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Impact of the gate-keeping policies of China's primary healthcare model on the future burden of tuberculosis in China: a protocol for a mathematical modelling study

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ABSTRACT

Introduction In the past three decades, China has made great strides in the prevention and treatment of tuberculosis (TB). However, the TB burden remains high. In 2019, China accounted for 8.4% of global incident cases of TB, the third highest in the world, with a higher prevalence in rural areas. The Healthy China 2030 highlights the gate-keeping role of primary healthcare (PHC). However, the impact of PHC reforms on the future TB burden is unclear. We propose to use mathematical models to project and evaluate the impacts of different gate-keeping policies.

Methods and analysis We will develop a deterministic, population-level, compartmental model to capture the dynamics of TB transmission within adult rural population. The model will incorporate seven main TB statuses, and each compartment will be subdivided by service providers. The parameters involving preference for healthcare seeking will be collected using discrete choice experiment (DCE) method. We will solve the deterministic model numerically over a 20-year (2021–2040) timeframe and predict the TB prevalence, incidence and cumulative new infections under the status quo or various policy scenarios. We will also conduct an analysis following standard protocols to calculate the average cost-effectiveness for each policy scenario relative to the status quo. A numerical calibration analysis against the available published TB prevalence data will be performed using a Bayesian approach.

Ethics and dissemination Most of the data or parameters in the model will be obtained based on secondary data (eg, published literature and an open-access data set). The DCE survey has been reviewed and approved by the Ethics Committee of the School of Public Health, Sun Yat-sen University. The approval number is SYSU [2019]140. Results of the study will be disseminated through peer-reviewed journals, media and conference presentations.

Strengths and limitations of this study

- ► This study will develop a mathematical model incorporating referral factors to evaluate the epidemiological impacts, costs/benefits and cost-effectiveness of different policy scenarios.
- ► This study will develop an easy-to-understand policy evaluation tool for policymakers to formulate important evidence to inform their decisions, using tuberculosis (TB) as an example.
- ► Compartmental models predict the epidemiological outcomes of TB only under predefined conditions but have limitation that will not be responsive to changes such as new treatment or vaccines.

INTRODUCTION

According to the WHO's Global Tuberculosis (TB) Report released in 2020, TB remains the leading fatal infectious disease and one of the top 10 causes of death worldwide.[1] Although China has made great progress in TB control in the past three decades, the TB burden remains high.[2] With the widespread implementation of modern prevention and control strategies, including early detection, improved treatment and increased advocacy based on the operational guidance as recommended by WHO since 2011, the national incidence rate of pulmonary TB has fallen from 71.09 per 100 000 in 2011 to 60.53 per 100 000 in 2017.[3 4] However, in 2019, China still ranked third among the eight countries that together accounted for two-thirds of the estimated global incident TB cases, with 8.4% of global cases, and was second only to India (26%) and Indonesia (8.5%).[1] In 2014, the WHO approved an ambitious End TB Strategy in alignment with the framework of the Sustainable Development Goals, aiming for a 90% reduction in global TB incidence rate and a 95% reduction in global TB deaths (compared with 2015) by 2035.[5] China is striving to achieve the goals set out by the

End TB Strategy. However, the progress towards global TB targets is threatened by the impacts of the COVID-19 pandemic in 2020.[1] In China, significant disparity exists in the incidence of TB between urban and rural areas. Previous studies showed that the prevalence of TB in rural areas was nearly three times the national average, and rural patients reported longer diagnostic and treatment delays than urban patients.[6] Successful case detection and management in China's rural areas are crucial for the Chinese government to achieve the aims of the End TB Strategy.

Over the past decade since the Chinese government proposed a comprehensive healthcare reform plan in 2009, universal health coverage has been steadily advanced.[7 8] The reform was intended to strengthen the primary healthcare (PHC) system to assure its central role in uniting clinical care and public health. A tiered PHC system was built to address the problems of limited access to healthcare and prohibitive costs.[9] Under the tiered model, different tiers of healthcare institutions could operate as initially designated, further to better plan the allocation of medical resources. However, after more than a decade of efforts, researchers found that the lowest tier of PHC providers was still not the preferred choice for both urban and rural residents with slightly more severe symptoms. Widespread gaps in the quality of primary care especially in rural areas were the most common reasons.[8] It can be seen that in order to achieve the goal of universal coverage, improving the quality of PHC services, achieving continuity of care and building an integrated delivery system based on PHC are considered top priorities.[9] The Healthy China 2030 Plan reinforced the importance of PHC and highlighted its gate-keeping role[10] by emphasising patients' first contact with lower tier medical providers such as village clinics (VCs) and township health centres (THCs) in rural areas. Two options are available to policymakers to standardise the use of PHC: (1) compulsory requirement for the first contact with PHC providers, prior to referral to higher tier providers and (2) incentive-based, rather than mandatory approach through financial incentives to induce patients to choose lower tier healthcare providers for first visits (ie, different reimbursement rates for different levels of institutions). However, under the gate-keeping policy, China's TB control programme still faces several challenges, and the impacts of different policy models on the future burden of TB remain unclear. PHC institutions take more and more responsibility for TB prevention and control, especially with the release of the new 'Technical Specifications for TB Prevention and Control in China' (2020 edition) by the National Health Commission in April 2020.[11] These medical institutions are mainly responsible for the screening, recommendation and referral of suspected patients with TB to higher tier designated TB institutions. In rural China, the detection of suspected TB cases is critically dependent on the initial diagnostic ability of practitioners in VCs and THCs, the bottom two tiers in the rural health system and the first stop where the majority of rural patients with TB with minor illness seek care.[12] In this study, we hypothesise that the gate-keeping policy may improve the overall efficiency of the health system but may not necessarily improve the overall quality of care, unless the quality of care provided by lower tier PHC facilities equals or exceeds that of the high tier.

The End TB Strategy has set interim milestones for 2025.[13 14] However, it is unclear whether China can achieve these targets, given that China's health system reforms are ongoing and many challenges still exist (eg, growing multidrug-resistant TB).[1] The lack of assessment tools for hypothetical TB interventions may be a major reason for the paucity of research in this area.[15] Although several mathematical models[16–18] have been developed for TB in China, they do not incorporate health system reform policies as a component. It is necessary to develop an estimation tool for the status of TB control in rural China accounting for the effect of the gate-keeping policy, in conjunction with China's current TB prevention and control policies, population structure and TB epidemic status.

Given the advantageous ability of mathematical modelling to compare several hypothetical intervention strategies and policies in a systematic framework to project future impacts,[19–21] we intend to mathematically model the outcomes of TB control projects in rural China. Modelling is particularly useful for conducting assessments at a population level and predicting the long-term impacts of policies.[22] The classical epidemic models, which are known as compartmental models,[23] have been used widely to model the dynamics of many infectious diseases, such as HIV,[24–27] hepatitis B virus,[28] COVID-19[29 30] and TB.[16 18] Besides, stochastic models like agent-based models offer an alternative approach to project future trends.[31] Integrated cost-effectiveness analysis provides an important perspective for health policymakers with a basis for effective resource allocation and objective decision-making, especially in resource-limited settings.[32 33] Combined with information on resource use (eg, cost data), model projections of health impacts can also be used to estimate the cost-effectiveness of competing policy options and identify the optimal policy portfolios. It is worth noting that, unlike previous studies of TB-related mathematical models, where the main parameters were primarily from conventionally designed observational studies, some of the key parameters in our model involving the rates of correct management (eg, diagnosis and referral) of patients seeking healthcare for the first time, which is derived from the study led by members of our research group, which took unannounced standardised patients (USPs) approach to assess the quality of PHC.[12] The use of USP could control for some confounding factors to enable comparison across different levels of medical institutions, as the 'same trained patient' is presented to all healthcare practitioners interviewed for evaluation.[34]

In this study, we propose to develop a mathematical model to project and evaluate the impacts of different gate-keeping policies on health outcomes and the

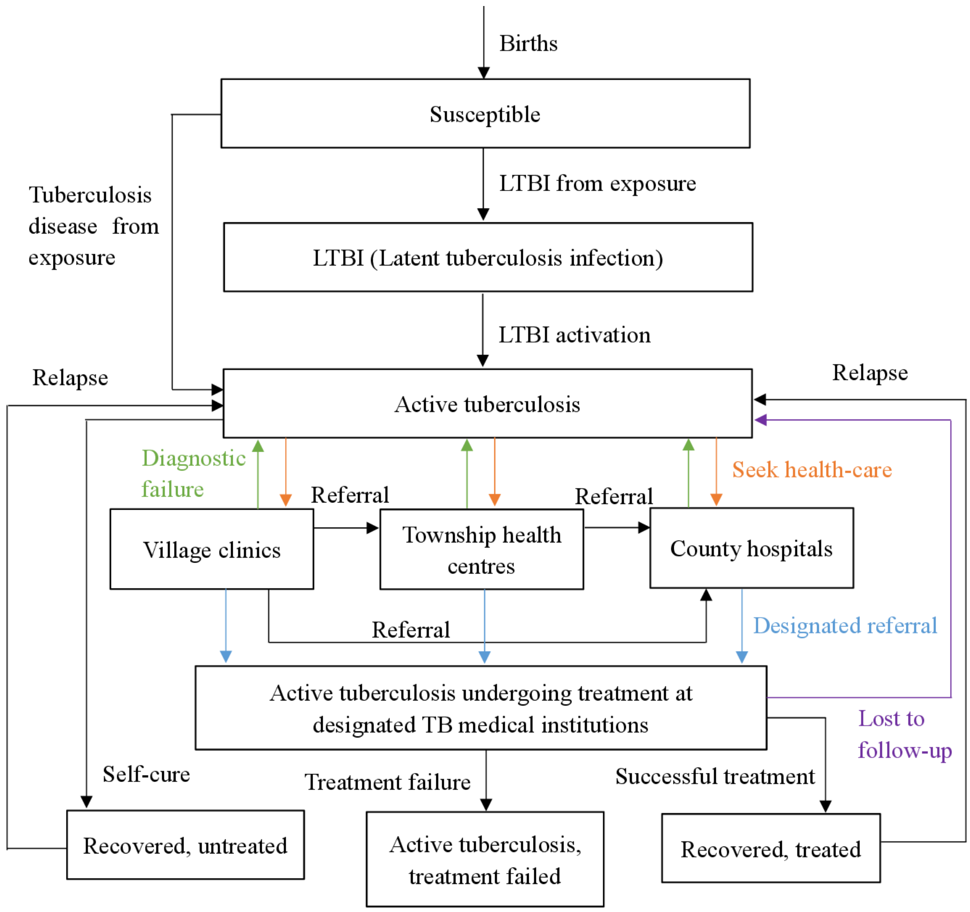

Figure 1 Compartmental model of tuberculosis (TB) transmission and referral. LTBI, latent tuberculosis infection.

cost-effectiveness of the policies. The exercise on TB will also inform evaluation work on the impacts of gate-keeping policy on other health conditions.

Objectives

1. To develop a compartmental mathematical model based on previous TB transmission models for evaluating TB control in China, which will incorporate the effects of gate-keeping policies.
2. To apply the model to simulate the epidemiological impacts, costs/benefits and cost-effectiveness of different policies, and to inform policymakers in subsequent PHC policy development.
3. To explore which type of primary care and referral policy are more appropriate for the TB control function of PHC facilities in rural China.

METHODS AND ANALYSIS

Model construction

We will develop a deterministic, population-level, compartmental model to capture the dynamics of TB transmission. The model will incorporate seven main TB statuses, and individuals in each of these compartments will be subdivided by service providers (ie, VCs, THCs and county hospitals, figure 1). The seven statuses of TB are as follows: (1) uninfected, (2) latent TB infection (LTBI), (3) undiagnosed active TB, (4) diagnosed active TB with ongoing effective treatment, (5) TB that has been successfully treated, (6) TB from which the patient spontaneously recovered without treatment, (7) TB that failed treatment. This model is adapted from classical TB transmission models with addition of the compartments for three-tier PHC institutions.[16 35 36] Population growth will be incorporated into the model to approximate the projections at the country level. Individuals may also exit any of these compartments due to background and/or TB-related mortality. We aim to simulate the process of TB transmission using the compartmental model. Once exposed, susceptible individuals may acquire LTBI or proceed directly to the active TB stage. Individuals with TB disease (ie, the symptomatic stage) may recover spontaneously, die from untreated TB or seek medical care through different tiers of the rural healthcare system (ie, VCs, THCs and county hospitals). Patients with TB who seek healthcare at each tier might be correctly diagnosed, referred to a higher tier of care or misdiagnosed. For instance, among patients whose first point of contact is a visit to the VC, the system might (1) correctly diagnose as suspected TB at the VC and refer to designated TB medical institutions, (2) refer the patient from the VC to the THC and correctly diagnose as suspected TB at the THC and refer to designated TB medical institutions, (3) refer the patient from the VC to the THC, then again to the county hospital and correctly diagnose as suspected

TB at the general county hospital and refer to designated TB medical institutions or (4) fail to diagnose as suspected TB correctly. Patients who are diagnosed with active TB might initiate treatment or not.[37] Those who initiate treatment for TB might be cured, acquire drug resistance, stop treatment or die during treatment. Individuals who have been cured of TB symptoms might relapse later due to a weakened immune system. Similarly, individuals with LTBI might become infected during contact with persons with active TB and, therefore, develop TB symptoms.

The compartmental structure of the model is shown in figure 1, from which the mathematical symbols have been removed for simplicity. The final framework may be slightly modified after consultation with clinical and public health experts. Arrows between the compartments indicate the possible directions of flow of the affected individuals. A system of ordinary differential equations (ODEs) will be developed to describe the flow of population into and out of each compartment. The full system of the ODEs and detailed formulae are given in Equations 1–10, online supplemental file 1. The system of developed ODEs will be solved numerically in MATLAB 2020 (The MathWorks, USA), using a difference equation method with a time step of 1 month. The model will be projected forward to 2040 (20 years from 2021), and a range of epidemiological outcomes (eg, TB incidence and TB prevalence) will be extracted under different policy scenarios. Prior to the projections, the model will be calibrated using a Bayesian approach based on published reports of recent estimates of TB.

Study population

The target population will be adults aged ≥18 years. Individuals will enter the model at an entry rate that will be derived from the background population growth and rates at which the age of adulthood is reached (as shown in Equation 11, online supplemental file 1). People will exit the model at the background mortality rate.

Policy scenarios to be modelled

Four alternative strategies will be compared in our study, which vary with respect to selection of the healthcare provider for the initial visit.

1. Status quo: no gate keeping with free choice of first-contact healthcare providers.
2. Scenario 1: compulsory first contact with village-tier providers.
3. Scenario 2: compulsory first contact with township-tier providers.
4. Scenario 3: patients are free to select first-contact healthcare providers, but different reimbursement rates defined by the government apply across the different tiers of providers.

We propose to simulate the epidemiological and economic outcomes under different policies by varying some parameters in the compartmental model. We plan to set the proportion of first visit to village-tier (scenario 1) or township-tier (scenario 2) healthcare providers between 90% and 100%, with the remaining proportion randomly assigned to other tiers, respectively. For policy scenario 3, we plan to model the reimbursement rates and their impact on patients' healthcare-seeking behaviours by using the parameters obtained from the face-to-face survey, which includes DCE and scenario simulation questions. The survey will be conducted in rural areas in China and designed to investigate individuals' preference for care seeking under different key attributes, such as under different reimbursement rates across different healthcare providers.

Model parameters and collection

The model will incorporate four domains of parameters: population demographic profiles, disease (TB) condition, health service system information and individuals' preferences for healthcare (as shown in table 1). The four domains of parameters will be collected and acquired only in rural areas. We provide details of the data sources and/or data collection methods below:

1. Sociodemographic profiles: information on demographic and epidemiological variables will be collected, such as the TB prevalence among the rural adult population, population data, annual population growth rate and background mortality rate across rural areas. This information will be collected from published literature, the China Statistical Yearbook and the China Health Statistical Yearbook.
2. Disease condition: these parameters pertaining to TB-related disease progression (eg, TB transmission probability, reactivation rate, treatment rate and cure rate) are shown in table 1 and will be mostly obtained through an extensive review of the published literature and from publicly available data sources (eg, governmental open data sets).
3. Health services: to obtain the statistics of correct diagnostic rates and appropriate referrals at each tier of the healthcare system, we will use the results from a survey led by members of our research team, which was conducted to assess the quality of PHC in real practice by using USPs from a random sample across three provinces in China.[12] A standardised patient is a healthy person trained to 'consistently' simulate the medical history, physical symptoms and emotional characteristics of a real patient. The standardised patients visited PHC providers unannounced and were debriefed via structured questionnaire, the results of which were confirmed against video records of interactions with PHC providers at different tiers. In addition, cost data related to TB services, such as cost of chest X-ray, sputum testing, consultation and TB treatment, will be obtained from the published literatures.[38 39]
4. Individuals' preference for care seeking: we will conduct a face-to-face survey using the DCE method to investigate individuals' preferences among several options for different levels of policy attributes. DCE guidelines will be followed.[40 41] Key attributes and attribute levels will be considered, such as compulsory

Table 1 Summary, description and resources of key model variables

Variables	Definition	Sources
Demographic and epidemiologic data		
Population data	Initial number of people with status i	Published literature, China Statistical Yearbook and China Health Statistical Yearbook
Annual entry rate	Sum of background population growth rate and the rate of reaching age of adulthood	
Mortality rate	1. Annual background mortality rate 2. Annual mortality rate due to untreated TB	
Prevalence	National TB prevalence among the target population	
TB disease-related variables		
Transmission probability	Probability of acquiring latent TB infection or active TB on contact	Published literature[22–27]
Reactivation rate	Reactivation rate from latent TB infection to active TB	
Lost to follow-up	Lost to follow-up rate for TB after initiating treatment	
Treatment rate	Rate of initiating TB treatment	
TB cure rate	Cure rate for TB after treatment	
Contact rate	Contact rate for persons with TB	
Primary health service variables		
Correct diagnostic rates	Correct diagnosis rate of suspected TB cases in VCs, THCs and county hospitals	USP project developed in three provinces by our team members,[12] published literatures[38 39]
Appropriate referral rate	Rate of appropriate referrals of suspected TB cases to designated medical institutions from VCs, THCs and county hospitals	
Cost data	Cost of chest X-ray, sputum testing, consultation and TB treatment	
Individuals' choices		
Preference of care	1. Proportion of individuals selecting different tiers of the rural healthcare system under different policy scenarios 2. Factors that influence health-care-seeking choices	Field work to be conducted using DCE method

DCE, discrete choice experiment; TB, tuberculosis; THC, township health centre; USP, unannounced standardised patient; VC, village clinic.

gate-keeping policies (three levels: not compulsory vs compulsory through VCs vs compulsory through THCs), reimbursement rate across the levels of providers (simulating three different reimbursement rates for each level of PHC providers) and distance from health service sectors (three levels: ≤15 min vs 15 min to 30 min vs >30 min). We will also include a question about intention to seek care if they have TB symptoms for 2 weeks among rural residents. Participants will be recruited from rural areas in Gansu province. The inclusion criteria are (1) over 18 years of age, (2) rural household, (3) without hearing impairment, (4) normal intelligence and comprehension. We intend to use stratified random sampling. First, three cities will be randomly selected according to administrative region and level of economic development within Gansu province. Second, two counties will be randomly selected from each of the three selected cities. Third, three townships and villages will be randomly selected from each county. Fourth, rural residents from the selected townships and villages will be randomly selected to participate in the survey. The participants will be briefed about the anonymity and voluntary nature of this survey and informed that declining to participate will have no consequences and that the data will only be used for research purposes. Informed consent will be obtained before completing the questionnaire. The DCE questionnaire will be designed to take approximately 15 min to complete. The target sample size is 300 (approximately 100 patients from each PHC provider tier). The participants will be informed that they will receive a coupon for the retailer Jingdong with a cash value of RMB100 (approximately US$15) as compensation for their time spent in the interview.

Model calibration

We will perform a numerical calibration analysis against the available published TB prevalence data,[2] using a Bayesian approach.[42] We plan to take a sample of 1000 sets of parameter combination within the fluctuating range of modifiable parameters, excluding those obtained from the USP survey, and then fit the output of the model to calibration targets. The model with the best goodness of fit will be selected as the best model. The first 400 simulation outputs with the best goodness of fit will be selected as the sensitivity interval.

Sensitivity analysis

Given that correct TB diagnosis at the primary care level often involves repeated visits instead of a single and initial interaction simulated by USPs, sensitivity analysis will be performed by varying the modifiable parameters, such as correct diagnostic rates and appropriate referral rates from the USP survey, using random sampling from their prior distribution.[43]

Model application and expected outcomes

Epidemiological prediction

We will solve the deterministic model numerically over a 20-year timeframe (from 2021 to 2040) and calculate the TB prevalence, incidence and cumulative new infections under the status quo or various policy scenarios. Given that changing diagnostics, new treatment and vaccines may be introduced to TB control strategies and increase uncertainty over a 20-year timeframe, we will report intermediate results at a 10-year time horizon.

Cost-effectiveness outcomes

We will conduct a cost-effectiveness analysis using standard protocols[44 45] by calculating the average cost-effectiveness for each policy scenario relative to the status quo and then calculating the incremental cost-effectiveness of each scenario relative to the next most cost-effective scenario. In particular, we will calculate the incremental quality-adjusted life years (QALYs) and costs of each policy scenario relative to the status quo, with an annual discount rate of 3%. A scenario is considered optimal if it has the highest net monetary benefit. All costs will be reported in 2020 International Dollars and calculated using the International Monetary Fund gross domestic product (GDP) deflator and implied purchasing power parity conversion rates. The WHO Commission on Macroeconomics and Health defined cost-effective interventions to be those that cost less than three times the GDP per capita if healthy life years gained.[46] In this study, we will use the criteria of the WHO: (1) interventions that cost less than the GDP per capita per QALYs gained will be defined as very cost-effective, (2) those that gain a QALY at a cost between one and three times the GDP per capita will be cost-effective and (3) the remainder will not be cost-effective.[47]

Ethics and dissemination

Most of the data or parameters in the model will be obtained based on secondary data (eg, published literature and open access data set). There are no specific ethical issues regarding these data except for the information to be collected through the DCE survey. The DCE survey has been reviewed and approved by the Ethics Committee of the School of Public Health, Sun Yat-sen University. The approval number is # SYSU [2019]140. Results of the study will be disseminated through peer-reviewed journals, media and conference presentations. We will also present our findings in the form of reports to the funding agency.

DISCUSSION

The high prevalence and incidence of TB across China have posed a great challenge to the country's health systems, especially PHC providers, following the proposal of the gate-keeping role of PHC by the Healthy China 2030 Plan. Despite more than 10 years of health system reforms, few researchers have focused on the impacts of ongoing reforms on the quality of PHC for patients with TB. Only one published study[12] evaluated the short-term intermediate outcomes (ie, correct management rate) and used neither sophisticated tools nor a cost-effectiveness analysis. This proposed study will contribute robust evidence to the limited national literature by developing a mathematical model to predict the future burden of TB in China under different PHC gate-keeping policy settings. The results from this study will provide important evidence for policymakers in China through an easy-to-understand but sophisticated scenario exercise. The model/tools developed will be freely available to the research and policy communities.

Individuals' preferences in terms of policy attributes and choice of healthcare providers at different tiers are another important factor that influences the implementation and promotion of the gate-keeping role of PHC. Our study design uses the DCE method to investigate the preferences of TB-infected persons in rural areas. The method was introduced into health economics more than 15 years ago to elucidate preferences in healthcare seeking.[41 48] The findings of the DCE survey from this study will help us to understand the difficulties of implementing compulsory gate-keeping policies in a real-world setting. The survey will also provide a critical basis for policymakers to continue to implement and adjust this policy in the future.

Our proposed study has several limitations. First, although compartmental models are widely used in mathematical modelling of infectious diseases, by design, these models predict the epidemiological outcomes of TB in rural China under predefined conditions but will not be responsive to changes in demographics and progression in new diagnostics, treatments or vaccines. For example, we have assumed that the demographics of the rural population and the epidemiological features of TB epidemics in rural areas are stable. If the TB incidence among rural residents changes rapidly over the next 20 years, the predictions of our model may be biased.[49] Second, although DCE is a relatively well-established method for predicting individual choices, the optimal design for alternative choices remains challenging.[41] A better understanding of the relationships between design efficiency and respondent efficiency is needed. Third, the experiences of other researchers suggest that it may be more difficult for rural participants to understand the design of DCE.[50] Therefore, we intend to recruit well-experienced local interviewers as our fieldworkers. They will also receive training before the study. Fourth, the USP tool for the assessment of quality of care has a limitation that it is hard to simulate repeated visits since multiple visits would increase their risk of being identified. The parameter of correct diagnostic rates may be underestimated through the evaluation of the USP's initial visit. Thus, we plan to carry out sensitivity analysis on the USP-derived parameters. Fifth, although we do not incorporate active case finding of TB cases or LTBI in the current study due to the low uptake of TB/LTBI screening programmes and the fact that rate of active case finding remains low in China, it is an important strategy to end TB and may be a future research direction.

Current status of study

The study is currently ongoing. This project is sponsored by the China Medical Board, and funding began in June 2019. As of the time of writing, November 2020, we have completed the design of the compartmental model structure. As of the time of major revision, June 2021, we have completed the design of the DCE questionnaire. The field survey of individual preferences for care seeking using DCE is on scheduled being conducted and expected to be completed by October 2021. The data analysis and model fitting will be conducted from November 2021 to May 2022.

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Contributors JLi and RL conceptualised the study, designed and refined the protocol to ensure that it accurately reflects the project approach and implementation strategy. XY drafted the original protocol and has prepared the publication. JG revised and edited the protocol. DRX, SH, HX, YR and RL provided expert advice to help refine the methodology and implementation strategy of this protocol. YH, JG, CH, SS, JLiao and YC assist with the development of data collection. LP assisted with data management. XW will be responsible for participant recruitment of DCE survey. All authors provided comments on the implementation of the project and the content of the manuscript. All authors read and approved the final manuscript.

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