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ORIGINAL ARTICLE

Cost-effectiveness of latent tuberculosis infection testing and treatment with 6-week regimen among key population in rural communities in China: a decision analysis study

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Abstract

Purpose Several model studies suggested the implementation of latent tuberculosis infection (LTBI) testing and treatment could greatly reduce the incidence of tuberculosis (TB) and achieve the 2035 target of the "End TB" Strategy in China. The present study aimed to evaluate the cost-effectiveness of LTBI testing and TB preventive treatment among key population ($\geq$ 50 years old) susceptible to TB at community level in China.

Methods A Markov model was developed to investigate the cost-effectiveness of LTBI testing using interferon gamma release assay (IGRA) and subsequent treatment with 6-month daily isoniazid regimen (6H) (as a standard regimen for comparison) or 6-week twice-weekly rifapentine and isoniazid regimen (6-week H_2P_2) in a cohort of 10,000 adults with an average initial age of 50 years.

Results In the base-case analysis, LTBI testing and treatment with 6H was dominated (i.e., more expensive with a lower quality-adjusted life year (QALY)) by LTBI testing and treatment with 6-week H_2P_2. LTBI testing and treatment with 6-week H_2P_2 was more effective than no intervention at a cost of $20,943.81 per QALY gained, which was below the willingness-to-pay (WTP) threshold of $24,211.84 per QALY gained in China. The one-way sensitivity analysis showed the change of LTBI prevalence was the parameter that most influenced the results of the incremental cost-effectiveness ratios (ICERs).

Conclusion As estimated by a Markov model, LTBI testing and treatment with 6-week H_2P_2 was cost-saving compared with LTBI testing and treatment with 6H, and it was considered to be a cost-effective option for TB control in rural China.

Keywords Tuberculosis · Cost-effectiveness · Latent tuberculosis infection · Preventive treatment · Markov model

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Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is accountable for nearly 1.3 million deaths worldwide, and 10.6 million people developed TB disease in 2022 [1]. Approximately, a quarter of the global population was infected with MTB, and it is estimated that 5–10% individuals with latent tuberculosis infection (LTBI) might develop active disease during their lifetime [2]. Therefore, the implementation of optimized preventative treatment in high-risk populations with LTBI is needed to reduce the global burden of TB disease as recommended by the World Health Organization (WHO) [3]. More crucially, 8 countries in the 30 high TB-burden countries accounted for about more than two-thirds of all estimated incident cases of TB worldwide in 2021, so it is more urgent to explore and provide suitable preventive treatment policies in such high TB-burden countries including China [1, 4, 5].

When preventive therapy is indicated for treating LTBI, isoniazid (300 mg) given daily for 6 months (6H) or 9 months (9H) is the most commonly used regimen [3]. However, the overall effectiveness of these regimens is limited by low compliance. A short regimen, 3-month once-weekly regimen with rifapentine plus isoniazid (3HP, both with a maximum dose of 900 mg), is also recommended by the WHO, which has higher treatment completion rates than 6H and 9H [3, 6]. In China, as the genetic background of Asians was different with Caucasians, 3-month regimen with twice-weekly rifapentine plus isoniazid ($3H_2P_2$, both with a maximum dose of 600 mg) has been practiced for years. This regimen reduced single dosage and increased frequency compared to 3HP, which has been proven to be safety and effective for Chinese population [6, 7]. In the context of half of the new TB infections and three-quarters of active TB emerge from the middle-aged and elderly people (≥ 50 years old) in rural China [4, 8, 9], we conducted a randomized controlled trial (RCT) to explore a new short-course regimen suitable for such a key population in 2015 [5, 10]. We found that the innovative 6-week twice-weekly rifapentine and isoniazid regimen (6-week H_2P_2) showed a 2-year protective efficacy of 69% and a 5-year protective efficacy of 61%, while 3HP recommended by the WHO showed that the risks of 3HP were considerable among the elderly and the protective efficacy of 3HP was poor (36.76%) at the 2-year follow-up. Such a short-course regimen (6-week H_2P_2) demonstrates good safety and adherence; it gives us great confidence to explore community-based preventive treatment among key populations with LTBI in China aimed at reducing the incidence rate.

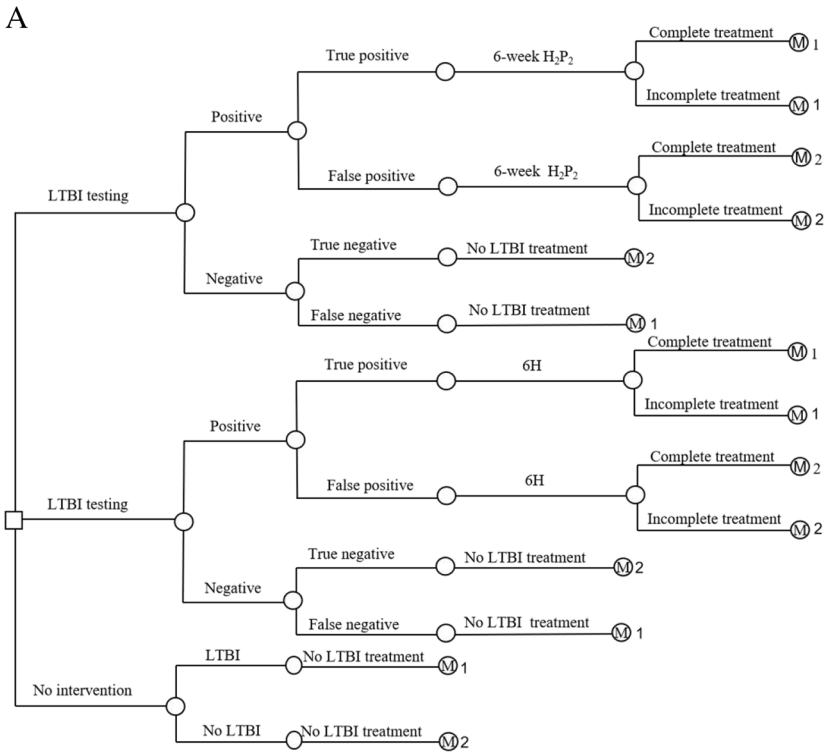
The health economics value has become a more concerned issue for policy makers to formulate public health programs. However, at present, the health economics analysis of LTBI testing and treatment aiming to reduce TB incidence at a community level has not been studied before in China. Therefore, this study aimed to evaluate the cost and cost-effectiveness of LTBI testing and treatment using a Markov model, which might provide important reference for the improvement of TB preventive treatment strategies in China.

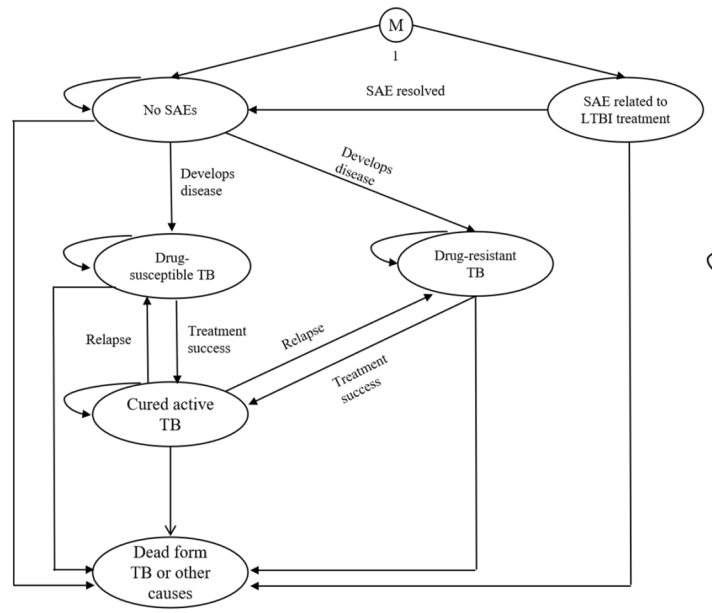
Methods

Model structure description

A decision tree followed by a Markov state transition model was developed in TreeAge Pro (version 2022; TreeAge Software Inc., Williamstown, MA, USA) to estimate and compare the costs, health outcomes, and cost-effectiveness of two different strategies: LTBI testing and treatment with 6-week H_2P_2 and LTBI testing and treatment with 6H (as a standard regimen for comparison), which has been proved to be safety and efficacy in Chinese population [6]. The baseline scenario against which each of the two strategies was assessed was a scenario whereby individuals without receiving LTBI testing and preventive treatment (no intervention). A hypothetical population of 10,000 adults was considered with an average initial age of 50 years in rural China.

Figure 1 shows the model structure and transition states. Individuals who received LTBI testing in the cohort underwent testing for LTBI by QuantiFERON-TB Gold In-Tube (QFT-GIT) (an interferon gamma release assay (IGRA)). Individuals who tested positive for LTBI (whether truly or falsely) were treated with 6-week H_2P_2 in one scenario and with 6H in the alternate scenario [11]. Both LTBI treatment regimens would be assumed to be delivered by directly observed treatment (DOT). Individuals received preventive treatment were assumed to not develop active TB during preventive therapy, and they were further divided based on treatment completion [5, 12]. Individuals infected with MTB entered Markov cycle 1 (Fig. 1B). While undergoing treatment for LTBI, patients had a probability of developing serious adverse events (SAEs) due to treatment and, as a consequence, experienced a small additional risk of death. Individuals with no SAEs had a risk of progressing to drug-susceptible TB or drug-resistant TB. During the period of TB treatment, individuals were at risk of death from TB. After the treatment course, drug-susceptible TB or drug-resistant TB patients were successfully treated or could experience treatment failure. Relapsed cases of drug-susceptible TB or drug-resistant TB were also considered, defined as a recurrent episode of drug-susceptible TB or drug-resistant TB after a period without TB. Conversely, individuals with false-positive test results or with no LTBI





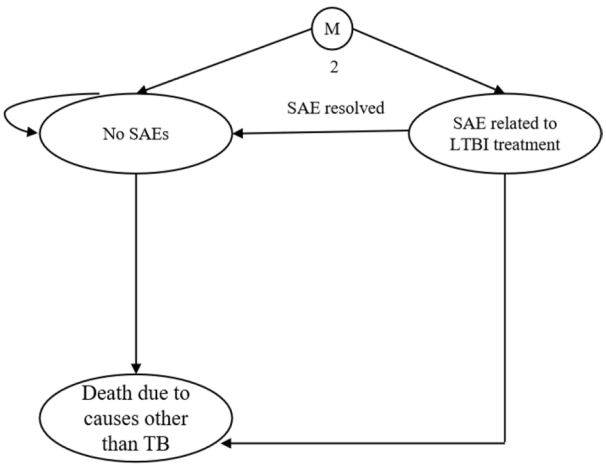


Fig. 1 The model first implements a decision tree among a hypothetical group of adults aged 50 years in rural China who are screened for latent tuberculosis infection (LTBI) with IGRA (**A**). Those who test positive are treated with 6-week twice-weekly rifapentine and isoniazid regimen (6-week H_2P_2) in one scenario or with 6-month daily isoniazid regimen (6H) in the alternative scenario. Participant with different infection states of *Mycobacterium tuberculosis* (MTB) enter Model 1 (**B**) or Model 2 (**C**) based on their future health states. The ovals represent mutually exclusive health states that each participant may reach during each Markov cycle

entered Markov cycle 2 (Fig. 1C), who were assumed to have no risk of reactivation to drug-susceptible TB or drug-resistant TB. Significantly, individuals who were not treated followed the same pathway as those treated with preventive therapy, except that their probability of having SAEs associated with LTBI treatment was set to 0 and their probability of progression from LTBI to active TB was not adjusted for the effectiveness of LTBI treatment. Considering indeterminate result of IGRA, which represents only 0.24% of the target population, cannot be directly used as the indicator for defining infection status, individuals with indeterminate results of IGRA were therefore not included in this study [13].

In our study, 6-week H_2P_2 was an innovative therapy, and the longest follow-up period currently available for this regimen is 5 years [10]. Besides, previous study reported that isoniazid's protective effect lasts almost 20 years [14]. Therefore, a Markov cycle duration of 1 year was employed, and patient outcomes were tracked from commencement of LTBI treatment for 5 years (or 20 years) or until death, whichever occurred earlier. Reinfection was not considered in this study.

Model inputs and data sources

Model input parameters are presented in Table 1. The LTBI prevalence at age 50 was 22.46%, which was estimated by Biased Sentinel Hospital-based Area Disease Estimation [15]. It was assumed that QFT-GIT had an estimated sensitivity of 84% and specificity of 95% [16, 17]. The probability of developing SAEs due to treatment came from published studies [5, 12, 18] and the probability of death from SAEs for 6-week H_2P_2 and 6H were 0% and 0.001%, respectively [5, 19]. The risk of progression from LTBI to drug-susceptible TB or drug-resistant TB was assumed to be the highest, at 0.57% or 0.04% per year, during the first 2 years following initial infection and then declined to a constant rate of 0.09% or 0.007% per year in subsequent years [3, 5, 11, 20]. Individuals who developed drug-susceptible TB or drug-resistant TB received treatment for the disease incurred additional costs due to this treatment and had an additional risk of death [21, 22]. For individuals with drug-susceptible TB, 94.00% of them was assumed to be successfully treated, and the probability of treatment success for drug-resistant TB was assumed to be 41.00% [23, 24]. The probability of relapse from successfully treated drug-susceptible TB and drug-resistant TB was 2.49% and 6.58%, respectively [25, 26]. In the absence of reactivation to active TB, individuals with LTBI were assumed to have the same age-specific annual probability of death as the general population, which was based on China Population and Employment Statistical Yearbook in 2016 (Supplemental Table 1).

In the base scenario, the cost of incomplete treatment of 6-week H_2P_2 was assumed to include 5/12 medication cost and 5/12 the DOT costs, and 6H was assumed to include 58/180 medication cost and 58/180 the DOT costs [5, 27]. Screening and preventive treatment costs were mainly taken from a RCT conducted among rural residents aged 50–69 years with LTBI in China [5]. Drug-susceptible TB and drug-resistant TB costs were taken from a cross-sectional study using data from national TB patient cost survey carried out in 22 counties from six provinces in China [28]. Calculations of cost inputs are presented in Supplemental methods. Due to most of the model parameters in our model were derived from a RCT conducted in 2015 [5], all costs were expressed in 2015 US dollars (US$1 = ¥6.1149). All future costs and health outcomes have been discounted at an annual rate of 3%.

Effectiveness was estimated as the number of quality-adjusted life years (QALYs) gained, assuming that utility for the LTBI state was similar to that of the underlying general population (1.00), whereas the utility for drug-susceptible TB or drug-resistant TB was assumed to be 0.83 or 0.60 based on published literature [19, 29]. Cured TB after successful treatment of drug-susceptible TB or drug-resistant TB was assumed to be without sequelae [19, 30]. The utility for the SAE state was 0.75 [19, 30]. Additionally, the utility for no SAEs in Markov cycle 1 was the same as LTBI, and the utility for no SAEs in Markov cycle 2 was the same as general population.

Base-case analysis

For each strategy, the expected costs, QALYs, and cases of active TB prevented were calculated. Furthermore, incremental cost-effectiveness ratios (ICERs) were estimated, defined as the additional cost per QALY gained compared with the next least expensive non-dominated strategy. A strategy was considered good value for money (i.e., cost-effective) if the ICER was equal to or less than the willingness-to-pay (WTP) threshold of three times China's 2015 gross domestic product (GDP) per capita.

One-way sensitivity analysis

The one-way sensitivity analysis was carried out to understand the key ICER drivers and the sensitivity of our results to the variables, where cost parameters, probability parameters, and utility parameters were varied by the uncertainty range of the base-case values while holding all other parameters constant. For parameters with an unknown uncertainty range, the plausibility range was assumed to be 25% of the base value. The results of one-way sensitivity analysis were displayed as tornado diagrams which demonstrated the change in the ICER.

Table 1 Model parameters used to evaluate the cost-effectiveness of LTBI testing and treatment among key population in rural China

Variable*	Base-case value	Uncertainty range	Source
LTBI prevalence	22.46%	17.81%, 27.11%	(15)
QFT-GIT sensitivity	84.00%	70.00%, 91.40%	(16) (17)
QFT-GIT specificity	95.00%	94.00%, 98.00%	(16) (17)
QFT-GIT positive predictive value	89.40%	79.40%, 95.60%	(11)
QFT-GIT negative predictive value	95.70%	91.40%, 98.30%	(11)
Probability of SAEs during a course of LTBI treatment			
6-week H_2P_2			
Incomplete treatment	4.20%	1.90%, 6.50%	(5)
Complete treatment	0.50%	0.10%, 0.90%	(5)
6H			
Incomplete treatment	3.00%	1.00%, 5.00%	(12) (18)
Complete treatment	1.00%	1.00%, 3.00%	(12) (18)
Probability of death from SAEs[#]			
6-week H_2P_2	0.00%	0.00%, 0.002%	(5)
6H	0.001%	0.00%, 0.002%	(19)
Treatment completion rate by regimen			
6-week H_2P_2	78.06%	75.89%, 80.39%	(5)
6H	75.00%	46.00%, 82.00%	(12)
Reduction in risk of progression to active TB due to LTBI treatment corresponding to different levels of treatment completion			
6-week H_2P_2			
Incomplete treatment	41.66%	31.25%, 52.08%	(5)
Complete treatment	69.00%	51.75%, 86.25%	(5)
6H			
Incomplete treatment	0.00%	-	(27)
Complete treatment	69.00%	51.75%, 86.25%	(27)
Annual risk of progression from LTBI to active TB in the absence of LTBI treatment	List as below		
First 2 years			
Drug-susceptible TB	0.57%	0.43%, 0.71%	(5) (11) (20)
Drug-resistant TB	0.04%	0.03%, 0.05%	(5) (11) (20)
After 2 years, for life			
Drug-susceptible TB	0.09%	0.07%, 0.11%	(3) (5) (11)(20)
drug-resistant TB	0.007%	0.005%, 0.009%	(3) (5) (11)(20)
Annual risk of progression from LTBI to active TB after LTBI treatment	List as below		
First 2 years			
6-week H_2P_2			
Incomplete treatment			
Drug-susceptible TB	0.33%	0.25%, 0.41%	
Drug-resistant TB	0.02%	0.02%, 0.03%	
Complete treatment			
Drug-susceptible TB	0.18%	0.14%, 0.22%	
Drug-resistant TB	0.01%	0.01%, 0.02%	
6H			
Incomplete treatment			
Drug-susceptible TB	0.45%	0.34%, 0.56%	
drug-resistant TB	0.03%	0.02%, 0.04%	
Complete treatment			
Drug-susceptible TB	0.18%	0.14%, 0.22%	
Drug-resistant TB	0.01%	0.01%, 0.02%	
After 2 years, for life			
6-week H_2P_2			

Table 1 (continued)

Variable*	Base-case value	Uncertainty range	Source
Incomplete treatment			
Drug-susceptible TB	0.05%	0.04%, 0.06%	
Drug-resistant TB	0.004%	0.003%, 0.005%	
Complete treatment			
Drug-susceptible TB	0.03%	0.02%, 0.04%	
Drug-resistant TB	0.002%	0.002%, 0.003%	
6H			
Incomplete treatment			
Drug-susceptible TB	0.07%	0.05%, 0.09%	
Drug-resistant TB	0.006%	0.005%, 0.008%	
Complete treatment			
Drug-susceptible TB	0.03%	0.02%, 0.04%	
Drug-resistant TB	0.002%	0.002%, 0.003%	
Age of cohort at start (years)	50	-	
Probability of treatment success for drug-susceptible TB	94.00%	91.65%, 96.35%	(23)
Probability of death while under treatment for drug-susceptible TB	1.77%	1.67%, 1.87%	(21)
Probability of relapse from successfully treated drug-susceptible TB	2.49%	1.87%, 3.11%	(25)
Probability of treatment success for drug-resistant TB	41.00%	30.75%, 51.25%	(24)
Probability of death while under treatment for drug-resistant TB	4.01%	3.01%, 5.01%	(22)
Probability of relapse from successfully treated drug-resistant TB	6.58%	4.94%, 8.23%	(26)
Age-specific probability of death[&]	Life table	-	
Quality of life adjustments (QALYs lost per year)			
LTBI	1.00	0.95, 1.00	(19)
Drug-susceptible TB	0.83	0.75, 0.87	(19)
Drug-resistant TB	0.60	0.40, 0.80	(29)
SAEs	0.75	0.67, 0.85	(19)(30)
Cured active TB	1.00	0.85, 1.00	(19)(30)
Cost for LTBI testing in baseline	58.85	44.14, 73.57	(5)
Cost for pre-intervention phase	73.23	54.92, 91.53	(5)
Cost per complete regimen			
6-week H_2P_2	88.59	66.45, 110.74	(5)
6H	327.58	245.68, 409.47	(27)
Cost per incomplete regimen			
6-week H_2P_2	52.90	39.68, 66.13	(5)
6H	112.78	84.59, 140.98	(27)
Cost of treatment for SAEs	654.14	490.60, 817.67	(5)
Cost of drug-susceptible TB treatment	2702.85	2027.14, 3378.57	(28)
Cost of drug-resistant TB treatment	24,240.91	18,180.69; 30,301.14	(28)

[*]For probabilistic analyses, cost parameters followed a gamma distribution, and the other variables followed a triangular distribution. The likeliest, minimum, and maximum parameters of the triangular distributions were set to equal the base-case, lower and upper values, respectively. All costs were presented in 2015 US dollars

[#]SAE include life threatening that can result in persistent or significant dysfunction/disability, death, permanent injuries to organ functions, carcinogenic, resulting in hospitalization or prolongation of hospitalization, etc.

[&]See Supplemental Table 1 in the electronic supplementary material for details

LTBI latent tuberculosis infection, QFT-GIT QuantiFERON-TB Gold In-Tube, SAEs serious adverse events, TB tuberculosis, 6H isoniazid daily for 6 months, 6-week H_2P_2 6-week twice-weekly rifapentine and isoniazid regimen, QALY quality-adjusted life year

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis using Monte Carlo simulation (N = 5000 iterations) was done to assess the effects of changing multiple parameters simultaneously (Table 1). Cost parameters were assigned gamma distributions, and probabilities were assigned triangular distributions. The results were presented as a scatter plot of 5000 ICERs on the cost-effectiveness plane and transformed into a cost-effectiveness acceptability curve based on the decision-makers' WTP for an additional QALY.

Results

Base-case analysis

Five-year time horizon

The results from the base-case analysis are shown in Table 2. Over a 5-year time horizon, LTBI testing and treatment with 6-week H_2P_2 was cheaper than LTBI testing and treatment with 6H, with an average lifetime cost per 10,000 participants of $1,152,457.47. Compared with no intervention, LTBI testing and treatment with 6-week H_2P_2 or with 6H could prevent 31 or 25 additional cases of active TB per 10,000 patients, respectively.

In an analysis of the cost-effectiveness of the alternative strategies, LTBI testing and treatment with 6H was dominated (i.e., more expensive with a lower QALY) by LTBI testing and treatment with 6-week H_2P_2 (Table 2 and Supplemental Fig. 1). LTBI testing and treatment with 6-week H_2P_2 was more effective than no intervention at an additional cost of $20,943.81 per QALY gained (Table 2).

Twenty-year time horizon

Over a 20-year time horizon, LTBI testing and treatment with 6-week H_2P_2 was also cheaper than LTBI testing and treatment with 6H, with an average lifetime cost per 10,000 participants of $1,231,086.00. In an analysis of the cost-effectiveness of the alternative strategies, LTBI testing and treatment with 6-week H_2P_2 was more effective than no intervention at an additional cost of $21,275.74 per QALY gained (Table 2).

One-way sensitivity analysis of parameters influencing the ICERs of LTBI testing and 6-week H_2P_2

One-way sensitivity analysis of key parameters and their impact on the ICERs of LTBI testing and treatment with 6-week H_2P_2 relative to no intervention at the 5-year time horizon is shown in Fig. 2. Among a number of variables, the change of LTBI prevalence in the target population was

Table 2 Projected health system costs and health outcomes per 10,000 participants aged 50 years on LTBI testing and treatment in rural China

Strategy	Average cost per 10,000 participants	Incremental cost 10,000 participants[&]	Expected total QALYs per 10,000 participants	Incremental effectiveness (QALY) per 10,000 participants[&]	ICER	Incident cases of active TB per 10,000 patients	Cases prevented[#] (n)
At the 5-year time horizon							
No intervention	389,055.78	-	46,102.83	-	-	60	-
LTBI testing and 6-week H_2P_2	1,152,457.47	763,401.70	46,139.28	36.45	20,943.81	29	31
LTBI testing and 6H	1,628,150.57	475,693.10	46,134.40	−4.88	Dominated*	35	25
At the 20-year time horizon							
No intervention	550,475.10	-	144,130.13	-	-	84	-
LTBI testing and 6-week H_2P_2	1,231,086.00	680,610.90	144,162.12	31.99	21,275.74	41	43
LTBI testing and 6H	1,723,034.69	491,948.70	144,158.18	−3.94	Dominated*	49	35

[&]Relative to the next least expensive, non-dominated strategy

*Dominated because the strategy was more expensive and had fewer QALYs than the next least expensive, non-dominated strategy

[#]Compared with no intervention

LTBI latent tuberculosis infection, QALY quality-adjusted life year, ICER incremental cost-effectiveness ratio, 6H isoniazid daily for 6 months, 6-week H_2P_2 6-week twice-weekly rifapentine and isoniazid regimen

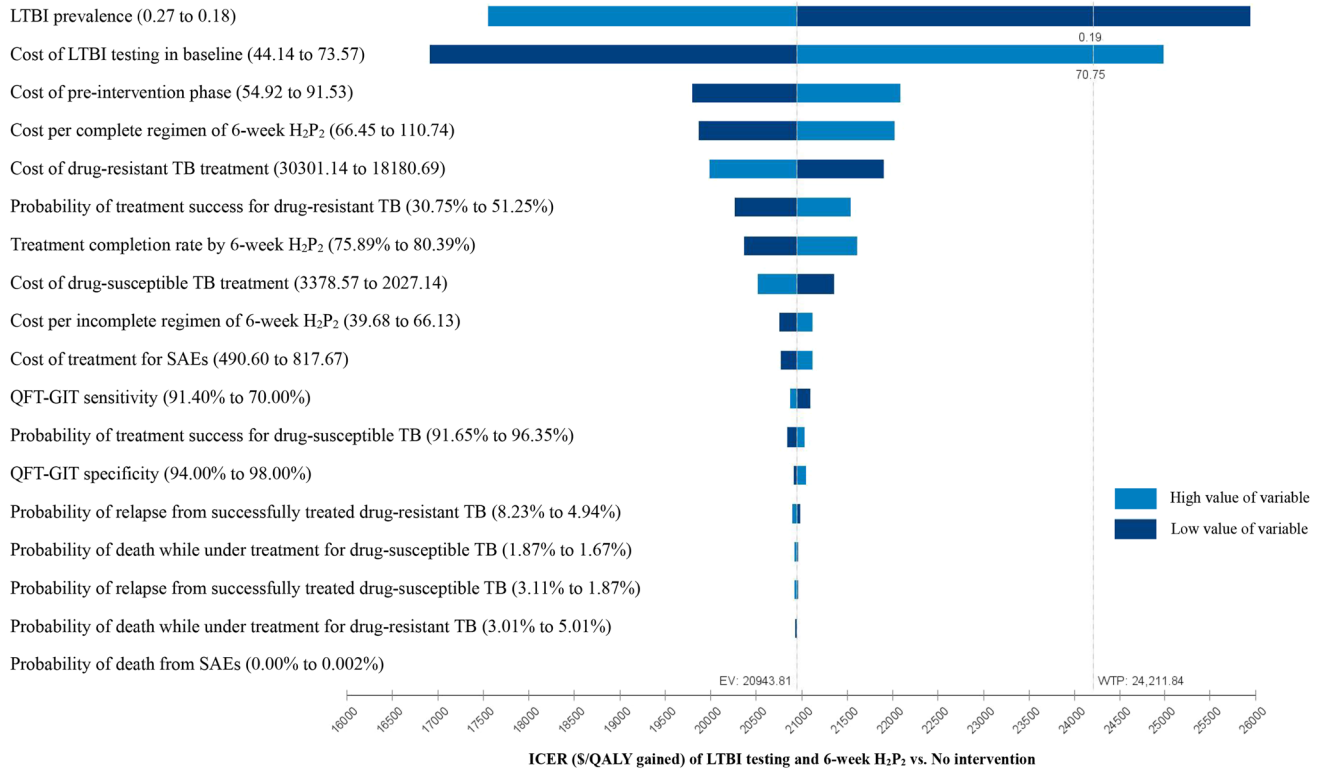


Fig. 2 The one-way sensitivity analysis of the ICER of LTBI testing and 6-week H_2P_2 versus no intervention. Bars show the ICER ($/QALY gained) of LTBI testing and treatment with 6-week H_2P_2 relative to no intervention under the uncertainty range of the parameter in question, holding all other parameters constant at the 5-year time horizon. The vertical line corresponds to the reference scenario ($20,943.81/QALY gained)

the parameter that most influenced the results of the ICER, and as it increased the cost-effectiveness of LTBI testing and 6-week H_2P_2, treatment was increased. The second influential variable in the model was cost of LTBI testing, and as it increased the cost-effectiveness of LTBI testing and 6-week H_2P_2, treatment decreased. Other input parameters had a relative small impact on the ICERs.

Probabilistic sensitivity analysis of parameters influencing the ICERs of LTBI testing and 6-week H_2P_2

The cost-effectiveness acceptability curve (Fig. 3) represents the probability of LTBI testing and treatment with 6-week H_2P_2 being cost-effective relative to no intervention over a range of WTP thresholds. The curve shows that the likelihood that LTBI testing and treatment with 6-week H_2P_2 was cost-effective at a WTP threshold of $24,211.84 per QALY gained was 73.12%.

The scatter plot for the ICERs of LTBI testing and treatment with 6-week H_2P_2 relative to no intervention is presented in Supplemental Fig. 2. The plane shows that the majority (72.41%) of the simulated ICERs were below the WTP threshold of $24,211.84 per QALY gained.

Discussion

To our knowledge, this is the first study to evaluate the cost-effectiveness of LTBI testing and treatment among key population (≥ 50 years old) at a community level in the Chinese population from a societal perspective. Our results suggested that following testing with QFT-GIT, treating key population with LTBI with 6-week H_2P_2 was less expensive and more effective than the standard regimen of 6H. Compared with no intervention, the incremental cost per QALY gained for LTBI testing and treatment with 6-week H_2P_2 was less than three times China's 2015 GDP per capita of $24,211.84. Hence, it meets criteria to be classified as cost-effective in the context of China.

In China, to establish a preventive treatment strategy aiming at reducing the incidence of TB, it should not only target populations at high risk of developing active TB from LTBI but also pay attention to key populations with significant contribution to TB incidence at the community level. The reason is that the distribution of risk factors and their contribution to TB incidence might vary in different regions. For example, as reported in 2021, people living with HIV, who were recommended by WHO as a high-risk population for preventive treatment, only contribute 1.3%

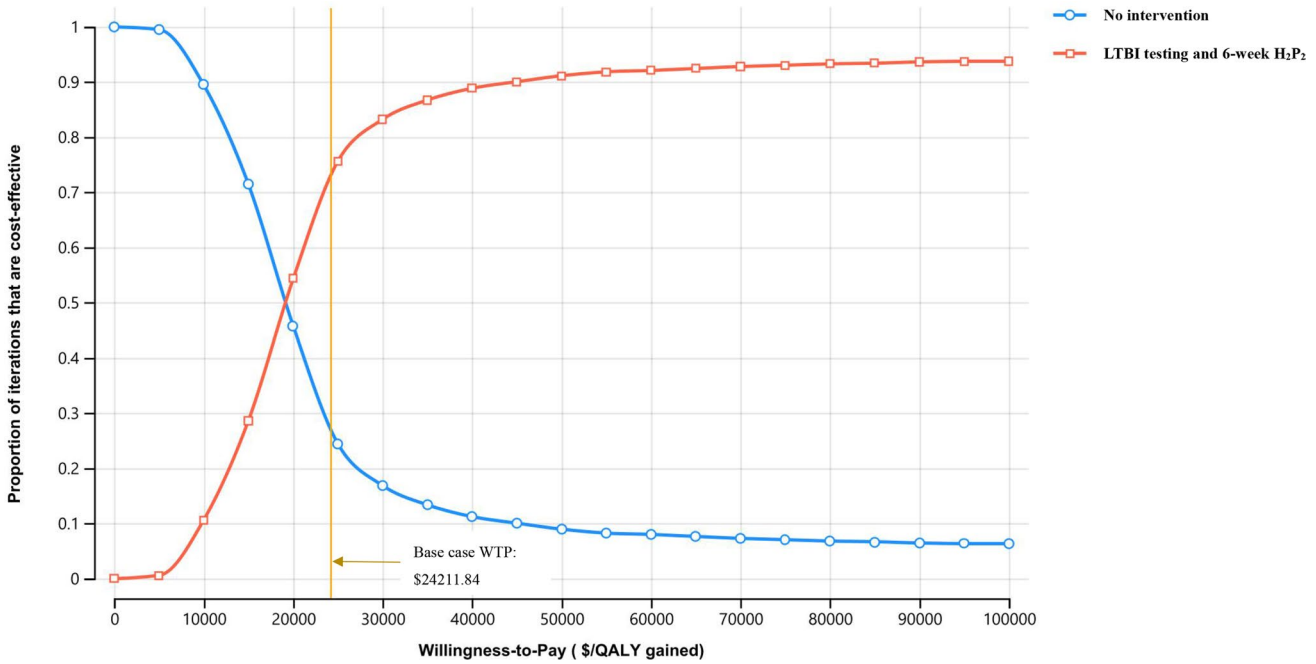


Fig. 3 The cost-effectiveness acceptability curve from probabilistic sensitivity analysis shows the percentage of simulations in which LTBI testing and treatment with 6-week H_2P_2 would be considered cost-effective compared to no intervention at varying WTP thresholds at the 5-year time horizon. The likelihood that LTBI testing and treatment with 6-week H_2P_2 was cost-effective at a WTP threshold of $24,211.84 per QALY gained was 73.12%

of active TB cases in China [1]. However, our previously prospective study consistently found that individuals with inactive TB suggested by chest radiographic abnormalities showed an increased risk of developing active TB, and this subgroup contributed about 30% of TB cases occurred in study settings in rural China [4, 8, 9]. Therefore, the promotion of preventive treatment strategies aimed at reducing TB incidence in high TB-burden countries including China is facing more challenges, and MTB infection detection technology and preventive treatment strategies that are easier to implement and manage are needed in the future. The 6-week H_2P_2 undoubtedly gives us the confidence to scale up preventive treatment at the community level.

In our model, 6H was more expensive and did not compare favorably to the 6-week H_2P_2. This finding was in accordance with those performed in other studies, which found that shorter regimens that included rifapentine were more effective and cost-saving compared to the standard 6H or 9H [31, 32]. Besides, compare with no intervention, LTBI testing and treatment with 6-week H_2P_2 was more effective at a cost of $20,943.81/QALY, which was less than the WTP threshold of $24,211.84/QALY, and it could prevent 31 additional cases of active TB per 10,000 patients over a 5-year time horizon. This finding indicated that, in the case where policy decision-makers are not willing to pay more than $24,211.84 for an additional QALY gained, LTBI testing by IGRA and subsequent treatment with 6-week H_2P_2 would therefore be considered cost-effective among elderly in China. In addition, the result also further supports the view of previous model-based studies that implementation of preventive treatment nationwide in the elderly could greatly reduce the number of TB cases [33, 34]. However, for the real world, it is clear that the feasibility of LTBI testing and treatment for the entire elderly population is relatively low. If LTBI testing and treatment can be targeted to subgroups of the elderly with high-risk of developing TB and with high contribution to TB incidence, such as those with prior TB [4, 35], the feasibility of the intervention could be significantly improved as precise intervention [36].

As shown in one-way sensitivity analysis, cost-effectiveness was most sensitive to LTBI prevalence, which was estimated by QFT-GIT surveys and Biased Sentinel Hospital-based Area Disease Estimation. A range of LTBI prevalence (0.18, 0.27) was used to test the influence of LTBI prevalence on cost-effectiveness, which found that LTBI testing and 6-week H_2P_2 might be more suitable for settings with high LTBI prevalence. Our data was consistent with previous analysis by Wingate and colleagues [37], which reported that LTBI testing followed by 3HP treatment was beneficial for refugees coming from countries with moderate to high prevalence of LTBI. Besides, the cost for LTBI testing in baseline was also key factors affecting cost-effectiveness. The LTBI testing method

we used in our RCT study was QFT-GIT [5], which was bought in the market at relatively high costs. Tuberculin skin test (TST) is also one of the LTBI testing techniques recommended by WHO guidelines with relatively inexpensive price. However, many previous studies have shown that the performance of TST is susceptible to a number of factors, such as Bacille Calmette-Guérin (BCG) vaccination and the infection of non-tuberculous mycobacteria (NTM) [8]. And a cost-effectiveness analysis also reported that using QFT-GIT as a LTBI testing method was more cost-effective than TST among adults in close contact [38]. Therefore, we did not evaluate the application of TST in this model. However, as our previous studies have shown that TST + /IGRA − also developed active TB in the following years, we cannot rule out the value of TST in the elderly population [4]. As there is still a lack of studies on the application of TST in Chinese elderly, more studies are needed to explore the performance of TST or TST-IGRA two-step approach (TST followed by QFT-GIT when TST was positive) in the elderly [39]. Additionally, emerging evidence suggests that MTB antigen-based skin tests (TBST) may offer similar specificity to IGRA, which might bring more options for LTBI testing [40]. However, as it has just been launched, more basic data needs to be accumulated. In addition, our results also showed that 6-week H_2P_2 was more cost-effective than 6H at both the 5- and 20-year time horizons, indicating that a longer time horizon affected cost-effectiveness by little. But in the real world, if the protection period of 6-week H_2P_2 is only 5 years, repeated interventions would be needed to maintain the protection effect, which would obviously increase the costs. Therefore, the protection period should be used as an important indicator for developing and evaluating new regimens. We would continue to follow the treated participants with LTBI to track and evaluate the exact protection period of the 6-week H_2P_2.

Strengths of this analysis was that most of the model parameters were obtained by our published literature [5, 10], which provided adequate data of our target population. Besides, we compared LTBI testing and treatment with 6-week H_2P_2 or 6H to a no intervention scenario. Thus, the results not only have guiding significance for the selection of treatment protocols but also provide data support for whether the current economic situation is suitable for LTBI testing and preventive treatment.

Nevertheless, our analysis also has some limitations. First, we did not explicitly include secondary transmission in this analysis, so our results were likely to be conservative, underestimating the benefit of LTBI testing and 6-week H_2P_2 in averting these transmission events. Secondly, the implementation of LTBI testing and treatment with 6-week H_2P_2 at a community level was a complex task, and we did not consider other costs and effects of the implementation process itself, including any differential in patients' willingness to accept LTBI testing and treatment relative to no intervention. Finally, the parameters in our model are estimated based on national averages, so the current strategy may not be applicable to different regions in China. Therefore, each region needs to determine more appropriate technical paths for LTBI testing and treatment in practice, taking into account locally available resources, TB epidemiology, and risk factors associated with incidence. Of course, the establishment of a technological path also needs to be consider the requirements of health economics.

Conclusion

In summary, this simulation analysis suggests that treatment with 6-week H_2P_2 is likely to improve health and save costs as compared to treatment with 6H among rural key population in China. LTBI testing and treatment with 6-week H_2P_2 could be considered a cost-effective option for TB control in China. As TB preventive treatment becomes an increasingly important tool for achieving the goal of TB elimination in high burden countries, accurately select target population and provide suitable preventive therapy is extremely important for developing suitable local strategies. Our results might provide important reference information for policy decision-makers to make good use of this tool for TB control in a cost-effective fashion in China.

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Author contribution LG and LW were responsible for study conception. XFC, TLG, LG, and LW planned and designed the study. XFC, TLG, HNX, JD, CLY, BXF, YJH, LYS, YZD, ZHL, YXC, JGL, QJ, LW, and LG contributed to the data acquisition. XFC conducted the analysis with TLG and CLY support. XFC drafted the manuscript. All authors reviewed the manuscript for scientific content and approved the final manuscript.

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Data availability The datasets used for this study are available on request from the corresponding authors.

Declarations

Ethics approval As human subjects were not involved, ethics approval was not required for this study.

Consent to participate Not applicable.

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Competing interests The authors declare no competing interests.

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