Effect of different interventions for latent tuberculosis infections in China: a model-based study

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Research Article

Keywords: Tuberculosis (TB), tuberculosis preventive treatments (TPTs), LTBI, SEIR, End TB Strategy

Posted Date: October 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1001647/v1>

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Abstract

Background

Tuberculosis (TB) has a serious impact on people's health. China is one of 30 countries that has a high TB burden. As the currently decreasing speed of the incidence of TB, the WHO's goal of "End TB Strategy" is hard to achieve by 2035. As a result, a dynamic model that determines the impact of different tuberculosis preventive treatments (TPTs) in different age groups, and the effect of different interventions on latent TB infections (LTBIs) in China is developed.

Methods

A Susceptible-Exposed-Infectious-Recovered (SEIR) model was established. Goodness-of-fit tests were used to assess model performance. Predictive analysis was used to assess the effect of different interventions on LTBIs and achieving the goals of the "End TB Strategy".

Results

The chi-square test indicated the model provided a good statistical fit to previous data on the incidence of TB ($\chi^2 = 0.3085$, $p > 0.999$). The 1HP treatment regimen (daily rifapentine + isoniazid for 4 weeks) was most effective in reducing the number of TB cases by 2035. The model indicated that several strategies could achieve the 2035 target of the "End TB Strategy": completion of active case finding (ACF) for LTBI and TPT nation-wide within five years; completion of ACF for LTBIs and TPT within two years in high-incidence areas; completion of TPT in the elderly within 2 years; or introduction of a new vaccine in which the product of annual doses and vaccine efficiency in each age group reached 14 million.

Conclusions

The incidence of TB in China declined gradually from 2005 to 2019. Although China have made a lot of efforts in TB prevention and control, there is still a long way to attain the 2025 and 2035 target of "End TB Strategy" with the present preventive interventions. Implementation of ACF for LTBIs and TPT nation-wide or in areas with high incidence, in the elderly, or administration of a new and effective vaccine could greatly reduce the number of TB cases and achieve the 2035 target of the "End TB Strategy" in China.

Background

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (Mtb), is a significant public health problem worldwide. China is one of 30 countries that has a high TB burden. During 2019, China had 833,000 new cases of TB, and was only surpassed by India and Indonesia¹. The 2020 Health Statistics Yearbook reported the incidence of pulmonary TB in China was 55.55 per 100,000 people², second in the ranking of class A and B notifiable infectious diseases. The World Health Organization (WHO) proposed the "End TB Strategy" in 2014, and this included a series of targets³. However, based on the current annual rate of decline in the incidence of TB⁴ (1–2%), these WHO targets may not be achieved.

In addition to active TB, many individuals have latent TB infections (LTBIs), in which Mtb is undetectable. In these individuals, the body's immune system controls the infection and prevents the development of active TB. Individuals with LTBIs have no clinical symptoms and cannot transmit the bacteria to others⁴. Nevertheless, 5 to 10% of people with LTBIs have a risk of developing active TB, especially within five years of the initial infection⁵, and this percentage is even higher among those with immunosuppressive diseases⁶.

There are now about 360-million individuals with Mtb infections in China⁷, most of which are LTBIs⁵. Many individuals with LTBIs in China eventually develop active TB, making prevention and treatment more difficult. Screening and preventive treatment of high-risk groups in China may help reduce the incidence of TB. In fact, recent screening and preventive interventions that targeted people with LTBIs in China have achieved some success^{4, 10–11}. However, due to the unique characteristics of the TB epidemic and the lack

of evidence-based results regarding the effect of preventive measures, the effects of different interventions are uncertain. Based on previous studies that developed dynamic models of TB^{8–12}, we modeled the combined effects of a large-scale TB preventive treatment (TPT) with traditional interventions, and examined the effects of vaccination and active case-finding (ACF) for LTBI on the incidence of TB in China.

Methods

Data collection

Demographic data from the National Bureau of Statistics, including the number of individuals in different age groups at different times², were converted into parameters of corresponding time units for construction of the model.

All data on TB incidence were from the Infectious Diseases Reporting System (IDRS) of the Chinese Bureau of Disease Control. Complete monthly and annual data were available from 2005 to 2020. The TB Information Management System (TBIMS) was examined to obtain data on patients diagnosed with TB from 2008 to 2018 for parameter acquisition and model construction. These data included statistical reports, with classification by gender, age, occupation, time, region of residence, registration, treatment outcome, and drug resistance.

Model formulation

Two models were developed as extensions of the classical susceptible-exposed-infectious-recovered (SEIR) model to examine the transmission of TB from 2005 to 2035 (Figure 1). Each model classified susceptible and exposed compartments into five age groups: 0 to 4 years-old (S_1, E_1), 5 to 14 years-old (S_2, E_2), 15 to 39 years-old (S_3, E_3), 40 to 64 years-old (S_4, E_4), and 65 years-old and above (S_5, E_5).

Model 1 (Figure 1A) had three major assumptions. First, it assumed the number of people of all ages was evenly distributed for calculation of the number of people who were susceptible and the number who had latent infections of five age groups through the total population and latent infection rate. Second, it assumed to there were no births or deaths during the study period. Third, it assumed that the proportion of recovered patients and the recovery rate remained constant during the study period. Model 1 was initially used to estimate unknown parameters. Then, using these estimated parameters, Model 2 was used to simulate the effects of the preventive treatment — screening for LTBI (Figure 1B). Table1, Supplementary Tables S1 and S2 define the parameters and provide the initial values.

Table 1
Parameters of different preventive treatment regimens

Parameters	Description	1HP	3HP	3HR	4R	6H	9H
η	Completion proportion of TPT	97% ¹³	96% ¹⁴	95% ¹⁴	92% ¹⁵	94% ¹⁶	95% ¹⁷
λ	Treatment rate of TPT	1	1/3	1/3	1/4	1/6	1/9
γ_1	Failure proportion of TPT in LTBI aged 0-4	1.95% ¹³	0.18% ¹⁸	0.25% ¹⁹	0.25% ²⁰	1% ¹⁶	0.29% ²⁰
γ_2	Failure proportion of TPT in LTBI aged 5-14	1.95% ¹³	0.18% ¹⁸	0.25% ¹⁹	0.25% ²⁰	1% ¹⁶	0.29% ²⁰
γ_3	Failure proportion of TPT in LTBI aged 15-39	1.95% ¹³	0.18% ¹⁸	0.25% ¹⁹	0.25% ²⁰	1% ¹⁶	0.29% ²⁰
γ_4	Failure proportion of TPT in LTBI aged 40-64	1.95% ¹³	0.18% ¹⁸	0.25% ¹⁹	0.25% ²⁰	1% ¹⁶	0.29% ²⁰
γ_5	Failure proportion of TPT in LTBI aged 65+	1.95% ¹³	0.18% ¹⁸	0.25% ¹⁹	0.25% ²⁰	1% ¹⁶	0.29% ²⁰

Data analyses

The model was fitted to data from various sources. The relevant parameters were obtained from basic demographic information, IDRS, TBIMS, and previous publications. A maximum likelihood method was used for parameter estimation. These parameters were used to determine the goodness of fit of the model to the observed data, and a chi-square test was used to examine the goodness

of fit. R software version 4.0.5 was used for all statistical analyses, including testing the goodness of fit. Estimation of unknown parameters and simulation of different scenarios were conducted with *deSolve* package²¹.

Results

Parameter estimation and model fitting

We initially modeled the incidence of TB in China from 2005 to 2019 using parameter values provided in Table S1. Overall, the results indicated the model had a good fit (Figure 2, $\chi^2 = 0.3085$, $p > 0.999$). However, there were some deviations of the model and observed data, especially during 2009 and 2012 when the model provided low estimates. We can suggest several possible reasons for these deviations. First, between 2002 and 2008, China's National TB Control Program created the "Health X Project", and this program greatly increased the identification and successful treatment of TB patients²². Second, in 2009, the preparatory work of the fifth national TB epidemiological sampling survey was completed, and this helped to improve case detection²³. Third, in 2009, China completed optimization of the TBIMS and organized related training, which was implemented nation-wide in March; these improved the monitoring and reporting of TB²³. Fourth, in early 2009, the Ministry of Health issued the "Guidelines for the Implementation of China's TB Control Plan", which provided technical support for the standardized implementation of the national TB control program²³. Fifth, by the end of 2011, the General Office of the State Council issued the "National TB Control Plan (2011-2015)", whose goal was to identify and treat 4 million patients with pulmonary TB²⁴.

Effect of different TPTs

We examined the effect of implementing two TPT scenarios beginning in 2021. Scenario 1 assumed that 1,697,248 close contacts (the data were from annual report of Chinese Center for Disease Control and Prevention) were identified each year, and all of them received preventive treatments (Figure 3A). Scenario 2 assumed that preventive treatments were received by all people infected with Human immunodeficiency virus (HIV) (Figure 3B).

Compared with no preventive treatment, the 1HP regimen (daily rifapentine [RPT] + isoniazid [INH] for 4 weeks) provided the greatest cumulative decrease in the number of cases by 2035, and this was followed by the 3HP (weekly RPT + INH for 3 months), 3HR (daily rifampin + INH for 3 months), 9H (daily INH for 9 months), 6H (daily INH for 6 months) and 4R (daily RPT for 4 months) regimens. For the first scenario (treatment of all close contacts), the 1HP therapy reduced the total number of TB cases by 12,793 in 2025 and by 172,194 in 2035 (Figure 3A). For the second scenario (treatment of all people with HIV), 1HP therapy reduced the number of TB cases by 3436 in 2025 and by 46,255 in 2035 (Figure 3B).

Effect of ACF for LTBI and TPT in high-risk populations

According to the results in Section 3.2, we only examined scenarios that used the 1HP regimen in subsequent analyses.

Identification of more close contacts: we first compared the number of TB cases for a baseline level of ACF (tracking 2 close contacts per TB patient) with tracking of 4, 10, and 16 close contacts. As expected, an increased intensity of ACF led to fewer TB cases. However, an ACF eight-times the baseline level (16 close contacts per TB patient) did not achieve the 2035 target (Figure 4A).

Focusing on people infected with HIV: providing all HIV infected people with TPT had a very small effect on the number of TB cases, and the total was well above the 2035 target (Figure 4B).

Increasing ACF for LTBI in children: we analyzed the effect of ACF for LTBI that targeted children and adolescents (age 0–14 years-old), assuming that the screening would be completed within 2, 4, or 6 years. (Figure 4C). Again, these interventions had only a negligible effect on the number of TB cases.

Increasing ACF for LTBI in the elderly: we analyzed the effect of ACF for LTBI that targeted the elderly (age of 65 years-old or more), assuming that the screening would be completed within 2, 4, or 6 years. Remarkably, this intervention was highly effective (Figure 4D). In particular, completion of this screening within 2 years achieved the 2035 target ahead of schedule (2031), although the 2025 target was not achieved (with an 11.3% excess of cases).

Effectiveness of a new vaccine against TB

We examined the impact of a new anti-TB vaccine that was introduced in 2021 and initially assumed it was 100% effective. The current Bacillus Calmette-Guérin (BCG) vaccine already provides protection to children aged 0 to 14 years. And there has been a growing tendency to focus on adolescents and adults.⁸ Thus, we examined the effect of 7.2 million, 9.6 million, 12 million, and 14.4 million annual doses of vaccines for the other four age groups. This intervention led to large decreases in the number of active TB cases (Figure 5A). When there were 14.4 million annual vaccine doses, the 2035 target of a 90% reduction in the incidence of TB was achieved.

We also examined the effects of using a vaccine that had lower effectiveness²⁵ and the effects of different rates of vaccine coverage (Figure 5B). These results indicated that the 2035 target was reached when the product of vaccine effectiveness and the number of annual inoculations in each age group was 14 million.

Effect of ACF for LTBI and TPT in areas with different TB burdens

We then examined the effects of preventive treatments in areas with different incidences of TB. The cumulative reduction in the number of TB cases was greatest when areas with incidences between 55 to 100 per 100,000 were targeted (Figure 6A). We therefore examined the effect of ACF for LTBI and TPT in the areas with incidences greater than 55 per 100,000. These results indicated that completion of ACF for LTBI in areas with high TB incidence within 2 years achieved the 2035 ahead of schedule (2033), although this intervention did not achieve the 2025 target (Figure 6B). When the ACF for LTBI is introduced at a nation-wide level and all patients with LTBI received TPT, the annual incidence of TB decreased at an even faster rate (Figure 6C). In particular, when this nation-wide ACF for LTBI was completed in 3 years, the 2035 target was achieved in 2030; if the nation-wide ACF for LTBI was completed in 5 years, this target was achieved in 2034. However, completion of a nation-wide ACF for LTBI within 3 years did not achieve the 2025 target.

Discussion

We used a SEIR model to simulate the impact of different strategies on the prevention and control of TB in China. Among the six preventive treatments, 1HP was the most effective, in that it led to the smallest number of TB cases by 2035. It is likely that this treatment had the best performance because it has the shortest duration, provides the fastest recovery, and has high patient compliance¹³.

Without vaccination, use of a nation-wide ACF and TPT for LTBI, focusing on high incidence areas, and focusing on the elderly were the most effective strategies. The 2035 target of the “End TB Strategy” was achieved when nationwide ACF and TPT are completed within five years, when ACF and TPT were completed in high incidence areas within two years, or when TPT in the elderly was completed within 2 years. A more rapid completion of the ACF and TPT for LTBI further reduced the cumulative number of TB cases.

Due to the protective effect of the BCG vaccine in children and adolescents, TB has a relatively low incidence in Chinese children. Thus, the ACF and TPT for LTBI only provide a small benefit for this age group. Previous study has also suggested that the introduction of tuberculosis vaccine targeting adolescents has little impact on the epidemic of tuberculosis in China. On the contrary, delivering new post-infection vaccines to older adults can be crucial to provide an important contribution to attaining WHO goals⁸. However, children have many contacts at school, in the family, and in the community, and can therefore have significant roles in the transmission of TB.¹² Therefore, TB surveillance in children and adolescents is essential for prevention and control of TB, especially in areas with low incidence. Individuals infected with HIV have a higher risk of TB¹³, and TB is the leading cause of death in people with HIV.¹⁴ Although the effects of TPT in HIV patients seem to be limited, this intervention remains essential for reducing overall mortality from TB in people with HIV.^{26,27}

We also evaluated the effect of a hypothetical anti-TB vaccine for people who were at least 14 years-old. Based on previous assessments of vaccine efficiency²⁵, we found that the 2035 target can be achieved when the product of annual vaccination doses and vaccine efficiency reached 14 million in each age group. Therefore, it is necessary to attain a high rate of coverage when a new and effective vaccine becomes available. Although there has been progress in the development of new anti-TB vaccines²⁸, the effectiveness of existing vaccines are insufficient for controlling the TB epidemic in China.

There are a huge number of people with LTBI in China⁹. Thus, even the identification of 16 close contacts per patient intense ACF was insufficient to achieve the 2035 target. In other words, simply relying on the expansion of ACF will not achieve the 2035 target.

Conclusion

The overall incidence of TB in China decreased by 9.2% from 2015 to 2019. Despite this progress, interventions that go beyond the present preventive interventions and strategies are needed to reach the 2025 and 2035 targets of the “End TB Strategy”^{29,30}. Introduction of a new tuberculosis vaccine, implementing ACF and TPT for LTBI at a nation-wide scale, in areas with high TB incidence, and in the elderly could allow China to attain the 2035 target.

Abbreviations

Abbreviations	English full name
TB	Tuberculosis
Mtb	<i>Mycobacterium tuberculosis</i>
LTBI	Latent tuberculosis infection
WHO	World Health Organization
IDRS	Infectious diseases report system
TBIMS	Tuberculosis information management system
ACF	Active case-finding
HIV	Human immunodeficiency virus
1HP	A daily dose of rifapentine plus isoniazid for 1 month
3HP	A weekly dose of rifapentine and isoniazid for 3 months
3HR	A daily dose of rifampicin plus isoniazid for 3 months
4R	A daily dose of rifampicin for 4 months
6H	A daily dose of isoniazid for 6 months
9H	A daily dose of isoniazid for 9 months

Declarations

Acknowledgments

We gratefully acknowledge our funders and the data provided by the Chinese Center for Disease Control and Prevention.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 82073612) and the Shanghai Municipal Health Commission (Grant No. GWV-10.1-XK16).

Author contributions

ZW, WZ and TL designed the study. WZ, TL and ZW extracted the data and constructed the database. ZW, WZ and TL analyzed the data and drafted the manuscript. WW, HZ and WC conducted critical revisions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

Availability of data and materials

The data that support the findings of this study are available from the Chinese Center for Disease Control and Prevention but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Chinese Center for Disease Control and Prevention.

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Figures

Figure 1

Transmission of TB in five age groups (A, Model 1) and with different interventions (B, Model 2). $\beta_1, \beta_2, \beta_3, \beta_4, \beta_5$: TB transmission rate from active TB patients (I) to susceptible people aged 0–4, 5–14, 15–39, 40–64 and 65+ years old; p_1, p_2, p_3, p_4, p_5 : proportion of LTBI patients (E) who become active TB patients in each age group; v_1, v_2, v_3, v_4, v_5 : rate at which LTBI patients become active TB patients in each age group; w : relapse rate; p and c : recovery proportion and rate, respectively; $Ep_1, Ep_2, Ep_3, Ep_4, Ep_5$: close contacts of different age groups; Sc : LTBI that are identified by screening (ACF); P_1, P_2, P_3, P_4, P_5 : proportion of people who finished TPT treatment in each age group; η and λ : proportion who completed treatment or a preventive treatment plan, respectively; $\gamma_1, \gamma_2, \gamma_3, \gamma_4, \gamma_5$: proportion of failures from a preventive treatment plan in each age group.

Figure 2

Annual reported TB cases in China from 2005 to 2019 and model results.

Figure 3

Cumulative reduction in the number of TB cases from 2021 to 2025 and 2035 when all close contacts receive treatment (A) and when people with HIV receive treatment (B).

Figure 4

Effect of different ACF strategies for LTBI on the annual incidence of TB in China from 2021 to 2035. A, Tracking intensity of close contacts. B, TPT for HIV infected people. C, ACF for LTBI in children aged 0 to 14 years. D, ACF for LTBI in the elderly (>65 years old). CT: identification of 2 close contacts for each TB patient (baseline); CT*2: twice the baseline (4 contacts), CT*5: five times the baseline (10 contacts); CT*8: eight times the baseline (16 contacts).

Figure 5

Impact of a new ANTI-TB vaccine on the incidence of tuberculosis from 2021 to 2035. A, Changes in the number of TB cases after vaccination, assuming 100% vaccine effectiveness. B, Number of TB cases in 2035 for lower levels of vaccine effectiveness and vaccination coverage ("eff" denotes the effectiveness of the new vaccine.).

Figure 6

Impact of different ACF and TPT strategies for LTBI on the number of TB cases from 2021 to 2035. A, Preventive treatment for people in close contact with TB in regions with different incidences (lower than 30 per 100,000 to above 100 per 100,000). B: ACF for LTBI and TPT in areas with incidences greater than 55 per 100,000. C, ACF for LTBI and TPT at a national scale.

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