



Benefit of treatment of latent tuberculosis infection in individual patients

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ABSTRACT We aimed to develop a decision aid that estimates whether treatment of latent tuberculosis infection (LTBI) is likely to have a net gain in quality-adjusted life-years for an individual.

A Markov model was developed which incorporated personalised estimates for risk of tuberculosis (TB) reactivation, TB death, quality-of-life impairments and treatment side-effects. The net effect of LTBI treatment was quantified in terms of quality-adjusted life-years gained or lost. Analyses were conducted for a representative set of hypothetical patients.

LTBI treatment was estimated to be beneficial when the annual risk of TB reactivation exceeded 13/100 000 to 93/100 000 for females aged 10–75 years and 15/100 000 to 119/100 000 for males aged 10–75 years; the numbers needed to treat to avoid one case of TB were 93, 77, 85 and 72, respectively, at these threshold levels.

LTBI treatment was estimated to confer a positive net benefit across a broad range of patients with characteristics typically seen in a low incidence setting for TB. Use of the decision aid has the potential to facilitate and increase confidence with LTBI treatment decisions by providing clinicians and patients with personalised estimates of likely net benefit.



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Personalised analysis showed that most people with latent tuberculosis infection benefit from preventive treatment <http://ow.ly/PDn6W>

This article has supplementary material available from erj.ersjournals.com

Received: April 12 2015 | Accepted after revision: June 24 2015 | First published online: Sept 24 2015

Conflict of interest: None declared.

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Introduction

The World Health Organization (WHO), supported by the European Respiratory Society (ERS), recently published an action framework for countries with a low incidence of tuberculosis (TB) that identified treatment of latent tuberculosis infection (LTBI) as key strategy to achieve TB elimination [1]. In order to achieve this ambitious goal it will be necessary to combine reducing primary transmission of *Mycobacterium tuberculosis* by prompt case-finding and treatment of infectious TB cases with targeted treatment of LTBI [2, 3].

In clinical practice, physicians must decide whether the potential benefit of LTBI treatment outweighs its risks at the individual patient level. This in turn requires an appraisal of what the net benefit is likely to be for individuals based on their personal risk–benefit profile. The long duration of LTBI treatment, lack of symptoms from LTBI, a good chance that LTBI may never develop into TB disease and potential side-effects of LTBI treatment are potential barriers to prescription and uptake of treatment of LTBI. In a study in the USA and Canada, 17% of those who were offered treatment for LTBI declined to accept it. The study found that among healthcare workers, 52% rejected treatment [4]. Another American study also showed poor uptake of treatment for LTBI among healthcare workers, possibly suggesting that they might have some doubts about whether treatment of LTBI is beneficial to them personally [5].

A number of decision analyses have examined treatment recommendations for LTBI in different population groups, weighing the risk of isoniazid-induced hepatitis against the benefit of reducing the risk of developing active TB. However, these studies were not designed to tailor the LTBI treatment decision to individual patients and thus ignored a range of pertinent factors [6–13]. These factors include the positive and negative predictive value of the tuberculin skin test (TST) or an interferon- γ release assay (IGRA), as well as factors that influence the risk of reactivation of TB and the risk of adverse effects of treatment with isoniazid [14].

The issue of personalised TB risk estimates was addressed by a group from McGill University (Montreal, Canada), who developed a web-based calculator which allows the user to estimate an individual's risk of reactivation of TB based on a positive predictive value for a TST or IGRA as well as sociodemographic and medical risk factors [15]. However, this calculator did not include important downstream events (consequences of TB and effectiveness of treatment for LTBI) and did not weigh the benefit of treatment of LTBI against the potential risk of adverse effects in order to enable clinicians to make an individually tailored treatment decision.

The aim of this study was to develop a novel personalised decision aid that estimates whether treatment of LTBI is likely to have a net benefit for an individual and which can be used as a point-of-care decision aid for clinicians. The wider goal was to overcome some of the barriers to prescription and uptake of treatment of LTBI described earlier by providing individualised information for physicians and patients to complement the public health perspective.

Methods

A decision analysis was constructed that estimated the net impact of LTBI treatment on quality-adjusted life-years (QALYs) for a range of individual risk profiles. In each analysis, the mid-point estimate for the net gain or loss in quality-adjusted life expectancy achieved by treating LTBI was used to determine whether treatment for LTBI or no treatment was the recommended option in an individual patient.

The analysis model comprised a decision tree (fig. 1) that reflected the alternative strategies (treatment or not) and the short-term outcomes (*e.g.* LTBI treatment side-effects), and a Markov process (fig. 2) that modelled the longer-term outcomes (*e.g.* TB reactivation) over a lifetime horizon. The Markov process modelled a patient's experience as a sequence of individual health states occurring over a series of discrete time periods, or cycles, each lasting 12 months. The simulated patient begins the process at cycle 1 in one of the five possible health states (fig. 2). The likelihood of moving from one state to another at the conclusion of each cycle was defined by a series of transition probabilities (table 1). Possible transitions between health states are shown in figure 2. The analysis was developed using TreeAge Pro 2014 (TreeAge Software Inc., Williamstown, MA, USA).

Each health state was assigned a utility value on a scale from 0 (death) to 1 (perfect health). Patients were credited with this incremental utility for each cycle they spent in a specific health state to derive a total QALY value at the conclusion of the Markov process. Utilities for uncomplicated treatment of LTBI, for an episode of active TB and for the post-TB state were derived from studies that used health-related quality-of-life (HRQoL) instruments (table 2). Additional information on utilities used in the decision aid, in particular relating to the post-TB state can be found in the online supplementary material.

The threshold values for annual risks of active TB above which treatment for LTBI was favoured were defined as annual risk of TB reactivation at which treatment for LTBI resulted in a gain of QALY >0, however small.

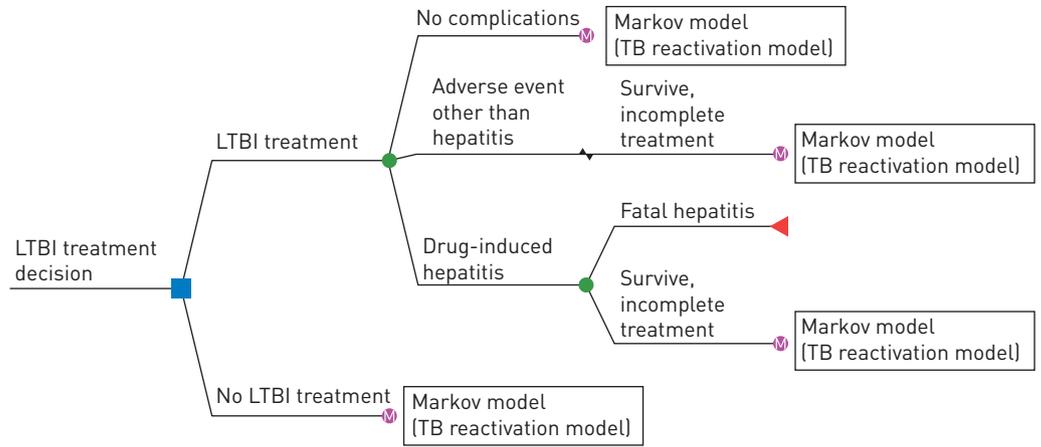


FIGURE 1 Decision tree for the complications of isoniazid treatment. LTBI: latent tuberculosis infection; TB: tuberculosis.

Supplemental metrics derived for information purposes (but not impacting on the treatment decision) included the number of patients needed to treat (NNT) to gain one QALY, NNT to avoid one case of TB, NNT to avoid one TB death, NNT for one episode of drug-induced hepatitis and NNT for one death from drug-induced hepatitis.

One-way sensitivity analyses were used to explore the influence of plausible uncertainty in the parameter estimates (*i.e.* probabilities and utilities) on the decision to treat or not to treat LTBI. Additionally, we conducted probabilistic sensitivity analyses with a subset of the most influential parameters in which they were allowed to vary simultaneously according to a specified set of probability distributions (tables 1 and 2).

The following simplifying assumptions were made for the purpose of this model. 1) Patients only develop active TB once (no recurrent episodes); 2) an episode of active TB is treated for 6 months with first-line treatment (not multidrug-resistant (MDR)-TB); 3) patients are not re-infected with TB; and 4) patients who developed an adverse event severe enough to require hospitalisation would not recommence isoniazid treatment and this would in turn reduce the effectiveness of treatment on TB rates.

Probabilities and relative risks

Table 1 shows the probabilities and relative risks used in the decision model, their plausible range evaluated in the sensitivity analyses, and sources of these estimates. The latest USA age- and sex-specific life tables were used to estimate the background risk of death from other causes [27]. Information on probabilities and relative risks is outlined below and in the online supplementary material.

Risk of developing TB

Estimates for the annual risk of developing active TB were based on a formula/online calculator for personalised TB risk estimates published by MENZIES *et al.* [15]. The calculator estimated the annual risk of

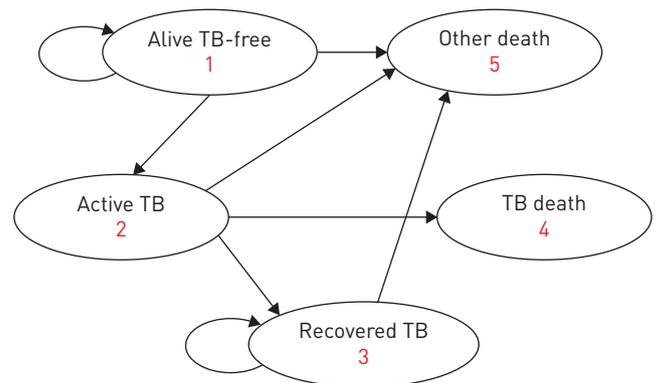


FIGURE 2 Markov model (tuberculosis [TB] reactivation model).

TABLE 1 Probabilities (per person per year) and relative risks used in the decision model

	Base value	Range for one-way sensitivity analysis	Distribution for probabilistic sensitivity analysis	Source
Risk of developing active TB				
Baseline risk	0.001	0.00065–0.005	Individual risk estimates calculated for every case	COMSTOCK <i>et al.</i> [16]
Risk for TB contacts during the first 2 years	0.05 for 2 years	0.0325–0.25 for 2 years	Individual risk estimates calculated for every case	0.00065: TST converters, after 2 years [17] 0.05: risk for TB contacts with TST \geq 10 mm during the first 2 years [18, 19]
TB case fatality rate (primary cause and contributory)				
0–19 years	0.01 (p1)	Sensitivity analysis range for p1=0.005–0.02	Distribution of p1: β 0.01 \pm 0.001 Low (2.5th percentile): 0.008124227 High (97.5th percentile): 0.012056	WALPOLA <i>et al.</i> [20] Range for sensitivity analysis: 50–200% of base estimate
20–49 years	0.036 (p1 \times 3.6)			
50–64 years	0.048 (p1 \times 4.8)			
65–74 years	0.112 (p1 \times 11.2)			
\geq 75 years	0.303 (p1 \times 30.3)			
Isoniazid-induced hepatitis requiring hospital admission				
\leq 35 years	0.000994915 (p2)	Sensitivity analysis range for p2=0.0004974575–0.0019898300	Distribution of p2: β 0.0009949155 \pm 0.00035 Low (2.5th percentile): 0.000430165 High (97.5th percentile): 0.001791393	SMITH <i>et al.</i> [21] Range for sensitivity analysis: 50–200% of base estimate
36–50 years	0.001776549 (p2 \times 1.7856289)			
51–65 years	0.006493506 (p2 \times 6.526793)			
>65 years	0.023920653 (p2 \times 24.04327)			
Hepatitis case fatality rate				
All ages	0.0085	0.00425–0.017	β -distribution 0.0085 \pm 0.003 Low (2.5th percentile): 0.003670959 High (97.5th percentile): 0.015292	SMITH <i>et al.</i> [21] for estimate of hepatitis cases MILLARD <i>et al.</i> [22] for estimate of hepatitis deaths in isoniazid recipients Range for sensitivity analysis: 50–200% of base estimate
Isoniazid-associated adverse events other than hepatitis requiring hospital admission				
\leq 35 years	0.001768738 (p3)	Sensitivity analysis range for p3=0.000884369–0.003537475	Distribution of p3: β 0.001768738 \pm 0.00055 Low (2.5th percentile): 0.000858887 High (97.5th percentile): 0.002994176	SMITH <i>et al.</i> [21] Range for sensitivity analysis: 50–200% of base estimate
36–50 years	0.005527043 (p3 \times 3.124851954)			
51–65 years	0.010552 (p3 \times 5.965808)			
>65 years	0.027421237 (p3 \times 15.5032818)			

Continued

TABLE 1 Continued

	Base value	Range for one-way sensitivity analysis	Distribution for probabilistic sensitivity analysis	Source
Relative risk of TB with a 6-month course of LTBI treatment				
All ages	Relative risk reduction of 56%=0.44 (relative risk)	0.27–0.73	β -distribution 0.44±0.125 Low (2.5th percentile): 0.21394 High (97.5th percentile): 0.68223	SMIEJA <i>et al.</i> [23] Range for sensitivity analysis: 95% confidence intervals in the original dataset
Relative risk of TB with LTBI treatment prematurely ceased due to hepatitis				
All ages	0.84 (relative risk reduction of 16%)	0.42–1.68	β -distribution with 0.84±0.18 Low (2.5th percentile): 0.41628 High (97.5th percentile): 0.99906	ROSE <i>et al.</i> [6] Range for sensitivity analysis: 50–200% of base estimate

Data are presented as mean±SD unless otherwise stated. TB: tuberculosis; LTBI: latent tuberculosis infection; TST: tuberculin skin test.

TABLE 2 Utilities used in the decision model

	Base value	Range for one-way sensitivity analysis	Distribution for probabilistic sensitivity analysis	Duration	Source
QoL during LTBI treatment	0.975	0.85–1.0	β 0.975±0.045 Low (2.5th percentile): 0.85 High (97.5th percentile): 1.00	6 months	DION <i>et al.</i> 2004 and 2002 [24, 25] Range of sensitivity analysis: clinical judgement
QoL during episode of drug-induced hepatitis[#]	0.667	0.4–0.8	β 0.667±0.08 Low (2.5th percentile): 0.50 High (97.5th percentile): 0.81	2 months (if patient survives), for 1 month (if patient dies)	SADATSAFARI <i>et al.</i> 2013 [11] Range of sensitivity analysis: clinical judgement
QoL during (treatment for) active TB	0.827	0.50–0.98	β 0.827±0.12 Low (2.5th percentile): 0.55 High (97.5th percentile): 0.98	6 months if patient survives 3 months if patient dies	AWAISU <i>et al.</i> 2012 [26] mean value interview 1–3 Range of sensitivity analysis: clinical judgement
QoL after successful TB treatment (pulmonary impairment after TB)	0.975	0.85–1.0	β 0.975±0.045 Low (2.5th percentile): 0.85 High (97.5th percentile): 1.00	Remainder of lifetime	DION <i>et al.</i> 2002 [25] Range of sensitivity analysis: clinical judgement

Data are presented as mean±SD unless otherwise stated. QoL: quality of life; LTBI: latent tuberculosis infection; TB: tuberculosis. [#]: median interval from treatment initiation to symptom onset in hepatitis was 16 weeks [22].

TB disease as a function of the TST result, the annual risk of TB in the population and the relative risk for specific risk factors [15, 19]. For known contacts of patients with active TB a higher risk of developing TB was assumed for the first 2 years after infection [19].

Mortality associated with TB

Age-stratified TB case-fatality ratios from an Australian study were used for the decision aid. The case-fatality rate among young adults and middle-aged people in this study was comparable to the case-fatality rates in a recent meta-analysis which mainly included studies on patients with TB aged 20–40 years (but did not provide age-stratified data) [28]. The population in the source study was representative of a setting with a low TB incidence, a low rate of HIV co-infection and a low rate of MDR-TB.

Risk of adverse events associated with isoniazid treatment

Estimates for significant adverse events associated with treatment of LTBI were based on a Canadian cohort study of 9145 patients on LTBI treatment who had 121 acute hospitalisations for adverse events associated with treatment of LTBI. 45 (37%) events were related to drug-induced hepatitis; the remaining adverse events were gastrointestinal, haematological, allergy or poisoning, based on International Classification of Diseases (ICD)-9 codes [21].

Mortality associated with isoniazid-induced hepatitis

The case-fatality rate among patients with isoniazid-induced hepatitis was calculated as the total mortality rate due to isoniazid-induced hepatitis divided by the incidence of isoniazid-induced hepatitis. For the former we used a value of 4.2 per 100 000 persons beginning isoniazid therapy for LTBI in the USA [22]. The estimated incidence of isoniazid-induced hepatitis requiring hospitalisation was 492 per 100 000 persons on isoniazid therapy, based on data from SMITH *et al.* [21]. Hence, the case-fatality rate among people with isoniazid-induced hepatitis requiring hospitalisation was 0.0085.

Effectiveness of treatment for LTBI

The relative risk reduction estimate for a 6-month course of treatment was derived from a Cochrane review on the effectiveness of isoniazid in preventing the development of TB [23]. The systematic review found a relative risk of 0.44 (95% CI 0.27–0.73) in people that took isoniazid for 6 months [23]. For the purpose of the model, we assumed that any adverse event severe enough to require hospitalisation would lead to cessation of isoniazid treatment in the 12th week of therapy, resulting in an effectiveness of 16% [6].

Results

LTBI treatment was favoured over a wide range of values for risk of progressing to active disease, age and sex. The threshold values for annual risks of active TB above which treatment for LTBI resulted in a gain of QALYs, stratified by age and sex, with and without assumption of post-TB long-term impairment, are shown in figure 3. The thresholds for patients' individual annual risk of developing active TB above which treatment of LTBI was beneficial increased with age and were higher in males than females. The threshold values for the annual risk of active TB above which treatment for LTBI was beneficial ranged from 13/100 000 to 93/100 000 for females aged 10–75 years and from 15/100 000 to 119/100 000 for males aged 10–75 years. At age ≥ 80 years the treatment thresholds rapidly increased.

Sensitivity analysis

The factor that most strongly influenced the effect of treatment *versus* no treatment of LTBI on expected change in cumulative QALYs was an individual's underlying risk of developing TB. The next most influential factors were the utility assigned to the post-TB state, the utility assigned to uncomplicated treatment for LTBI and the estimate for effectiveness of treatment for LTBI in reducing the risk of developing active TB. Figure 4 shows the difference in QALYs when each of the parameters was varied through its plausible range in sensitivity analysis for the example of a 20-year-old male.

Assuming that patients return to perfect health once they have recovered from TB increased the threshold for the annual risk of active TB above which LTBI treatment was favoured (fig. 3). If we did not incorporate the negative impact of (uncomplicated) treatment of LTBI and of past (recovered or cured) TB on HRQoL, the threshold for the annual risk of active TB above which LTBI treatment was beneficial was lower compared to when HRQoL adjustments were used for both health states. In other words, the use of HRQoL adjustments in the model tended to shift the outcomes towards “no treatment” as a preferred strategy. Online supplementary figure E-1 shows the impact that discounting of future events would have on treatment thresholds.

Case studies of benefits and risks of LTBI treatment

We analysed various clinical scenarios to demonstrate the use of the decision aid for patient-tailored treatment decisions (online supplementary tables E-1A–E). To illustrate how the decision aid works, we describe the case of a 45-year-old woman, born in the Philippines, who immigrated to the USA at the age of 44 years, has a TST of 11 mm, her bacille Calmette–Guerin vaccination status is unknown, her chest radiograph is clear and she has diabetes mellitus. Based on this profile, her annual risk of TB is 270/100 000. The decision aid recommendation is to treat LTBI. The probabilistic sensitivity analysis shows that treatment of LTBI is the preferred strategy in 99% of simulations in which sets of parameter values are randomly selected from their respective uncertainty distributions. The mid-point estimate for the net gain in quality-adjusted life expectancy achieved by treating LTBI, compared with not treating LTBI, is 45 days, and thus the benefit of LTBI treatment outweighs the risk in this patient. The number of similar patients needed to treat to gain 1 QALY is nine, the NNT to avoid one case of TB is 10, the NNT to avoid one death from TB is 141, the NNT to cause one episode of severe isoniazid-induced hepatitis is 316 and the NNT to cause one death from drug-induced hepatitis is 38462.

The case studies (online supplementary tables E-1A–E) illustrate that, in a diverse range of clinical scenarios in which treatment for LTBI might be considered, treatment for LTBI is estimated to result in a net gain in expected cumulative QALYs.

Discussion

The decision aid presented here is designed to assist clinicians with deciding whether or not to recommend initiation of treatment for LTBI in individual patients based on their sociodemographic and clinical characteristics. Using a simulation model that incorporates personalised estimates of risks and benefits, we found that the benefit of treatment of LTBI outweighs the risks in the majority, but not all, patients with evidence of LTBI. The most influential parameters were: an individual's underlying risk of developing TB followed by the utility (that is, value relative to perfect health) assigned to the post-TB state, the utility assigned to uncomplicated treatment for LTBI, and the effectiveness of treatment for LTBI in reducing the risk of developing active TB.

Guidelines on the management of LTBI published by the World Health Organization in 2014 emphasise that “Individual benefit outweighing risk should be the mainstay of latent TB testing and treatment” [29]. However, without using a model to incorporate and analyse the available evidence, it is likely that the risks and benefits of treatment for LTBI will be inaccurately assessed in many cases [30]. The decision model was developed to address this need. As the global community is working together to achieve TB elimination, it is essential to overcome barriers to prescription and uptake of treatment of LTBI at the clinical practice level. The decision aid can help to overcome these barriers by providing individualised information for physicians and patients to complement the public health perspective.

Our decision model showed that the threshold for LTBI treatment in women is lower than for men despite using the same value estimates for all variables and utilities in both sexes. The discrepancy can be explained by longer life expectancy for women resulting in a higher life time cumulative risk for active TB and thus lower thresholds for treatment. A somewhat surprising finding was that LTBI treatment in elderly people can lead to a substantial gain in QALYs (online supplementary tables 1A–E). This can be explained by the high TB case-mortality rate in the elderly, which outweighs the increased risk of death from isoniazid-induced hepatitis in many cases.

One strength of the model is that it can be applied in any setting with a low incidence of TB. While life tables from the USA were used for the manuscript, the model can also be adjusted to include life tables from other countries. When we used lifetables from Australia, Italy and the UK instead of life tables from the USA the treatment recommendation was not changed in any of the case studies that we modelled.

No model can ever reflect reality in its entirety. However, models, including the one presented here, can be very helpful in assimilating complex available information to inform decision making. As with any model-based analysis, this decision model has a number of limitations. In any model simplifying assumptions have to be made in order to develop a feasible model. The simplification that patients only develop active TB once (no recurrent episodes of TB) seems reasonable based on a study we conducted in a low incidence setting for TB that showed that the risk of TB recurrence (re-infection with a new TB strain or reactivation with the previous TB strain) was only 0.4% over 13 years [31]. However, this assumption limits the applicability of the decision aid to settings with a low incidence of TB, as the risk of recurrent TB *via* re-infection is substantial in settings with a high incidence of TB, and a previous course of treatment for LTBI does not protect a person from being re-infected. Further, this decision aid is only designed for decisions on treatment of LTBI in people who are not likely to be infected with an



Age years	10	20	30	40	50	60	70	80	90
Threshold annual TB risk [¶] for females	13	14	18	24	31	45	81	149	508
Threshold annual TB risk [¶] for males	15	17	22	30	39	58	105	194	644
Threshold annual TB risk [¶] for females, utility post-TB state=1	19	20	24	31	37	52	88	157	533
Threshold annual TB risk [¶] for males, utility post-TB state=1	23	24	30	39	48	67	113	204	676

FIGURE 3 Thresholds for annual risk of active tuberculosis (TB) above which latent TB infection treatment is favoured (based on one-way sensitivity analysis) with quality-adjusted life-years as outcome. [#]: assumes that people return to perfect health and do not have any long-term impairment following an episode of TB; [¶]: per 100 000.

isoniazid-resistant strain. Its applicability in settings with high rates of isoniazid-resistant TB strains is thus limited.

We acknowledge that estimating the true annual risk of active TB in an individual is associated with many uncertainties. While it would be desirable to validate all individual risk estimates in clinical trials, it is not feasible to obtain trial-based data for numerous combinations of demographic characteristics and risk factors for TB reactivation. There are uncertainties regarding the utilities for TB-related health states, as the values will depend on which quality of life measurement instrument was used to elicit the values, at what time during the course of treatment utilities were obtained, disease site of active disease and other factors. No single utility value can therefore be representative for a broad range of patients. However, we do believe that despite these limitations, adjusting for quality of life during different TB-related health states with utility values elicited from patients better approximates real-life experience compared to not adjusting for quality of life at all or using utility estimates based on expert opinion only.

The decision aid was not designed to evaluate screening strategies or definitions of target groups for LTBI screening. The decision to screen a certain high risk population is based on a public health approach, which must include a cost-benefit analysis. It cannot be directly extrapolated from the individual patient perspective. The decision aid should therefore only be used for decision making at the individual patient level in people who have been screened for LTBI because they belong to a predefined risk group.

While the decision aid was designed to support decision making in cases in which the benefits and risks of LTBI treatment need to be carefully weighed against each other, we found that it never contradicted

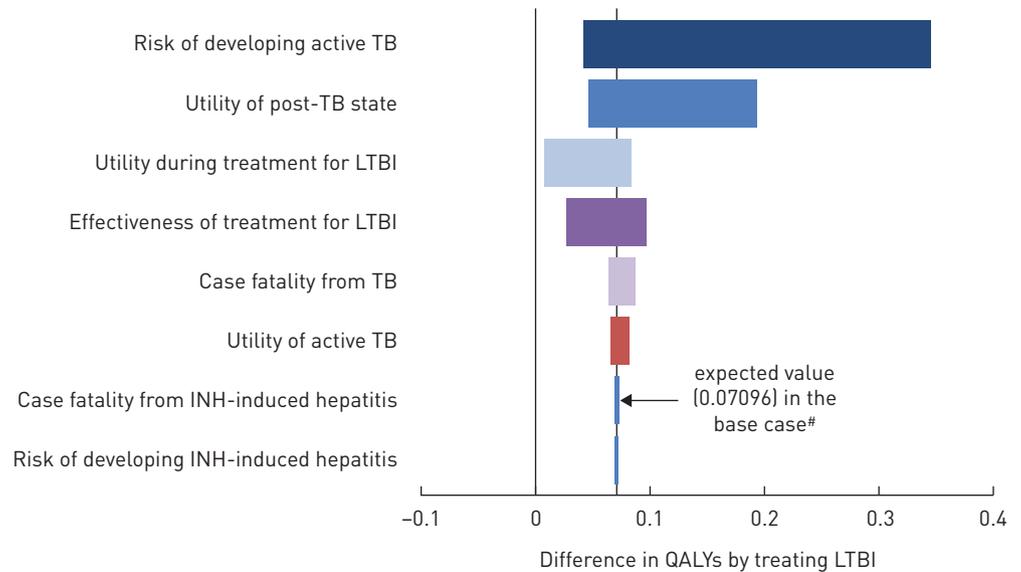


FIGURE 4 Results of one-way sensitivity analyses showing difference in quality-adjusted life-years (QALYs) when each of the parameters was varied through its plausible range (specified age of 20 years, male). Values to the right of the vertical 0-line indicate a net gain and those to the left indicate a net loss in QALYs. TB: tuberculosis; LTBI: latent TB infection; INH: isoniazid. #: the vertical axis for the expected value in the base case indicates the expected net benefit in QALYs (0.07096) when the base estimates for all parameters are used.

current LTBI treatment recommendations for very high-risk groups. All modelled scenarios, including HIV-positive people, for example, always resulted in a recommendation to give LTBI treatment.

The study focused on treatment of LTBI with isoniazid monotherapy, the most commonly used preventive treatment regimen. Alternative treatment regimens for LTBI include a directly observed 12-dose once-weekly regimen of isoniazid and rifapentine [32] and a 4-month regimen of rifampicin [33]. As effectiveness, efficacy and adverse events associated with different treatment regimens for LTBI vary, the results of the decision aid cannot directly be extrapolated to treatments other than isoniazid monotherapy.

In summary, we have developed a decision aid that estimates whether an individual patient stands to benefit from treatment of LTBI based on their sociodemographic and clinical characteristics. Analysing various scenarios, we found that the individual benefit of treatment of LTBI outweighs the risk in the majority of patients with evidence of LTBI. Individual information on QALYs to be gained or lost when treating LTBI and information on how often the treatment recommendation remains valid when taking into account parameter uncertainty, assists the shared decision making between physicians and patients. This decision aid is in the process of being made freely available online.

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