[24] CD4 cell count was assumed to influence HIV-related and

See Online for appendix

tuberculosis-related mortality rates and the tuberculosis self-cure rate. For simplicity, we did not model future acquisition of HIV infection within the analytical cohort. For individuals receiving both ART and tuberculosis treatment, we assumed that discontinuation would be dependent: individuals lost to follow-up from one service would also discontinue the other service.

We used disability weights to quantify reductions in quality of life attributable to HIV, tuberculosis treatment, and post-tuberculosis lung damage. HIV disability weights were based on CD4 cell count and ART status. Tuberculosis and post-tuberculosis disability weights were based on FEV_1.

All-cause mortality rates were calculated as the sum of background and disease-specific mortality rates. Background mortality rates by sex, age, and country were based on tuberculosis-deleted and HIV-deleted life tables. Disease-specific mortality risks from HIV, tuberculosis treatment, and post-tuberculosis lung damage were calculated as a function of HIV and ART status, CD4 cell count, tuberculosis status, tuberculosis treatment status, and FEV_1 (appendix pp 17–20).

Analytical scenarios

We simulated outcomes for the analytical cohort under three scenarios: prompt tuberculosis treatment, as would result from a correct tuberculosis diagnosis (assuming a 2-week provider delay before the regimen is initiated); delayed tuberculosis treatment, as would result from an incorrect false-negative tuberculosis diagnosis, with the possibility that the individual would eventually return to care with ongoing symptoms (4·0 months [95% uncertainty interval 2·1–8·1] delay for individuals receiving ART, 7·5 months [3·6–15·5] delay for individuals not receiving ART); and no tuberculosis treatment, in which the individual never receives tuberculosis treatment despite ongoing symptoms. Under all scenarios, individuals with untreated tuberculosis (eg, with delayed treatment or after loss to follow-up) would have ongoing lung damage (quantified through FEV_1 reductions) until starting or restarting treatment, self-cure, or death. We also examined a no tuberculosis counterfactual scenario that simulated future health outcomes for the analytical cohort without tuberculosis disease, to calculate the incremental difference in life expectancy and other outcomes that is attributable to tuberculosis.

Alternative model specifications

We re-estimated study outcomes under three alternative model specifications, to test whether approaches to modelling lung function and post-tuberculosis sequelae affected study conclusions, as compared with earlier modelling approaches.

Alternative specification 1 assumed no post-tuberculosis sequelae. All modelling assumptions and parameter values matched the main analysis, except that individuals with tuberculosis were assumed to have immediate, complete, and permanent recovery of lung function after tuberculosis cure.

Alternative specification 2 assumed no progressive lung damage. All modelling assumptions and parameter values matched the main analysis, except that all parameters affected by progressive lung damage in tuberculosis patients (ie, tuberculosis-specific mortality rates, self-cure rates, and disability weights) were assumed fixed over time. We operationalised this by fixing FEV_1 at the mean starting value across all simulated individuals and holding it fixed at this value until tuberculosis cure or death.

Alternative specification 3 assumed no post-tuberculosis sequelae and no progressive lung damage. All modelling assumptions and parameter values matched the main analysis, except that individuals with tuberculosis were assumed to have no progressive lung damage (as in alternative specification 2), and individuals cured of tuberculosis were assumed to have immediate, complete, and permanent recovery of lung function (as in alternative specification 1).

Outcomes

Outcomes were the proportion dying with tuberculosis disease (deaths among individuals with untreated tuberculosis disease or while receiving tuberculosis treatment), 5-year survival, life expectancy, and disability-adjusted life-years (DALYs) lost. To calculate DALYs we summed the non-fatal health losses due to reduced quality of life (years lived with disability) and health losses from premature mortality (years of life lost) due to tuberculosis, and also decomposed total DALYs to report the DALYs accruing during the disease episode and the DALYs from post-tuberculosis sequelae.

Statistical analysis

We created probability distributions quantifying uncertainty in each parameter and used second-order Monte Carlo simulation to propagate this uncertainty through the analysis.[25] To do so, we sampled 1000 values from each probability distribution with a Latin hypercube sampling design, and re-estimated outcomes for each of these 1000 parameter sets. We used the distribution of results to calculate equal-tailed 95% uncertainty intervals and calculated partial rank correlation coefficients (PRCCs) describing the sensitivity of study outcomes to uncertainty in each parameter.[26] The model was programmed in R (version 4.3.2) and C++ with the Rcpp package (version 1.0.12).[27]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the overall cohort, 661 (55·1%) of 1199 people were male and 538 (44·9%) were female, mean age was

38 years (SD 12), and 588 (49·0%) of 1199 were living with HIV; of those with HIV, 498 (84·7%) were enrolled on ART. Mean FEV_1 was 63% (SD 16), and for individuals with HIV, the mean CD4 count was 400 cells per µL (301). Table 1 describes cohort characteristics by country. Cohort characteristics were reweighted to match the age, sex, and HIV distribution of tuberculosis notifications for each country (appendix p 5).

Figure 1 shows survival curves for people with and without HIV under each analytical scenario. For individuals without HIV, mean survival (from the beginning of the analysis) was 27·9 years (95% uncertainty interval 26·3–29·4) with prompt treatment, 24·9 years (21·5–27·5) with delayed treatment, and 12·0 years (9·8–14·4) with no treatment. Life expectancy estimates were lower for individuals living with HIV, with mean survival of 12·5 years (6·6–15·5) with prompt treatment, 10·7 years (5·8–13·6) with delayed treatment, and 3·3 years (2·2–4·2) with no treatment. Country-specific survival curves for each scenario are in the appendix (p 6).

Table 2 shows lifetime health outcomes for each scenario stratified by HIV status, and incremental differences in outcomes for each scenario as compared with individuals without tuberculosis (representing the health losses attributable to tuberculosis). For the overall cohort (combining people who are HIV positive and HIV negative), tuberculosis was estimated to reduce life expectancy by 5·1 years (95% uncertainty interval 3·8–6·4) with prompt treatment, 7·7 years (5·5–10·1) with delayed treatment, and 18·5 years (15·5–20·6) with no treatment. Total DALYs attributable to tuberculosis were estimated to be 11·4 years (8·9–14·2) with prompt treatment, 17·1 years (13·1–22·1) with delayed treatment, and 37·7 years (34·3–40·3) with no treatment. Table 2 also reports incremental differences in each health outcome for delayed treatment and no treatment compared with prompt treatment (representing the health losses resulting from a missed tuberculosis diagnosis). Compared with prompt tuberculosis treatment, life expectancy was reduced by 2·6 years (1·5–4·0) with delayed treatment and 13·4 years (11·2–15·0) with no treatment, and total DALYs attributable to tuberculosis increased by 5·7 years (3·5–8·6) with delayed treatment and 26·3 years (23·6–28·5) with no treatment. These outcomes are also stratified by country (appendix p 7).

Figure 2 reports tuberculosis-attributable DALYs disaggregated according to the form of health loss (reduced quality of life *vs* premature mortality) and when the health losses occur (during tuberculosis episode *vs* post-tuberculosis). These results show the distribution of DALYs to vary by scenario and by HIV status. The proportion of total DALYs accruing during the tuberculosis episode increased with greater delays to diagnosis and was higher for individuals with HIV infection, a consequence of higher tuberculosis case fatality in these situations. For the overall cohort, prompt

	Uganda, n=400	Kenya, n=399	South Africa, n=400
Sex			
Female	168 (42%)	163 (41%)	207 (52%)
Male	232 (58%)	236 (59%)	193 (48%)
Age, years	36 (11)	38 (12)	40 (13)
Living with HIV	214 (54%)	206 (52%)	168 (42%)
Receiving ART, among people with HIV	169/214 (79%)	187/206 (91%)	142/168 (85%)
CD4 cell count, cells per µL	455 (337)	364 (294)	372 (248)
FEV_1, %	63% (16)	62% (16)	63% (16)

Data are n (%), n/N (%), or mean (SD). ART=antiretroviral therapy. FEV_1=forced expiratory volume in 1 s.

Table 1: **Summary statistics of the study cohort**

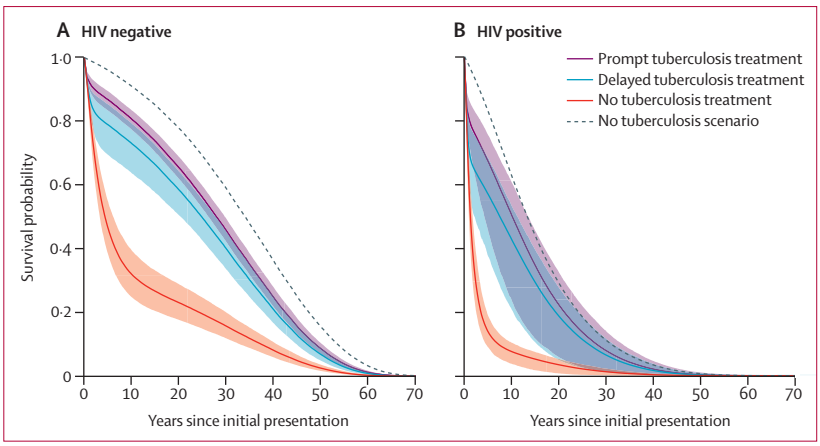

Figure 1: **Survival curves for individuals with symptomatic tuberculosis under prompt, delayed, and no treatment scenarios**

treatment resulted in 52·5% (95% uncertainty interval 41·9–62·5%) of DALYs accruing during the post-tuberculosis period (5·4 DALYs [95% uncertainty interval 4·0–7·2] during the tuberculosis episode *vs* 6·0 DALYs [4·1–8·0] post-tuberculosis). For the delayed treatment scenario, 42·7% (31·6–54·0%) of DALYs accrued during the post-tuberculosis period (9·8 DALYs [6·9–13·9] during the tuberculosis episode *vs* 7·3 DALYs [5·1–10·1] post-tuberculosis), and for the no treatment scenario the proportion was 9·1% (6·0–13·3%) post-tuberculosis (34·3 DALYs [30·7–37·2] during the tuberculosis episode *vs* 3·4 DALYs [2·3–5·0] post-tuberculosis). These outcomes are also presented stratified by HIV status in the appendix (p 8).

The main analysis reports results from a model that accounted for the dynamics of tuberculosis-associated lung damage and post-tuberculosis sequelae. Table 3 shows how major health outcomes changed under alternative model specifications used by earlier modelling studies (ie, not accounting for progressive tuberculosis lung damage or post-tuberculosis sequelae). In the specification that omitted post-tuberculosis sequelae (alternative scenario 1), estimated life expectancy was longer under each scenario (prompt, delayed, or no

	HIV negative			HIV positive		
	Prompt treatment	Delayed treatment	No treatment	Prompt treatment	Delayed treatment	No treatment
Life expectancy, years*						
Absolute value	27·9 (26·3–29·4)	24·9 (21·5–27·5)	12·0 (9·8–14·4)	12·5 (6·6–15·5)	10·7 (5·8–13·6)	3·3 (2·2–4·2)
Difference *vs* no tuberculosis scenario	6·2 (4·6–7·7)	9·2 (6·6–12·5)	22·0 (19·6–24·2)	3·3 (1·3–4·9)	5·2 (2·2–7·9)	12·5 (5·3–16·2)
Difference *vs* prompt treatment	0·0 (ref)	3·0 (1·5–5·2)	15·8 (14·1–17·9)	0·0 (ref)	1·9 (0·7–3·5)	9·2 (4·1–11·8)
5-year survival, %†						
Absolute value	86·9% (83·5–89·5)	79·0% (69·6–85·4)	47·0% (38·8–55·3)	67·4% (46·0–75·6)	57·1% (37·8–68·3)	14·1% (9·1–19·3)
Difference *vs* no tuberculosis scenario	9·3% (6·6–12·6)	17·1% (10·8–26·5)	49·2% (41·0–57·3)	15·7% (9·1–21·5)	26·1% (14·8–38·1)	69·1% (43·5–77·2)
Difference *vs* prompt treatment	0·0 (ref)	7·9% (3·6–14·6)	39·9% (33·5–46·5)	0·0 (ref)	10·3% (4·7–19·0)	53·3% (34·8–59·5)
Tuberculosis-attributable deaths, %						
Absolute value‡	8·8% (6·0–12·3)	17·0% (10·3–27·3)	67·6% (60·0–75·1)	20·2% (14·1–27·5)	32·8% (22·3–47·2)	90·6% (87·8–93·3)
Difference *vs* prompt treatment	0·0 (ref)	8·2% (3·8–15·6)	58·9% (52·6–65·5)	0·0 (ref)	12·6% (6·4–22·2)	70·4% (64·3–75·2)
DALYs due to tuberculosis						
Absolute value‡	11·7 (8·6–14·7)	17·0 (12·2–23·4)	36·2 (32·9–39·4)	11·1 (7·9–14·2)	17·3 (12·1–23·4)	40·3 (34·4–42·4)
Difference *vs* prompt treatment	0·0 (ref)	5·4 (2·7–9·2)	24·6 (22·1–27·2)	0·0 (ref)	6·2 (3·2–10·6)	29·2 (25·2–31·6)

Data are model outputs (95% uncertainty intervals). DALYs=disability-adjusted life-years. *Life expectancy under the no tuberculosis counterfactual scenario was 34·0 years (95% uncertainty interval 33·8–34·3) among HIV-negative patients and 15·8 years (7·9–19·8) among HIV-positive patients. †5-year survival for the no tuberculosis counterfactual scenario was 96·2% (95·8–96·5%) among HIV-negative patients, and 83·2% (54·3–90·5%) among HIV-positive patients. ‡As tuberculosis-attributable deaths and DALYs are 0 under the no tuberculosis counterfactual scenario, the absolute value of these outcomes is the same as the difference *vs* the no tuberculosis counterfactual scenario.

Table 2: **Summary health outcomes under prompt, delayed, and no treatment scenarios, stratified by HIV status**

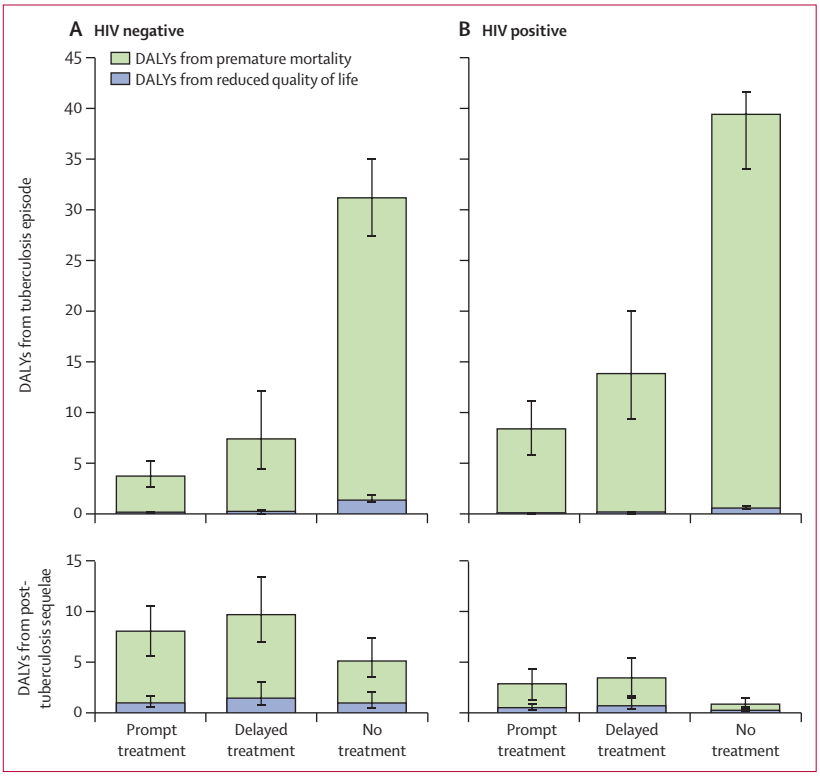

Figure 2: **DALYs attributable to tuberculosis disease for each scenario by HIV status**
DALYs are stratified by whether DALYs resulted from reduced quality of life or premature mortality and by whether DALYs occurred during the tuberculosis episode or after tuberculosis cure. Bars represent 95% uncertainty intervals. DALYs were calculated by comparing each scenario to a no tuberculosis counterfactual scenario. Numerical results for plotted values are shown in the appendix (p 8). DALYs=disability-adjusted life-years.

treatment) than in the main analysis. For these model specifications, the estimated reduction in life expectancy caused by tuberculosis was substantially lower (8–53% lower) than estimated in the main analysis. For the specification that omitted tuberculosis disease progression (alternative scenario 2), estimates of the additional life expectancy loss with delayed or no tuberculosis treatment (*vs* prompt treatment) were substantially lower (56–67% lower) than estimated in the main analysis. In alternative specification 3 (omitting both post-tuberculosis sequelae and tuberculosis disease progression) most outcomes differed substantially from the results of the main analysis, with estimates of tuberculosis-attributable reductions in life expectancy 51–55% lower across scenarios, and estimates of the additional life expectancy loss from delayed or no tuberculosis treatment (*vs* prompt treatment) reduced by 50–62%.

Estimates of tuberculosis-attributable DALYs showed similar changes under the alternative model specifications. Compared with the main analysis, alternative specification 3 (omitting both post-tuberculosis sequelae and tuberculosis disease progression) produced estimates of tuberculosis-attributable DALYs that were 48–57% lower across scenarios, and with the estimated DALYs resulting from delayed or no tuberculosis treatment (*vs* prompt treatment) reduced by 45–64%.

PRCCs describing the relative sensitivity of results to changes in individual parameters are reported in the appendix (pp 9–10). For total tuberculosis DALYs under the prompt treatment scenario, the most influential parameters were the extent of FEV_1 recovery after

	Prompt treatment		Delayed treatment		No treatment	
	Estimate	Percent change *vs* main analysis	Estimate	Percent change *vs* main analysis	Estimate	Percent change *vs* main analysis
Life expectancy, years						
Main analysis						
Absolute value	22·1 (19·7 to 23·8)	0%	19·5 (17·0 to 21·6)	0%	8·8 (7·2 to 10·5)	0%
Reduction due to tuberculosis	5·1 (3·8 to 6·4)	0%	7·7 (5·5 to 10·1)	0%	18·5 (15·5 to 20·6)	0%
Reduction compared with prompt treatment	0·0 (ref)	0%	2·6 (1·5 to 4·0)	0%	13·4 (11·2 to 15·0)	0%
Alternative specification 1 (no post-tuberculosis sequelae)						
Absolute value	24·8 (22·4 to 26·3)	12·2% (8·3% to 16·3%)	22·7 (20·0 to 24·6)	16·3% (10·9% to 21·8%)	10·2 (8·3 to 12·2)	16·8% (12·3% to 21·9%)
Reduction due to tuberculosis	2·4 (1·6 to 3·3)	52·8% (41·8% to 62·7%)	4·5 (2·9 to 7·0)	41·6% (29·9% to 52·8%)	17·0 (14·0 to 19·3)	8·0% (5·2% to 11·3%)
Reduction compared with prompt treatment	0·0 (ref)	..	2·1 (1·1 to 3·6)	19·3% (9·7% to 29·2%)	14·6 (12·2 to 16·4)	–9·0% (–13·6% to -4·8%)
Alternative specification 2 (no tuberculosis disease progression)						
Absolute value	22·4 (20·3 to 23·8)	1·5% (–1·9% to 5·0%)	21·6 (19·3 to 23·0)	10·6% (4·1% to 19·3%)	16·5 (14·7 to 18·3)	89·6% (71·8% to 107·8%)
Reduction due to tuberculosis	4·8 (3·8 to 5·7)	5·6% (–10·4% to 17·9%)	5·6 (4·4 to 6·9)	25·9% (14·1% to 35·7%)	10·7 (8·3 to 12·7)	42·3% (37·0% to 47·5%)
Reduction compared with prompt treatment	0·0 (ref)	..	0·9 (0·5 to 1·5)	66·6% (60·4% to 72·5%)	5·9 (4·3 to 7·4)	56·0% (49·5% to 62·4%)
Alternative specification 3 (no post-tuberculosis sequelae and no tuberculosis disease progression)						
Absolute value	24·9 (22·5 to 26·3)	12·7% (7·6% to 18·0%)	23·9 (21·5 to 25·4)	22·7% (14·1% to 33·1%)	18·2 (16·1 to 20·1)	108·9% (88·8% to 129·6%)
Reduction due to tuberculosis	2·3 (1·6 to 3·0)	54·7% (41·5% to 65·1%)	3·3 (2·3 to 4·5)	57·1% (47·5% to 65·3%)	9·0 (6·6 to 11·1)	51·4% (44·6% to 58·1%)
Reduction compared with prompt treatment	0·0 (ref)	..	1·0 (0·5 to 1·7)	61·9% (55·6% to 68·1%)	6·7 (5·0 to 8·4)	50·1% (42·7% to 57·0%)
DALYs due to tuberculosis						
Main analysis						
Absolute value*	11·4 (8·9 to 14·2)	0%	17·1 (13·1 to 22·1)	0%	37·7 (34·3 to 40·3)	0%
Reduction compared with prompt treatment	0·0 (ref)	0%	5·7 (3·5 to 8·6)	0%	26·3 (23·6 to 28·5)	0%
Alternative specification 1 (no post-tuberculosis sequelae)						
Absolute value	5·3 (4·1 to 7·3)	51·5% (41·1% to 61·6%)	9·9 (7·0 to 14·0)	42·1% (30·9% to 53·4%)	34·4 (30·8 to 37·2)	9·0% (5·9% to 13·2%)
Reduction compared with prompt treatment	0·0 (ref)	..	4·4 (2·6 to 7·0)	23·0% (12·1% to 36·9%)	28·8 (25·9 to 31·4)	–9·5% (–14·9% to -4·6%)
Alternative specification 2 (no tuberculosis disease progression)						
Absolute value	10·8 (8·6 to 12·8)	5·3% (-11·6% to 18·4%)	12·5 (10·0 to 15·0)	26·3% (14·6% to 35·9%)	23·5 (19·8 to 26·6)	37·9% (32·9% to 43·3%)
Reduction compared with prompt treatment	0·0 (ref)	..	1·8 (1·0 to 2·9)	69·1% (62·1% to 76·5%)	12·7 (10·3 to 15·1)	51·9% (45·4% to 58·1%)
Alternative specification 3 (no post-tuberculosis sequelae and no tuberculosis disease progression)						
Absolute value	5·3 (4·1 to 6·6)	53·7% (40·9% to 64·3%)	7·3 (5·4 to 9·6)	57·2% (47·4% to 66·1%)	19·8 (16·2 to 23·3)	47·5% (41·1% to 53·7%)
Reduction compared with prompt treatment	0·0 (ref)	..	2·0 (1·2 to 3·4)	64·3% (57·5% to 71·7%)	14·6 (11·8 to 17·3)	44·7% (37·1% to 51·8%)

Data are model outputs (95% uncertainty intervals) or percentage change (95% uncertainty interval percentage change). DALYs=disability-adjusted life-years. *As tuberculosis-attributable DALYs are 0 under the no tuberculosis counterfactual scenario, the absolute values of these outcomes are the same as the difference *vs* the no tuberculosis counterfactual scenario.

Table 3: **Summary health outcomes under prompt, delayed, and no treatment scenarios for alternative model specifications compared with the main analysis**

tuberculosis cure (PRCC –0·66), the probability of loss to follow-up from ART (0·47), and the HIV-specific mortality rate on ART (0·46). For the increase in DALYs with delayed treatment (*vs* prompt treatment), the most influential parameters were the rate of care-seeking for individuals with untreated tuberculosis off ART (–0·92), the rate of care-seeking for individuals with untreated tuberculosis on ART (–0·86), and the extent of FEV_1 recovery after tuberculosis cure (–0·51). In a sensitivity analysis that assumed a proportion (27%; 95% uncertainty interval 21%–37%) of the initial FEV_1 loss was attributable to non-tuberculosis causes (equivalent to a pre-tuberculosis FEV_1 of 90%), the estimated DALYs and life expectancy reductions attributable to tuberculosis were smaller for all scenarios (appendix p 11), with this reduction more pronounced for post-tuberculosis DALYs versus DALYs accruing during the tuberculosis episode (appendix p 12).

Discussion

In this study, we estimated the lifetime health losses caused by tuberculosis among individuals attending

routine tuberculosis diagnosis in settings with high levels of coprevalent HIV. We estimated these outcomes with a novel mathematical model of tuberculosis progression and treatment that incorporates a growing understanding of the progressive lung damage caused by tuberculosis and the health consequences of post-tuberculosis sequelae among people cured of tuberculosis.

Our results show substantial reductions in life expectancy associated with tuberculosis. Even with prompt treatment, individuals with tuberculosis had a reduction in life expectancy of 5 years. Delayed treatment, as can result from a missed tuberculosis diagnosis or loss to follow-up, increased the loss in life expectancy by approximately 50%, highlighting the urgency of prompt diagnosis treatment initiation and continuity of care. Estimated DALYs (capturing the effect of tuberculosis on both mortality and quality of life) showed similar results and revealed the extent of health losses associated with post-tuberculosis sequelae. These post-tuberculosis health losses were particularly large for individuals with delayed diagnosis, reflecting the additional lung damage associated with a prolonged duration of disease. The magnitude of these post-tuberculosis health losses are consistent with global estimates[28] published in 2021 and empirical estimates for Malawi[29] that point to substantial ongoing morbidity and elevated mortality among people cured of tuberculosis.

Similar to the main analysis, the alternative modelling approaches we examined found that life expectancy was shorter (and tuberculosis-attributable DALYs greater) with increasing delays to diagnosis, and for individuals with HIV compared with those without HIV. However, the magnitude of these estimates was starkly different, with the results of the alternative specifications (reflecting earlier modelling approaches) suggesting smaller effects of tuberculosis on life expectancy and DALYs. These differences in the estimated magnitude of health effects could be consequential for policy analyses, as they suggest that the health gains achieved by preventing tuberculosis could be substantially greater than indicated in earlier analyses. Similarly, the health gains produced by interventions that achieve prompt treatment for individuals with symptomatic disease could be greater than previously thought. Future economic evaluations taking account of our results would probably find greater cost-effectiveness for interventions that prevent tuberculosis or that achieve earlier treatment initiation, due to the greater health losses that these interventions avert, and possibly due to reductions in health-care resources devoted to post-tuberculosis sequelae.

This study has several limitations. First, the modelled analyses used to project lifetime health consequences relied on several assumptions (in particular, the long-term causal effects of tuberculosis under different treatment scenarios) that are difficult to verify empirically. However, quasiexperimental studies are starting to generate evidence supporting the magnitude of post-tuberculosis health effects.[10,11,30] These studies are valuable, yet more are needed (and with larger cohorts) to understand how post-tuberculosis health consequences vary across settings and under different treatment conditions. Second, this study examined only a small number of scenarios, reflecting the potential effect of delays in tuberculosis treatment or poor access to treatment. Although these results have clear relevance for programme strategy, additional analyses will be needed to assess the health effect of interventions designed to increase the timeliness and coverage of tuberculosis treatment, taking account of the specific health benefits that can be achieved by the intervention and the costs. Moreover, new interventions could allow for greater recovery of lung function during tuberculosis treatment or better rehabilitation for people cured of tuberculosis, reducing the long-term health consequences of tuberculosis compared with those estimated in this analysis.[31–33] Third, this analysis did not consider the consequences of secondary tuberculosis cases resulting from ongoing *M tuberculosis* transmission by individuals with an extended duration of untreated disease. Although there is little evidence on the number of secondary cases that result from delayed diagnosis, the inclusion of these outcomes would only increase the health benefits estimated with earlier treatment initiation. Fourth, we did not consider tuberculosis drug resistance in our analysis. Individuals with multidrug resistant tuberculosis have been found to have worse treatment outcomes[34,35] and poorer lung function after tuberculosis cure,[8] and therefore can have greater tuberculosis-associated DALYs than estimated in our analysis.[36] Fifth, although we used FEV_1 to track tuberculosis-attributable lung damage, it will not fully capture the range of lung changes and sequelae associated with tuberculosis. Tracking multiple measures of lung performance could provide richer projections of future lung health. Sixth, we used CD4 cell count to track HIV-related changes in immune function and did not consider viral load, although viral load could predict tuberculosis risk independent of CD4 cell count.[37] Seventh, our analyses were done for three settings with high rates of tuberculosis and HIV burden, and with notable gaps in health-care access. Results will probably be different for other settings, and results should be generalised with caution.

Despite these limitations, our analysis shows the implications of new natural history evidence on tuberculosis lung damage and post-tuberculosis sequelae for the lifetime health consequence caused by tuberculosis, and the timeliness of tuberculosis diagnosis. To our knowledge, this study is the first to assess the implications of delayed diagnosis for the long-term outcomes of tuberculosis disease, accounting for ongoing lung damage and post-tuberculosis sequelae.

Analyses for tuberculosis health burden and the effect of tuberculosis interventions should take account of these factors to capture the full consequences of tuberculosis during the life course of affected individuals.

Contributors

Conceptualisation: NAM and MHC. Methodology: MHC, SS, BWA, SED, TC, and NAM. Data curation and analysis: MHC. Writing (original draft): MHC. Writing (review and editing): MHC, SS, BWA, SED, TC, and NAM. NAM, MHC, and SED had access to the data. MHC and NAM have directly accessed and verified the underlying data reported in the manuscript. All authors were responsible for the decision to submit the manuscript.

Declaration of interests

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Data sharing

Data to create the initial study population were derived from a randomised trial in Kenya, Uganda, and South Africa (Dorman and colleagues, 2018)[19] and can be obtained by contacting the authors of this study. All other data were extracted from publicly available sources. Analytical code is available upon request to the corresponding author.

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