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Transmissibility of tuberculosis among students and non-students: an occupational-specific mathematical modelling

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Abstract

Background: Recently, despite the steady decline in the tuberculosis (TB) epidemic globally, school TB outbreaks have been frequently reported in China. This study aimed to quantify the transmissibility of *Mycobacterium tuberculosis* (MTB) among students and non-students using a mathematical model to determine characteristics of TB transmission.

Methods: We constructed a dataset of reported TB cases from four regions (Jilin Province, Xiamen City, Chuxiong Prefecture, and Wuhan City) in China from 2005 to 2019. We classified the population and the reported cases under student and non-student groups, and developed two mathematical models [nonseasonal model (Model A) and seasonal model (Model B)] based on the natural history and transmission features of TB. The effective reproduction number (R_{eff}) of TB between groups were calculated using the collected data.

Results: During the study period, data on 456,423 TB cases were collected from four regions: students accounted for 6.1% of cases. The goodness-of-fit analysis showed that Model A had a better fitting effect ($P < 0.001$). The average R_{eff} of TB estimated from Model A was 1.68 [interquartile range (IQR): 1.20–1.96] in Chuxiong Prefecture, 1.67 (IQR: 1.40–1.93) in Xiamen City, 1.75 (IQR: 1.37–2.02) in Jilin Province, and 1.79 (IQR: 1.56–2.02) in Wuhan City. The average R_{eff} of TB in the non-student population was 23.30 times (1.65/0.07) higher than that in the student population.

Conclusions: The transmissibility of MTB remains high in the non-student population of the areas studied, which is still dominant in the spread of TB. TB transmissibility from the non-student-to-student-population had a strong

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influence on students. Specific interventions, such as TB screening, should be applied rigorously to control and to prevent TB transmission among students.

Keywords: Tuberculosis, Transmission, Compartmental model, Occupational-specific dynamics, Student, Non-student, China

Background

Despite widespread implementation of control measures, including pharmaceutical therapy and vaccination, tuberculosis (TB) remains a major cause of disease and death in most high-burden countries. In 2021, most TB cases occurred in the 30 high-burden countries (87%), in which 8 countries account for two-thirds, with China (7.4%) ranking after India (28%) and Indonesia (9.2%) [1]. China is also on the three lists of high-burden countries for TB, HIV-associated TB, and multidrug resistant tuberculosis (MDR-TB) of the World Health Organization (WHO). Despite the difficulties that remain, such as the emergence of drug-resistant strains of *Mycobacterium tuberculosis* (MTB) and the coinfection of TB with the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), the global incidence of tuberculosis is estimated to slowly decline by 1.6% per year, far from the 4–5% estimated to be required to reach the objectives of the WHO's End TB Strategy [2]. Due to the emergence of the COVID-19 pandemic, there is a large global drop in people newly diagnosed with TB and reported in 2020, compared to 2019[3].

In China 2021, the number of reported TB cases is ranked second highest after viral hepatitis, and in terms of death is the second highest after AIDS [4]. There are about 250 million students in China (about 20% of the population). The reported TB cases in students account for about 4–6% of the total reported TB cases [5]. TB cases in the 15–24-year age group accounted for about 85% of the total reported TB cases in students, which means the number of TB cases in high school and college students is higher, especially in the 18-year-old age group [6–8]. When MTB spreads in schools, it can be transmitted rapidly and have a major impact on young people simply because of cluster. Therefore, it is one of the reasons why school TB outbreaks have been reported frequently in China, despite the steady global decline of the TB incidence trend [9–13]. Moreover, MDR-TB outbreaks have also been reported in schools, making TB control in schools much more difficult [14, 15].

Theoretical epidemiology, also known as the mathematical model of epidemiology, uses mathematical formulas to express the law of disease prevalence explicitly and quantitatively between cause, host and environment, and to theoretically explore the effects of different control measures. Mathematical modelling has become a powerful tool for analysing epidemiological characteristics [16], which is used to reveal the characteristics of the internal spread of infectious diseases. Transmission dynamic models are commonly used in infectious disease models, including Susceptible-infectious-recovered model, Susceptible-exposed-symptomatic-recovered (SEIR) model, and Autoregressive integrated moving average model. Some studies use models to analyse TB, such as TB intervention assessments [17], analysis of vaccine control effectiveness [18, 19], and TB treatment [20–23]. Different models have been developed to treat latent TB infections (LTBI) that incorporate certain factors such as drug-resistant strains [24], coinfection with HIV [25], and TB reinfection [26], and to study the epidemiology of TB [27]. Specific targeted sub-populations have been defined, including age-specific subgroups [28], adults and children [29], and smokers and non-smokers [30]. However, only a few studies have used occupational mathematical models to study TB transmission in China. The construction of TB models which are used to explore the dynamics of TB transmission between students and non-students is unclear.

The prevention and control of TB in schools has been improved with the efforts of medical personnel staff at all levels. In the past 10 years, control measures have been continuously strengthened and improved, but the transmission characteristics of TB in schools are still unclear. The aim of this study is to establish a mathematical model of TB between students and non-students, to analyse and explore the transmissibility of MTB in schools, and then to take reasonable and effective measures to control TB in schools.

Methods

Study design

In this study, based on the reported and observed morbidity characteristics, we developed a SEIR model with two occupational groups (students and non-students). We investigated the role of occupation in the transmission process and evaluated feasible control strategies to achieve the objectives outlined in the WHO End TB Strategy [3]. Furthermore, this study classified active TB patients into high or low transmissibility groups according to their pathogenic status [31].

Firstly, in this study, a dataset was constructed, including basic information (sex, age, occupation, and location)

and case classification (positive and negative cases of pathogen). Demographic data was obtained from the Chinese Statistical Yearbook [32–35], including the total population, the total student population, birth rate, and the death rate for each city (Additional file 1: Table S1).

Secondly, two mathematical models (Models A and B refer to non-seasonal and seasonal models, respectively) were constructed to simulate the reported TB cases of the four regions in China, based on the natural history and seasonality of TB. In each model, we divided the collected data into four subpopulations of active diseases in two dimensions. The first dimension for all calculations and outputs was the occupation of students ($_1$ subscript) or non-students ($_2$ subscript), while the second dimension was the pathogenic status, including pathogen positive ($_p$ subscript) and pathogen negative ($_n$ subscript) pulmonary disease. In addition, goodness-of-fit was conducted to evaluate the effectiveness of model fitting.

Finally, we simulated the sub-population-to-sub-population transmission process, to determine the combination with the most distinctive impact, via calculating effective reproduction number (R_{eff}) and performing knock-out analysis. This enabled the formulation of effective and targeted control measures for TB transmission in China, in accordance with occupation-specific prevention and control (Fig. 1).

Data collection

We collected year-based TB incidence data from the China Public Health Science Data Center (http://www.phsciencedata.cn/Share/index.jsp) from January 1, 2005 to December 31, 2017 for each province in China (not included Hong Kong, Macao, and Taiwan) [36]. After we calculated the average annual incidence rate and plotted the incidence map (Fig. 2), we found an inequality in the disease burden.

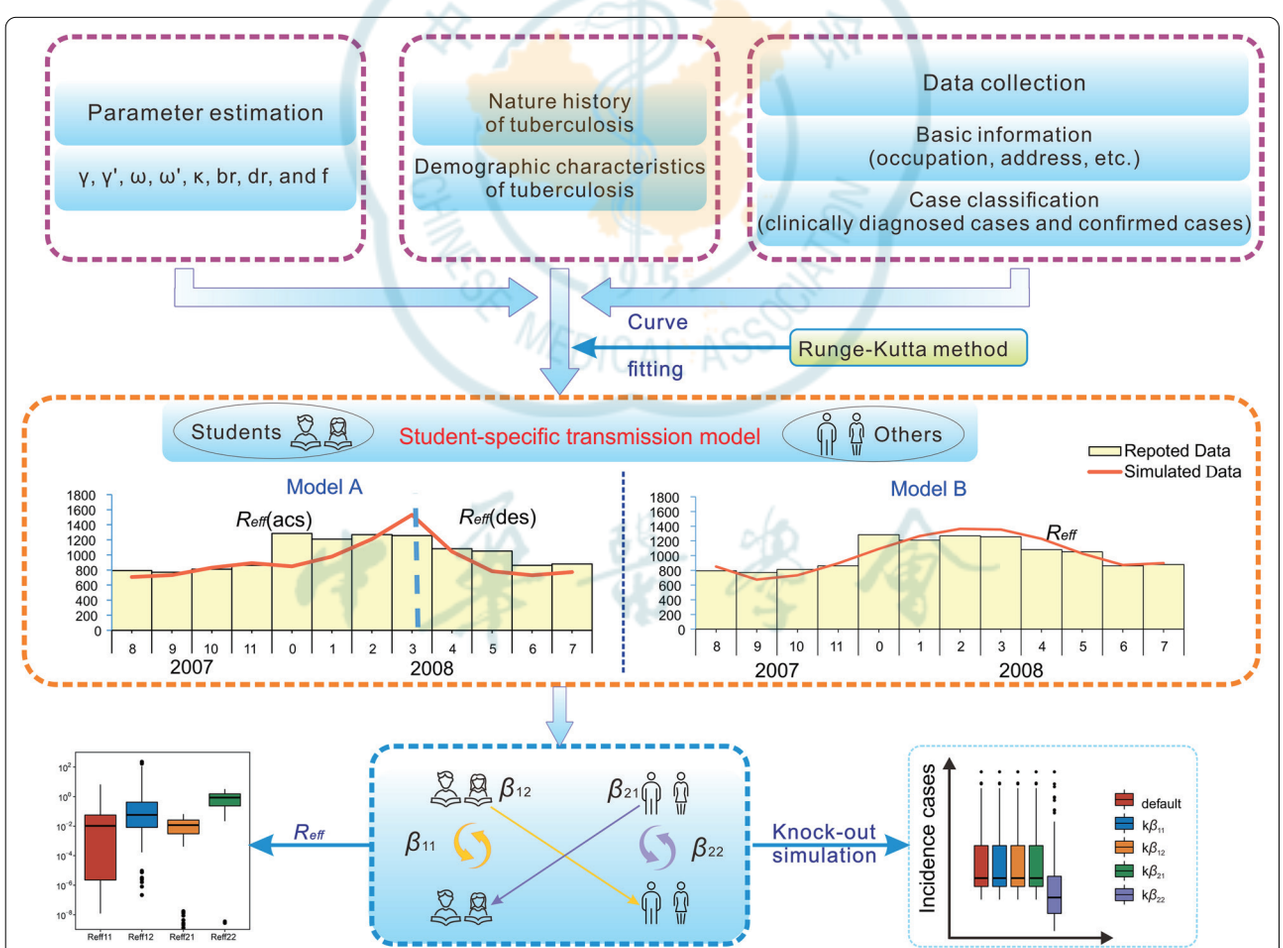

Fig. 1 Study design for analysing the transmissibility of TB among students and non-students. The four subscripts are denoted as follows: TB transmission in student groups ($_{11}$ subscript), TB transmission of student-to-non-student groups ($_{12}$ subscript), TB transmission in non-student groups ($_{22}$ subscript), TB transmission of non-student-to-student groups ($_{21}$ subscript)

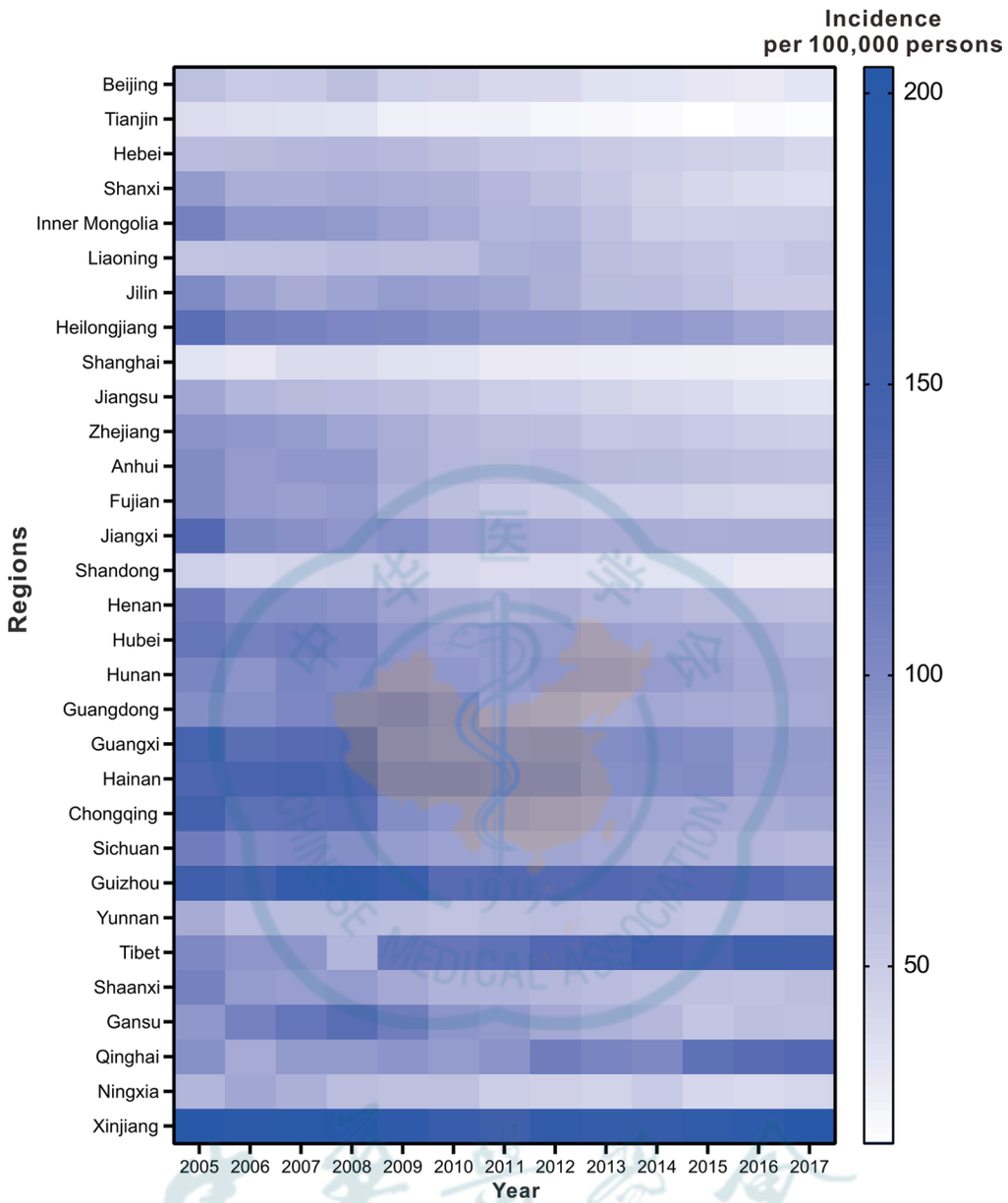

Fig. 2 Regional and national distribution of reported TB incidence. Reported TB incidence in different regions (not included Hong Kong, Macao, and Taiwan) in China from 2005 to 2017

Considering the geographic position, the TB incidences in four regions (located in the north, south, southwest, and middle of China) are average incidences compared to those of the other regions in China, which is consistent with the population distribution [37], which means that the selection can better reflect the TB epidemiological characteristics in geographical differences.

This study collected data on reported TB cases, populations, and areas in four regions [Jilin Province, Wuhan City in Hubei Province, Chuxiong Yi Autonomous Prefecture (Chuxiong Prefecture) in Yunnan Province, and Xiamen City in Fujian Province] (Additional file 1: Table S1), which are from the Health Commission of each region, the Statistics Bureau of each region and data mentioned in some researches [38, 39], etc. Therefore, the TB results from these four regional analyses are effectively representative of TB epidemiological characteristics in China.

Classification of TB patients

Reported TB cases included in this study consisted of laboratory confirmed pulmonary tuberculosis (PTB), and clinical diagnostic PTB. Since the Chinese government implemented the National Notifiable Disease Surveillance System (NNDSS) for infectious diseases in 2004, the diagnostic criteria for TB has changed several times ("WS288–2008 Diagnosis of tuberculosis" [40] with the adjusted notice in 2017 [41], and the "WS 288–2017 Diagnosis of Tuberculosis" [42] and the "WS 196–2017 Classification of Tuberculosis" standards [43], with the adjusted notice in 2018 [31]). All TB cases were classified on the base of the following criteria. The confirmed PTB cases were denoted as people with possible PTB symptoms, such as a continuous cough for more than 2 weeks, hemoptysis, and night sweat, and confirmed by a sputum smear and/or a sputum culture with the result of detectable acid-fast bacilli or positive result from a rapid molecular diagnostic instrument (e.g., GeneXpert). The clinical diagnosis of PTB was defined as people with obviously abnormal chest radiography along with no curative effect from anti-inflammatory treatment under the circumstance of negative results from laboratory tests or absence of related results [44–46].

The PTB cases are classified as follows, based on pathogenic findings: sputum smear positive, sputum smear negative, sputum culture positive, sputum culture negative, molecular biology positive, and without sputum PTB [42]. In the latest notice published in 2018, the classification of TB cases, which must be reported in the NNDSS, was adjusted to "pathogen positive (including sputum smear positive and only sputum culture positive PTB)", "pathogen negative (including sputum smear negative PTB)", "rifampicin resistant", "no pathogenic findings (including without sputum PTB and tuberculous pleurisy" [31]. We have reclassified all historical data according to the new classification notice for consistency (see detail in Additional file 2: Table S2).

Diagnosis criteria of PTB patients

The diagnosis of PTB is based on a pathogenic examination (including bacteriology and molecular biology), combined with epidemiological history, clinical manifestations, chest imaging, relevant auxiliary examinations, differential diagnosis, and other comprehensive analyses [47]. Pathogenic and pathological results were used as the basis for diagnosis. Therefore, the following inclusion criteria were TB cases with pathogen positive ["positive cases with MTB detected by sputum smear, culture-confirmed or molecular biology (nucleic acid of MTB)"] and negative ["TB cases without MTB detected (including patients with negative sputum smear and without sputum)"]. The rifampicin resistance category was officially reported in 2019 and represented a small percentage (< 5%) of the total data collected. Therefore, to maintain the consistency of the overall data, we excluded these data from the analysis.

Occupational-specific transmission model of TB

Based on the model, the total population (N) was divided into the following five compartments: susceptible population (S), exposed population (or low-risk latent tuberculosis infection, LTBI) (E), pathogen positive tuberculosis population (I_p), pathogen negative tuberculosis population (I_n), and recovered or removed population (R).

1) Susceptible population (S): people who have not been exposed to MTB or those who experienced self-clearance by their own immune system. The latter is a state in which the bacteria in the body cannot replicate to the extent that self-clearance occurs due to the strong immunity of the body after exposure, a state in which the body has a sustained immune response to MTB antigen stimulation.
2) Exposed population (or low-risk LTBI) (E): A susceptible population is exposed to MTB through contact with a highly infectious or less infectious population and is in an MTB carrier state but is temporarily noninfectious.
3) Pathogen positive TB population (I_p): positive cases with MTB detected by sputum smear, culture-confirmed, or molecular biology (nucleic acid of MTB).
4) Pathogen negative TB population (I_n): TB cases without MTB detected (including patients with negative sputum smear and no sputum), with low infectiousness.
5) Recovered or removed population (R): This is a state of cure or recovery, noninfectious and asymptomatic, referring to the population undergoing successful treatment, including the treatment success for the "pathogen negative" population and the "pathogen positive" population (both the cured and the treatment success population).

Based on the natural history of TB, we developed a mathematical model Susceptible-exposed-symptomatic (pathogen positive)-symptomatic (pathogen negative)-recovered (SEI_pI_nR) model to investigate the transmission process of TB. The proposed SEI_pI_nR model is based on the following facts and assumptions:

1) Births and natural deaths change the total population (N); the birth rate and the death rate are br and dr, respectively. The entire birth population enters group 2(the non-student group).

2) This population is generally susceptible to MTB infection. When an infected individual is exposed, the exposed population (E) progresses to the active TB-infected population (I) at a rate of β. Since the transmissibility of the pathogen positive TB population (I_p) is higher than the pathogen negative TB population (I_n), the transmissibility of I_n is set to be a κ times ($\kappa < 1$) compared to I_p.
3) Approximately 5–10% of the exposed population (E) infected with MTB will develop symptoms and become I_p or I_n; both belong to the active TB-infected population and will receive treatment. Most exposed people do not develop symptoms, but undergo a process of self-clearance and become a susceptible population (S). If E progresses to I_p at a rate of ω_1 (incubation period coefficient) with a scale factor of q, and E progresses to I_n at a rate of ω_2 (latent period coefficient) with a scale factor of (1-q). The progression from E to S occurs at a rate of θ (early self-clearance rate) on a scale factor of m. At time t, the progression from E to I_p, from E to I_n and from E to S is proportional to the number of exposed populations, which is $q\omega_1 E$, (1-q)$\omega_2 E$, and $m\theta E$, respectively.
4) Studies have shown that the proportion of patients with TB cured by the directly observed treatment and short course chemotherapy (DOTS) who require retreatment in the next 1–2 years is 2 to 7% [48, 49]. Patients who are retreated can be broadly divided into two categories: those who were not successfully cured following treatment, and those who relapsed after being cured.
5) There were two outcomes for the I_p compartment: First, a certain proportion of treatment success individuals (1-λ) transform into a recovered or removed population (R), while another proportion of treatment failure individuals (λ) transform into an exposed population (E). At time t, the rate of development from I_p to R, which is proportional to the I_p population, is given as (1-λ)$\gamma_1 I_p$, while the rate of development from I_p to E, which is proportional to the E population, is given as $\lambda\mu_1 I_p$. γ_1 is the removal coefficient, whereas μ_1 is the coefficient of development from I_p to E. Similarly, the rate of development to R in the I_n compartment is given as (1-λ)$\gamma_2 I_n$, while the rate of development to E is given as $\lambda\mu_2 I_n$. γ_2 is the removal coefficient and μ_2 is the coefficient of development of I_n to E.
6) The people in the I_p and I_n compartments recover or are removed (R) after successful treatment (completion of treatment for I_n and I_p [50]). Reinfection occurs after the completion of treatment or cured, that is, the active TB-infected population (I_p, I_n) returns to the exposed population (E).
7) Reactivation (or relapse) is often associated with immunodeficiency, such as the onset of disease due to HIV/TB coinfection or low resistance, such as severe cold. If people in the R compartment develop into E with a relapse ratio a where τ represents the relapse coefficient, the rate of development from R to E at time t is proportional to R, which is $a\tau R$.
8) The pathogen positive TB population (I_p) and the pathogen negative TB population (I_n) die of disease, in addition to natural deaths. Suppose the fatality rates for I_p were f_1 and that for I_n were f_2; then, at time t, the death rates for I_p and I_n are $f_1 I_p$ and $f_2 I_n$, respectively.
9) The student population was set as S_1, E_1, I_{p1}, I_{n1}, and R_1, whereas the non-student population was set as S_2, E_2, I_{p2}, I_{n2}, and R_2. Interactions were observed between students and non-students. We defined the relative transmission rate of student-to-student as β_{11}, non-student-to-non-student as β_{22}, student-to-non-student as β_{12}, and non-student-to-student as β_{21}. Therefore, the number of newly emerging infections was $\beta_{11}S_1(I_{p1}+\kappa I_{n1})$ from the student-to-student population, $\beta_{22}S_2(I_{p2}+\kappa I_{n2})$ from the non-student-to-non-student population, $\beta_{12}S_2(I_{p1}+\kappa I_{n1})$ from the student-to-non-student population, and $\beta_{21}S_1(I_{p2}+\kappa I_{n2})$ from the non-student-to-student population.

A framework diagram of the SEI_pI_nR model is shown in Fig. 3. The mathematical expression of the differential equation of the SEI_pI_nR model are as follows:

$$\frac{dS_1}{dt} = -\beta_{11}S_1(I_{p1}+\kappa I_{n1}) + m\theta E_1 - \beta_{21}S_1(I_{p2}+\kappa I_{n2}) - drS_1$$

$$\begin{aligned}\frac{dE_1}{dt} =& \beta_{11}S_1(I_{p1}+\kappa I_{n1}) - m\theta E_1 + \beta_{21}S_1(I_{p2}+\kappa I_{n2}) \\ & - drE_1 - q\omega_1 E_1 + \lambda\mu_1 I_{p1} - (1-q)\omega_2 E_1 \\ & + \lambda\mu_2 I_{n1} + \alpha\tau R_1\end{aligned}$$

$$\frac{dI_{p1}}{dt} = q\omega_1 E_1 - \lambda\mu_1 I_{p1} - (1-\lambda)\gamma_1 I_{p1} - (dr + f_1)I_{p1}$$

$$\frac{dI_{n1}}{dt} = (1-q)\omega_2 E_1 - \lambda\mu_2 I_{n1} - (1-\lambda)\gamma_2 I_{n1} - (dr + f_2)I_{n1}$$

$$\frac{dR_1}{dt} = (1-\lambda)\gamma_1 I_{p1} + (1-\lambda)\gamma_2 I_{n1} - \alpha\tau R_1 - drR_1$$

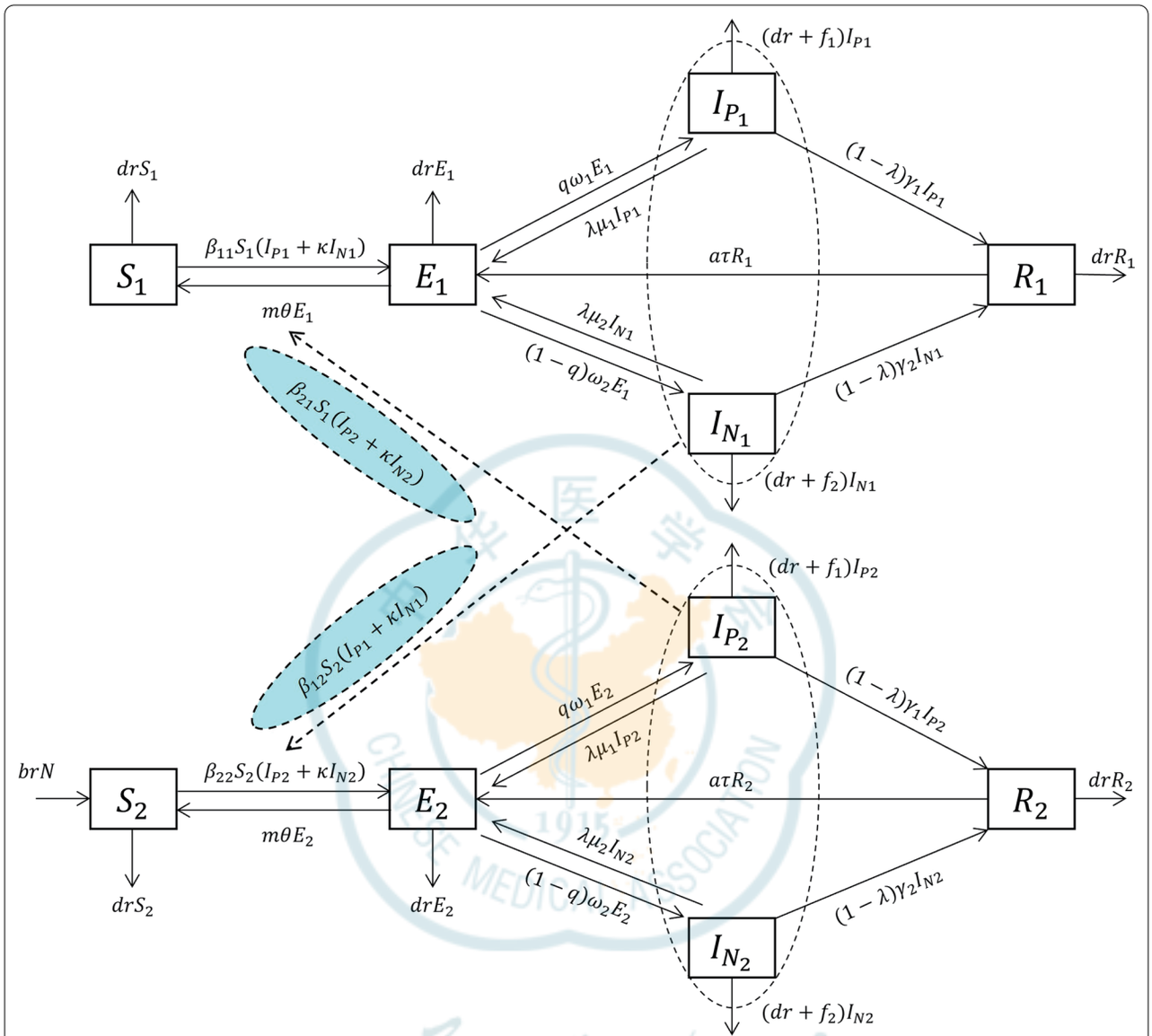

Fig. 3 Flowchart of the SEI_pI_nR model. The four occupational compartments are denoted as follows: pathogen positive students (I_{p1} subscript), pathogen positive non-students (I_{p2} subscript), pathogen negative students (I_{n1} subscript) and pathogen negative non-students (I_{n2} subscript)

$$\frac{\mathrm{d}S_2}{\mathrm{d}t} = brN - drS_2 - \beta_{22}S_2\left(I_{p2} + \kappa I_{n2}\right) + m\theta E_2 - \beta_{12}S_2(I_{p1} + \kappa I_{n1})$$

$$\frac{\mathrm{d}E_2}{\mathrm{d}t} = \beta_{22}S_2\left(I_{p2} + \kappa I_{n2}\right) - m\theta E_2 + \beta_{12}S_2(I_{p1} + \kappa I_{n1}) - drE_2 - q\omega_1 E_2 + \lambda\mu_1 I_{p2} - (1-q)\omega_2 E_2 + \lambda\mu_2 I_{n2} + \alpha\tau R_2$$

$$\frac{\mathrm{d}I_{p2}}{\mathrm{d}t} = q\omega_1 E_2 - \lambda\mu_1 I_{p2} - (1-\lambda)\gamma_1 I_{p2} - f_1 I_{p2} - drI_{p2}$$

$$\frac{\mathrm{d}I_{n2}}{\mathrm{d}t} = (1-q)\omega_2 E_2 - \lambda\mu_2 I_{n2} - (1-\lambda)\gamma_2 I_{n2} - f_2 I_{n2} - drI_{n2}$$

$$\frac{\mathrm{d}R_2}{\mathrm{d}t} = (1-\lambda)\gamma_1 I_{p2} + (1-\lambda)\gamma_2 I_{n2} - \alpha\tau R_2 - drR_2$$

Parameter estimation

Fourteen parameters were obtained from references or actual data in this model: birth rate (*br*), death rate (*dr*), transmission relative rate (β), proportion of early clearance (m), rate of early clearance (θ), transmission relative rate between pathogen negative and positive TB population (κ), proportion of exposed to TB population (q), rate of exposed to TB population (ω), proportion of treatment failure (λ), rate from TB population to exposed population (μ), TB population removal coefficient (γ), Case fatality rate of TB population (f), recurrence ratio- proportion of recovered or removed population developing into exposed population (a), and reciprocal of time to recurrence rate at which recovered or removed population progresses to exposed population (τ).

Parameter β was derived from the curve-fitting results. Some parameters (*br*, *dr*, and q) were obtained from actual data, while other parameters were obtained from the literature. The description of each variable and parameter in this model is detailed in Table 1.

1) Early self-clearance (early clear) was defined as a persistent negative interferon-gamma release test (IGRA) (patients with pathogenically positive TB were tested at baseline and after 14 weeks). Studies in Indonesia have shown that early self-clearance is 25% [51]. The time to self-clearance was set at 14 weeks, which is the interval between the two IGRA tests; thus $\theta = 1/(14/4) = 0.286$.
2) Treatment failure: The WHO 2021 TB report [3] showed the treatment success rate was 95.9% in 2019 and 95.7% in 2020. Previous reports revealed that this value did not change much between 2000 and 2020. Therefore, we considered the treatment success rate as 95% and set the treatment failure rate (λ) to 5%, that is $\lambda = 0.050$. The conventional treatment course was 6 months. Therefore, the time to complete the treatment was set as 6 months, that is, $\mu 1 = \mu 2 = 1/6 = 0.167$ [52].
3) Relapse: Studies [53–55] in China showed the relapse rate was 5.3–6.9%. Therefore, the median was chosen and the relapse proportion was set at $a = 0.062$ (recurrence ratio). A domestic study [53] showed that the median time from the first attack to relapse in TB patients was 1.3 years [interquartile range (IQR) 0.6–2.8 years]. Therefore, the relapse rate was established at 1/(1.3*12), i.e., $\tau = 0.064$ (reciprocal of time to recurrence).

Table 1 The description and features of estimated parameters

Parameter	Description	Unit	Value	Source
br	Birth rate	1	Null	Reported data
dr	Death rate	1	Null	Reported data
β	Transmission relative rate	Per person. per month	Null	Curve fitting
β_{11}	Transmission relative rate among students	Per person. per month	Null	Curve fitting
β_{22}	Transmission relative rate among non-students	Per person. per month	Null	Curve fitting
β_{12}	Transmission relative rate from students to non-students	Per person. per month	Null	Curve fitting
β_{21}	Transmission relative rate from non-students to students	Per person. per month	Null	Curve fitting
κ	Transmission relative rate between population I_n and population I_p	1	0.2	Reference [56]
m	Proportion of early clearance	1	0.25	Reference [51]
θ	Rate of early clearance	Per month	0.286	Reference [51]
q	Proportion from E to I_p	1	Null	Reported data
1-q	Proportion from E to I_n	1	Null	Reported data
ω_1	Rate from E to I_1	Per month	0.667	Reference [93]
ω_2	Rate from E to I_2	Per month	0.667	Reference [93]
λ	Proportion of treatment failure	1	0.05	Reference [3]
μ_1	Rate from I_1 to E (reciprocal time to retreatment)	Per month	0.167	Reference [52]
μ_2	Rate from I_2 to E (reciprocal time to retreatment)	Per month	0.167	Reference [52]
γ_1	I_1 removal coefficient	Per month	0.286	Reference [57]
γ_2	I_2 removal coefficient	Per month	0.286	Reference [57]
f_1	Case fatality rate of I_1	1	0.1284	References [94, 95]
f_2	Case fatality rate of I_2	1	0.1284	Reference [94, 95]
a	Proportion of R developing into E (recurrence ratio)	1	0.062	References [53–55]
τ	Rate at which R progresses to E (reciprocal of time to recurrence)	Per month	0.064	Reference [53]

E for the exposed population (or low-risk latent tuberculosis infection, LTBI), I_p for pathogen positive tuberculosis population, I_n for pathogen negative tuberculosis population, I_1 for student tuberculosis population, I_2 for non-student tuberculosis population, and R for recovered or removed population

4) The transmissibility coefficient of I_n relative to I_p was set as κ to 0.2 [56] with reference to the actual data and the relevant literature.
5) After approximately two weeks of effective treatment, TB cases with a nondrug-resistant active infection usually do not remain infectious to others and become low in infection status [57]. Short-course (3-to 4-month) rifamycin-based treatment regimens are preferred over longer-course (6 to 9 months) isoniazid monotherapy for the treatment of low-infection cases of TB [8]. Therefore, we set the duration of the illness at 14 weeks (average value 3–4 month), $\gamma_1 = \gamma_2 = 1/(14/4) = 0.286$.
6) The birth rate (*br*) and the death rate (*dr*) for each year in each region were obtained from the statistical offices of each study area.

Transmissibility index

The basic reproduction number (R_0) is an important parameter for determining the infectiousness of a disease. R_0 refers to the number of new cases expected from an infected case in a susceptible population during an average infectious period. We set R_{eff} as the evaluation index, which denotes R_0 after intervention measures were taken, to evaluate the impact of intervention measures on the relative transmissibility of MTB in the population.

In this study, R_{eff} was calculated using the next-generation matrix method, and all source codes are accessible at GitHub (https://github.com/rorschachkwok/tb_reff). In this study, R_{eff1} represents the transmissibility of the population of students with active TB [sum of transmissibility from student cases to student cases (R_{eff11}) and from student cases to non-student cases (R_{eff12})], while R_{eff2} represents the transmissibility of the population of non-student active TB cases [sum of transmissibility from non-student cases to non-student cases (R_{eff22}) and from non-student cases to student cases (R_{eff21})].

Simulation methods and statistical analysis

Berkeley Madonna 8.3.18 (developed by Robert Macey and George Oster of the University of California in Berkeley. Copyright ©1993–2001 Robert I. Macey & George F. Oster) was used to fit the curves of the incidence data. The estimated model coefficients and the simulation of the intervention effects were also generated using this software. The curving fit was performed using the fourth order Runge–Kutta method to obtain the key parameter values: student-to-student (β_{11}), non-student-to-non-student (β_{22}), student-to-non-student (β_{12}), and non-student-to-student (β_{21}) transmission rates.

To consider the potential seasonality transmission of TB, although seasonality remains unclear, we developed two models in this study, which are described as follows:

Model A: seasonality excluded.

In Model A, the epidemic curve for each year was divided into ascending and descending periods according to the characteristics of the reported number of TB cases (Fig. 1). The SEI_pI_nR model without seasonality was adopted to fit the data in each period, and the corresponding transmission relative rates (β, β_{11}, β_{12}, β_{22}, and β_{21}), the ascending and descending R_{eff} ($R_{eff(asc)}$ and $R_{eff(des)}$, respectively) were calculated.

Model B: seasonality included.

In Model B, we used a seasonality function in the SEI_pI_nR model to fit the reported TB epidemic curve (Fig. 1), which is shown as follows:

$$\beta_t = \beta_0\left(1 + sin\left(\frac{2\pi(t-c)}{T}\right)\right)$$

In this equation, β_t, β_0, c, and T refer to the transmission rate at time t, the transmission rate at time = 0, the correcting value of time (month) and the potential seasonality cycle, respectively.

The goodness-of-fit test was performed between the fitted results and the collected data by calculating the R^2 and P values. Key parameters (β_{11}, β_{12}, β_{22}, β_{21}) were knocked out, and the cumulative number of cases was calculated to assess the main parameter affecting transmissibility. SPSS Statistics for Windows, version 13.0 (SPSS Inc., Chicago, Ill, USA) was used to perform statistical analyses. The coefficient of determination (R^2) was used to evaluate the curve fitness.

Results

Epidemiology of tuberculosis in the four regions

The age range of the TB patients was between 15 and 90 years, with two peaks in the incidence of TB: a large and a small peak in the age groups 35–90 and 15–35, respectively. In Wuhan City, Jilin Province and Chuxiong Prefecture, there were two age distribution peaks of non-student TB patients (15–35 and 45–60 years group), while in Xiamen City, there was only one peak (15–35 years group). Student patients with TB were among 15–25 year group (Fig. 4A). Most patients with TB in the four regions were male, with a male-to-female ratio of 7 : 3 (Fig. 4B). The Chinese Infectious Disease Report Card categorises cases into 18 categories, and the top six occupations (88.4% of the total cases) in the four regions were: farmers, housework and unemployment, others, workers, students, and retirees. Among these four regions, the top three occupations of TB patients in Wuhan were

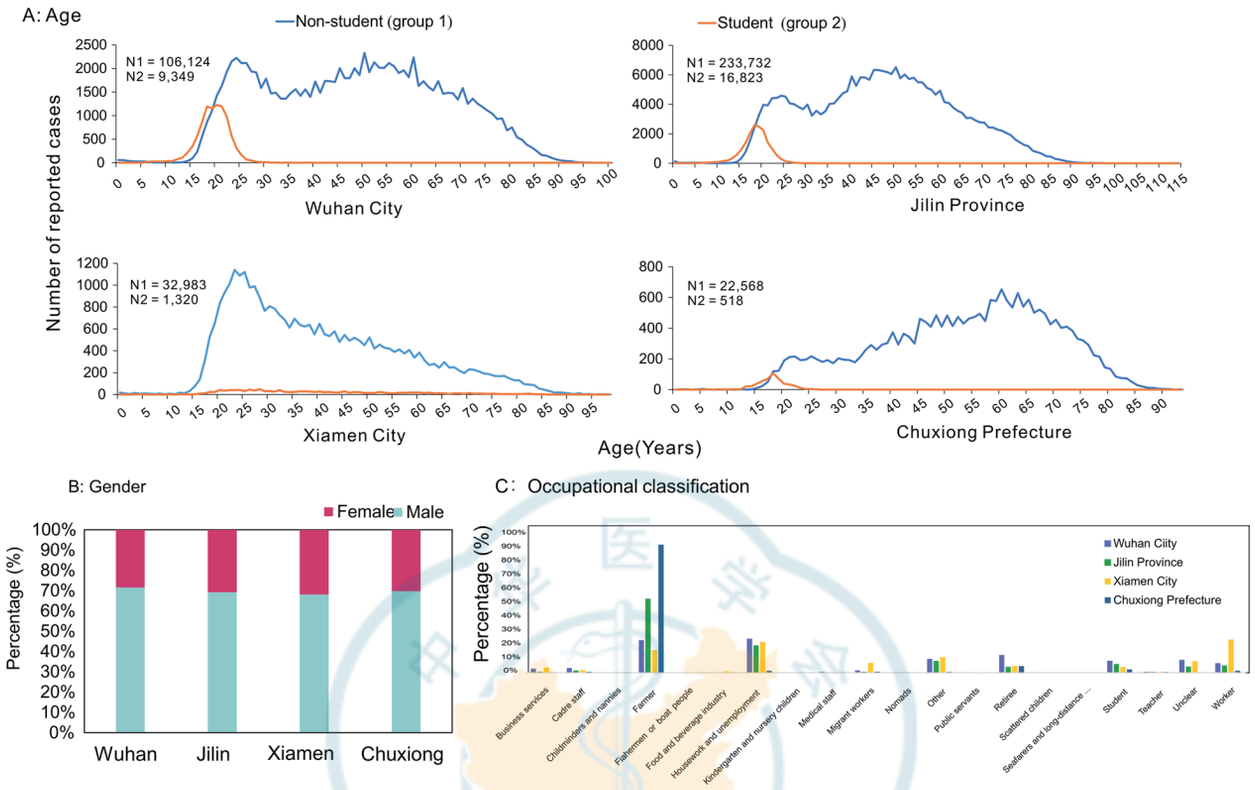

Fig. 4 Age, gender, and occupation distributions: **A** Wuhan City, **B** Jilin Province, **C** Xiamen City, and **D** Chuxiong Prefecture

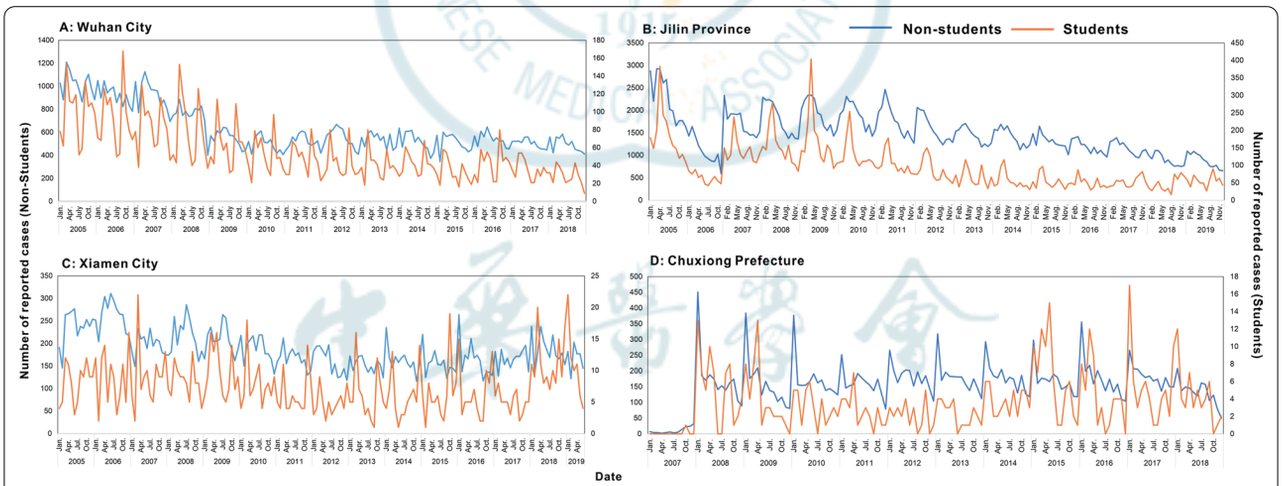

Fig. 5 Temporal distribution by month: **A** Wuhan City, **B** Jilin Province, **C** Xiamen City, and **D** Chuxiong Prefecture

domestic and unemployed (23.2%), farmers (22.2%), and retirees (12.1%). The top three occupations of TB patients were farmers (50.3%), domestic and unemployed (18.6%), and others (8.0%) in Jilin Province; workers (22.5%), farmers (15.3%), and others (10.6%) in Xiamen; farmers (87.2%), retirees (4.5%), and students (2.2%) in Chuxiong Prefecture (Fig. 4C). The ranking of students with TB was sixth, sixth, eighth and third in Wuhan, Jilin, Xiamen, and Chuxiong Prefecture, respectively.

The number of reported TB cases in Wuhan City and Jilin Province showed a decreasing annual trend, while the number of reported TB cases in Xiamen City and Chuxiong Prefecture showed a slight fluctuation trend (Fig. 5). The incidence in the student population was

distinctly low during the winter holidays (January–February, approximately 30 days) and summer vacation (July–August, approximately 60 days), with one or two distinct peaks after returning to school (the remaining months of the year). There were slight differences between regions in the time of occurrence of these peaks: Wuhan (March and September–October), Xiamen (March and October), Jilin (April and September), and Chuxiong (April and October). However, for the non-student population, there were no clear lows or peaks.

Most cases had either positive or negative pathogen results (87.3%), and the ratio was 1:1.13. The proportion of cases without pathogenic findings was 12.6%; rifampicin resistant results accounted for 0.1%. The number of pathogen positive and negative cases was essentially the same in Jilin Province, while the other three regions reported more pathogen negative cases than positive. The proportion of patients without pathogenic findings was the lowest in Xiamen City and the highest in Chuxiong Prefecture. Very few cases of resistance to rifampicin were reported in any region (Fig. 6).

Curve fitting

We conducted goodness-of-fit tests for the two models based on the case datasets from the four regions (Wuhan City, Jilin Province, Chuxiong Prefecture, and Xiamen City) (Figs. 7 and 8). R^2 values were calculated for the four model groups (pathogen positive cases in the student group, I_{p1}; pathogen negative cases in the student group, I_{n1}; pathogen positive cases in the non-student group, I_{p2}; and pathogen negative cases in the non-student group, I_{n2}). The values showed that, although the two established TB models fitted well with the trend of TB incidence rates (Table 2), Model A had better fitting results than Model B.

Transmissibility for interactions among the four groups

The results of R_{eff} among and between the different populations in each region are shown in Fig. 9.

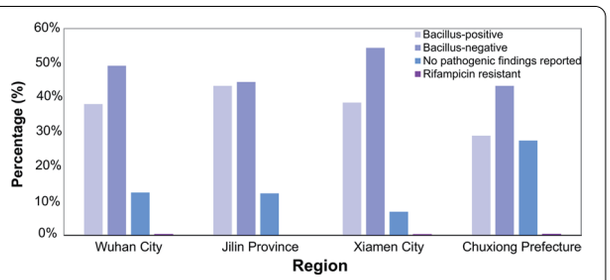

Fig. 6 Proportions of patients reporting pulmonary tuberculosis in the four study areas

In Wuhan City, the median R_{eff} for TB among the mixed population was 1.79 (IQR: 1.56–2.02). Most TB transmissions occurred due to the high transmission in non-student populations, including among non-student populations [median R_{eff22} was 1.57 (IQR: 1.41–1.72)] and non-student-to-student populations [median R_{eff21} was 0.14 (IQR: 0.11–0.15)], with a median R_{eff2} of 1.71(IQR: 1.54–1.87). The values of R_{eff22} and R_{eff21} slowly descended from 2005 to 2018. The values of R_{eff12} and R_{eff11} were nearly zero excluding in 2006 (R_{eff12} was 6.39, R_{eff11} was 0.19) and 2013 (R_{eff11} was 0.58) (Table 3).

In Jilin Province, the median R_{eff} for TB among the mixed population was 1.75 (IQR: 1.37–2.02). Most TB transmission occurred due to the high transmission in the non-student population, including among non-student populations [median R_{eff22} was 1.57, (IQR: 1.27–1.77)] and from non-student-to-student populations [median R_{eff21} was 0.09, (IQR: 0.07–0.11)], with a median R_{eff2} of 1.66 (IQR: 1.35–1.89). The R_{eff21} and R_{eff12} values maintained stable fluctuations at values lower than 1 from 2007 to 2019. The value of R_{eff11} was nearly zero excluding in 2009, when it reached 1.19 ($R_{eff(asc)}$ 1.17, $R_{eff(des)}$ 0.02) (Table 4).

In Chuxiong Prefecture, the median R_{eff} of TB among the mixed population was 1.68 (IQR: 1.20–1.96). Most TB transmissions occurred due to the high transmission in non-student populations with a median R_{eff22} 1.59 (IQR: 1.14–1.80), and the other three values (R_{eff11}, R_{eff21}, R_{eff12}) were nearly zero each year. The values of R_{eff2} and R_{eff1} fluctuated smoothly from 2008 to 2018, with a median R_{eff2} of 1.63 (IQR: 1.17–1.82) and a median R_{eff1} of 0.05 (IQR: 0.02–0.09), respectively (Table 5).

In Xiamen City, we excluded data analysis in 2019 for only 3 months data collection from January to March, which was not a valid TB representation for the entire year. Except that the median R_{eff} for TB among the mixed population was 1.67 (IQR: 1.40–1.93). Most TB transmissions of occurred due to the high transmission in non-student populations, with a median R_{eff22} of 1.58 (IQR: 1.32–1.80). R_{eff2} values slowly decreased between 2005 and 2018, with a median R_{eff2} of 1.61 (IQR: 1.35–1.85). Although there were several values of R_{eff12} higher than 0.10 in student-non-student transmission ($R_{eff\ (des)}$ in 2005, 2012, 2016, and $R_{eff\ (asc)}$ in 2006, 2008, 2010), the overall transmissibility was annual decreasing with a median R_{eff12} of 0.04 (IQR: 0.00–0.07) (Table 6).

A similar transmission relationship among and between student and non-student populations was calculated in Model B. However, the model revealed exceedingly high values of R_{eff} over many years in the four regions, which indicates that the findings of Model B may be unsuitable to show the characteristics of TB. Additional details of the results are provided in Additional file 3: Tables S3,

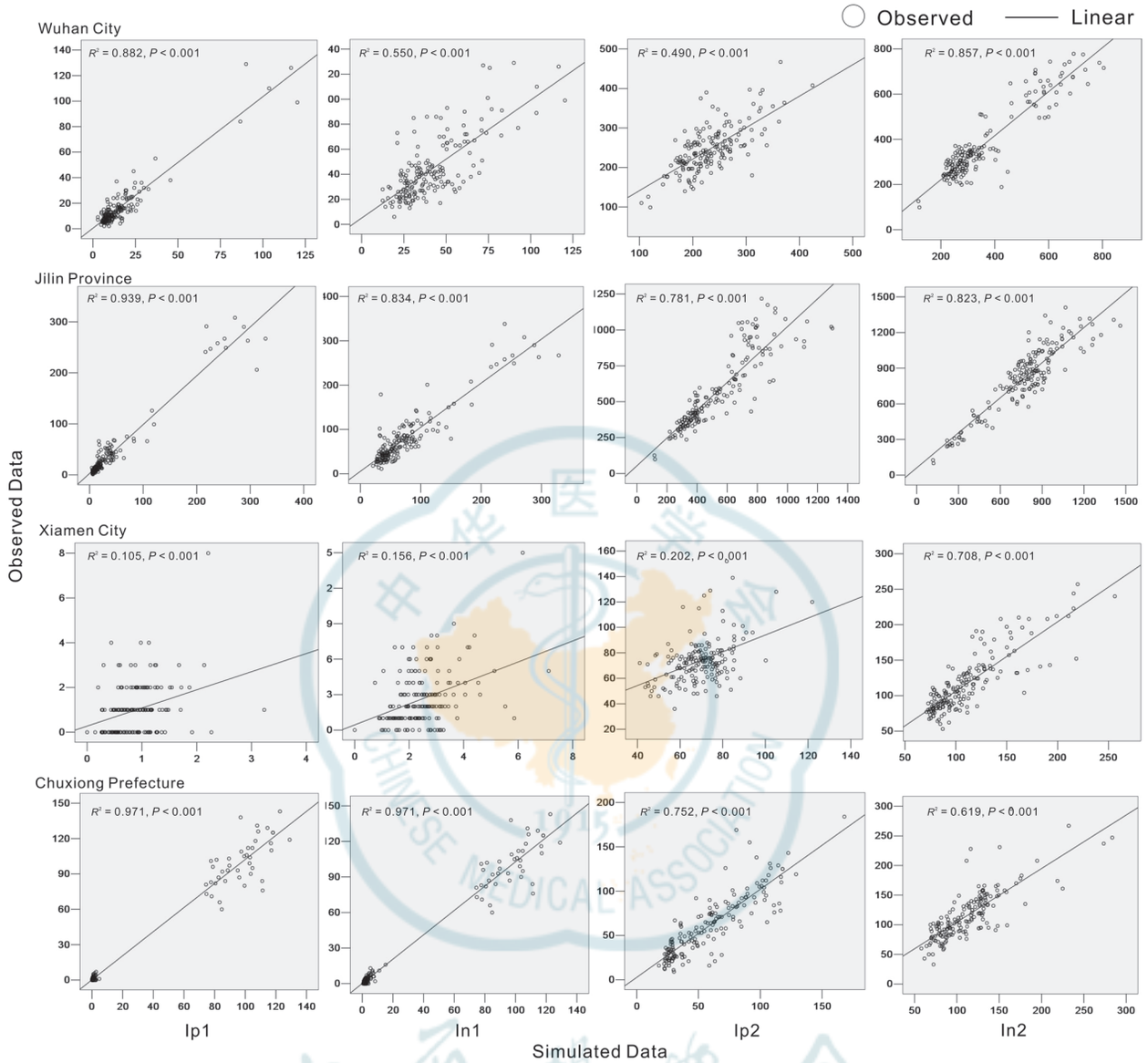

Fig. 7 Plot of goodness-of-fit results for the non-seasonal model (Model A)

Additional file 4: Table S4, Additional file 5: Table S5, Additional file 6: Table S6.

Cumulative incidence rate after the knock-out-pathways, β_{11}, β_{12}, β_{22}, and β_{21}

According to the knock-out results (Fig. 10), the number of TB cases among students was significantly reduced by more than half (60–70%) when the transmissibility of non-student-to-student populations ($\beta_{21)}$ was knocked out. When TB transmission among non-students ($\beta_{22)}$ was blocked, the number of TB cases was reduced by approximately 67% (65–70%) among non-students and by approximately 28% (25–30%) among students. There was only a 5% reduction (2–12%) among students when TB transmission among students ($\beta_{11)}$ was blocked, and TB reported cases had barely changed (less than 1%) while TB transmission from non-student-to-students ($\beta_{12)}$ was blocked.

Discussion

This study is the first to address the occupational-specific transmission dynamics of TB and emphasise the importance of control between student groups, which can

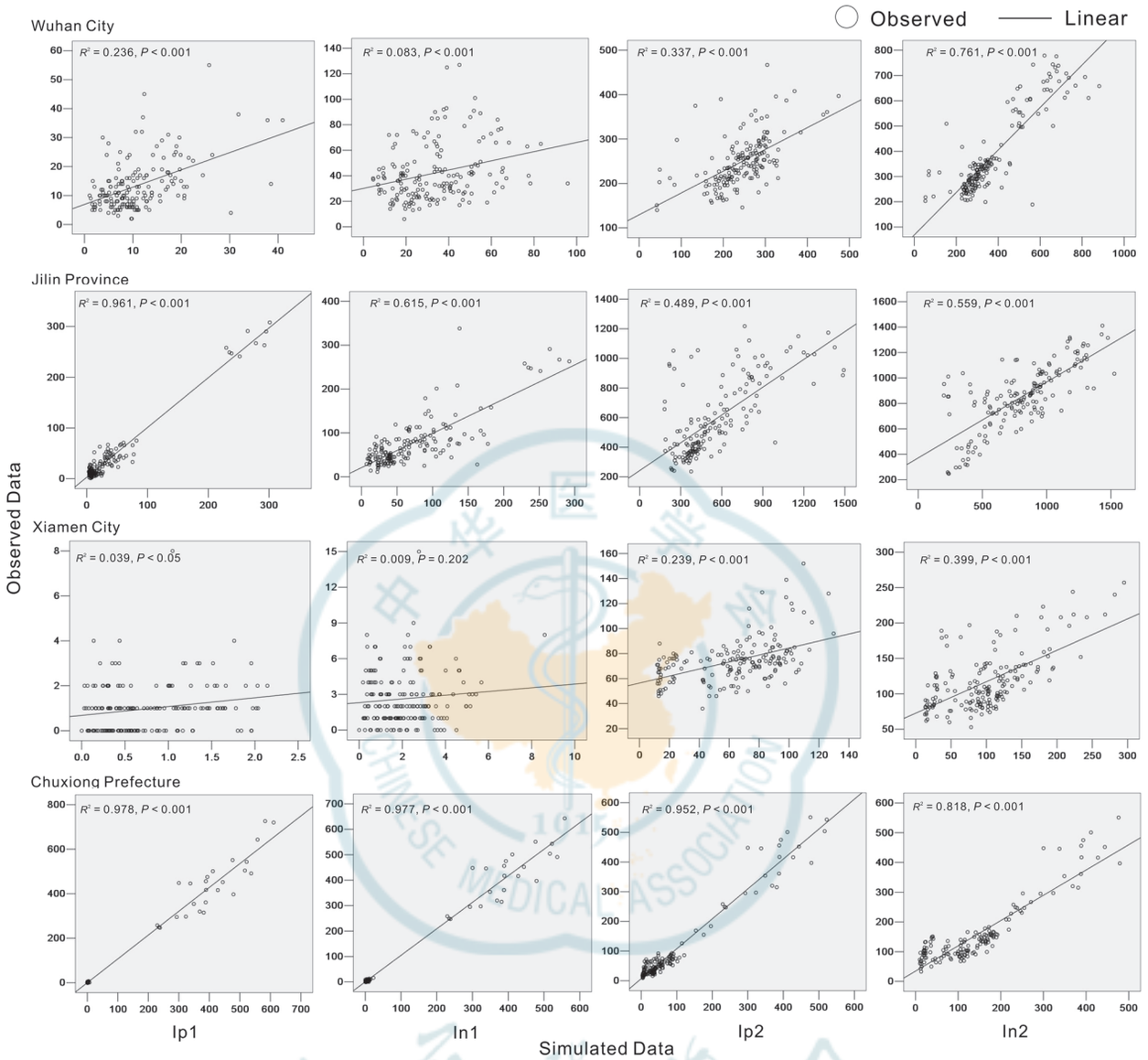

Fig. 8 Plot of goodness-of-fit results for the seasonal model (Model B)

increase our understanding of the characteristics of TB transmission in different occupational groups.

Analysis of epidemiological characteristics

The incidence rate of TB decreased in the study regions, which is in good agreement with previous global reports [3], but was unevenly distributed between these four regions. This phenomenon may be attributed to several reasons. First, the inclusion of previously untreated patients in the management after several years of continuous active screening led to a certain decline in the number of subsequent patient detection cases. Second, since 2017, a nationwide survey of underreporting and underregistration of TB [58] and a diagnostic review [59] were carried out, which improved the quality of TB reporting and diagnosis in each region. However, the reported incidence rate of TB is still higher in areas less economically developed than in the west, such as Chuxiong Prefecture, although the attention and support of governments and health administrations, as well as the support for precise health poverty alleviation have been undertaken at all levels [9].

Remarkably, the reported incidence of TB in the student population has increased. The reported data also

Table 2 Goodness-of-fit test results of the two models (Models A and B) in the study areas

Region	I_{p1}		I_{n1}		I_{p2}		I_{n2}	
	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*
Model A								
Wuhan City	0.882	< 0.001	0.55	< 0.001	0.49	< 0.001	0.857	< 0.001
Jilin Province	0.939	< 0.001	0.834	< 0.001	0.781	< 0.001	0.823	< 0.001
Xiamen City	0.105	< 0.001	0.156	< 0.001	0.202	< 0.001	0.708	< 0.001
Chuxiong Prefecture	0.971	< 0.001	0.971	< 0.001	0.752	< 0.001	0.619	< 0.001
Model B								
Wuhan City	0.236	< 0.001	0.083	< 0.001	0.337	< 0.001	0.761	< 0.001
Jilin Province	0.961	< 0.001	0.615	< 0.001	0.489	< 0.001	0.559	< 0.001
Xiamen City	0.039	0.009	0.009	0.202	0.239	< 0.001	0.399	< 0.001
Chuxiong Prefecture	0.978	< 0.001	0.977	< 0.001	0.952	< 0.001	0.818	< 0.001

Correlation between the simulated and observed data was tested using R_2 and *p* values. We divided all the compartments representing active diseases (*I*) into four occupational compartments: pathogen positive students (I_{p1} subscript), pathogen positive non-students (I_{p2} subscript), pathogen negative students (I_{n1} subscript) and pathogen negative non-students (I_{n2} subscript)

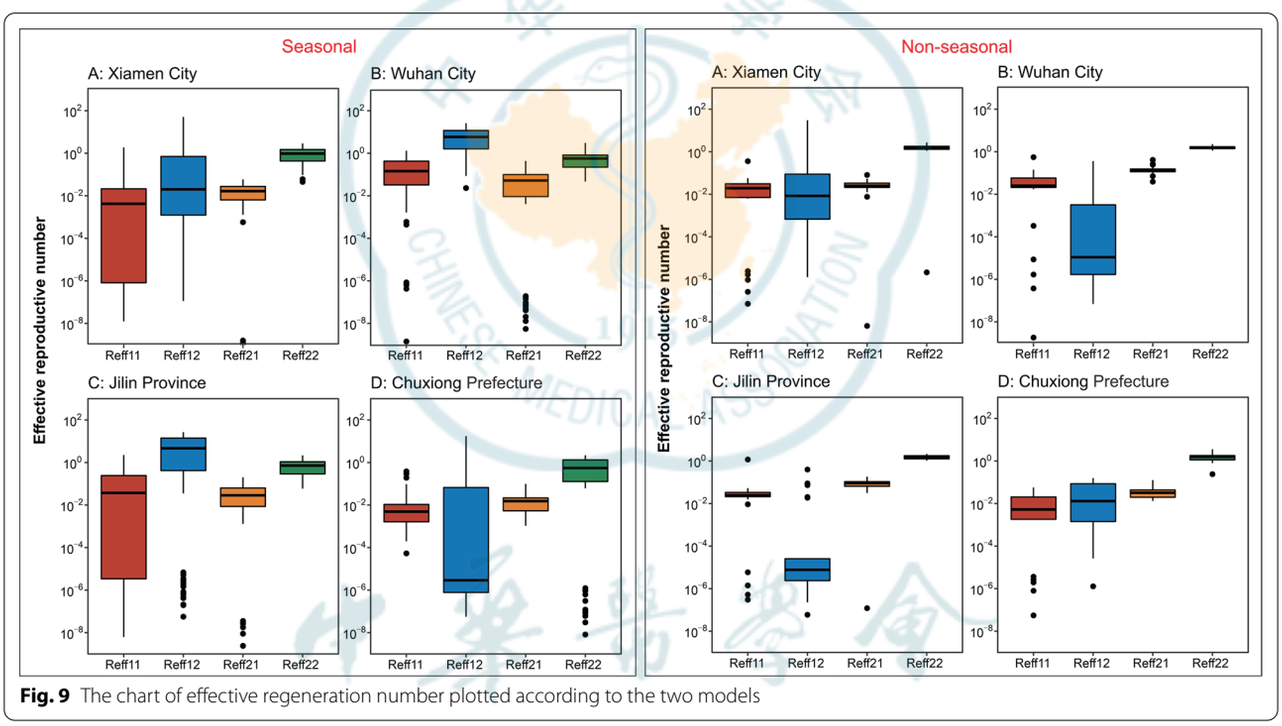

Fig. 9 The chart of effective regeneration number plotted according to the two models

confirmed that the proportion of student patients has increased from 4.0% in 2015 to 6.2% in 2019, with a difference of 2.2% [9]. This is mainly due to the fact that early warning of individual cases of TB in schools has been included in the National Automatic Early Warning System for Infectious Diseases since July 2018 [60]. Furthermore, disease control agencies at all levels have strengthened the information verification process of school-age patients and improved the sensitivity of the surveillance of student patients [61]. Schools have also strengthened medical examinations and handled clusters of TB outbreaks [62]. Our results highlight an obvious incidence peak among students at the beginning of the semester. There are several explanations for this observation. Students are in close contact with social residents and are exposed to TB patients in the community during holidays. Considering LTBI [8, 63], students infected with MTB on vacation do not become ill immediately,

Table 3 R_{eff} of Model A between students and non-students (Wuhan City)

Year	R_{eff11}	$R_{eff\,12}$	$R_{eff\,22}$	$R_{eff\,21}$	R_{eff1}	R_{eff2}
2005 (asc)	0.04	0.00	2.12	0.24	0.04	2.37
2005 (des)	0.08	0.00	1.73	0.13	0.08	1.87
2006 (asc)	0.05	0.36	1.62	0.16	0.41	1.79
2006 (des)	0.14	0.00	1.75	0.16	0.14	1.91
2007 (asc)	0.06	0.00	1.86	0.14	0.07	2.00
2007(des)	0.04	0.00	1.49	0.13	0.04	1.62
2008 (asc)	0.02	0.00	2.27	0.42	0.02	2.68
2008 (des)	0.02	0.00	1.41	0.14	0.02	1.55
2009 (asc)	0.10	0.00	1.79	0.27	0.10	2.05
2009 (des)	0.00	0.00	1.12	0.14	0.00	1.26
2010 (asc)	0.06	0.00	1.75	0.20	0.06	1.94
2010 (des)	0.03	0.00	1.20	0.12	0.03	1.32
2011 (asc)	0.03	0.00	1.62	0.15	0.03	1.77
2011(des)	0.02	0.00	1.43	0.11	0.02	1.54
2012 (asc)	0.02	0.00	1.57	0.10	0.03	1.67
2012 (des)	0.02	0.00	1.45	0.08	0.02	1.53
2013 (asc)	0.55	0.01	1.61	0.08	0.56	1.69
2013 (des)	0.03	0.00	1.57	0.12	0.03	1.69
2014 (asc)	0.02	0.00	1.59	0.12	0.02	1.71
2014 (des)	0.02	0.00	1.25	0.12	0.02	1.37
2015 (asc)	0.00	0.02	1.57	0.15	0.02	1.72
2015 (des)	0.02	0.00	1.29	0.09	0.02	1.38
2016 (asc)	0.00	0.00	1.62	0.13	0.00	1.75
2016 (des)	0.06	0.00	1.41	0.15	0.06	1.56
2017 (asc)	0.11	0.01	1.71	0.16	0.11	1.87
2017 (des)	0.00	0.03	1.36	0.12	0.03	1.47
2018 (asc)	0.00	0.07	1.56	0.04	0.07	1.60
2018 (des)	0.02	0.00	1.21	0.07	0.02	1.28
Median	0.06	0.02	1.57	0.14	0.07	1.71
P25	0.02	0.00	1.41	0.11	0.02	1.54
P75	0.06	0.00	1.72	0.15	0.07	1.87

R_{eff11} denotes the transmissibility of MTB from student cases to student cases. $R_{eff\,12}$ denotes the transmissibility of MTB from student cases to non-student cases. $R_{eff\,21}$ denotes the transmissibility of MTB from non-student cases to student cases. $R_{eff\,22}$ denotes the transmissibility of MTB from the non-student cases to non-student cases. R_{eff1} represents the transmissibility of the population of students with active TB cases (sum of R_{eff11} and $R_{eff\,12}$), whereas $R_{eff\,2}$ represents the transmissibility of the population of non-student active TB cases (sum of $R_{eff\,22}$ and $R_{eff\,21}$)

asc denotes the ascending R_{eff} ($R_{eff(asc)}$). des denotes the descending R_{eff} ($R_{eff(des)}$)

but become ill after returning to school when they are exposed to several inducements, including high pressure and cold, among others. Farmers always had the highest reported incidence rates. However, this is not surprising if we consider that the rural population represents most of the total population of China, and the allocation of medical and health resources in rural areas is inadequate, resulting in unequal access to medical resources for urban and rural residents [13]. Furthermore, it may be related to the lower level of education of farmers, poorer living conditions, and lack of awareness of health protection [64].

The diagnosis results in the study areas, which had a low pathogen positive rate of less than 50%. A previous report showed the pathogen positive rate for PTB reported in China in 2020 was 57%, up from 45.03% in 2019 [3]. However, a gap still exists when this is compared with surveillance results based on laboratory pathogenic diagnostic evidence in other countries worldwide. Both the TB laboratory diagnostic and the TB imaging detection capacity need to be improved in primary care institutions in China, which is consistent with the outcomes of one diagnostic and therapeutic survey on TB sentinel medical institutions [65] and on the current

Table 4 R_{eff} of Model A between students and non-students (Jilin Province)

Year	R_{eff11}	$R_{eff\,12}$	$R_{eff\,22}$	$R_{eff\,21}$	R_{eff1}	R_{eff2}
2007 (asc)	0.00	0.00	1.27	0.03	0.00	1.30
2007 (des)	0.01	0.00	1.22	0.11	0.01	1.33
2008 (asc)	0.05	0.00	1.80	0.18	0.05	1.98
2008 (des)	0.00	0.00	1.23	0.11	0.00	1.35
2009 (asc)	1.17	0.02	1.60	0.00	1.19	1.60
2009 (des)	0.02	0.09	1.16	0.09	0.10	1.26
2010 (asc)	0.02	0.00	1.53	0.12	0.02	1.65
2010 (des)	0.00	0.02	1.25	0.09	0.02	1.34
2011 (asc)	0.05	0.00	1.99	0.15	0.05	2.14
2011 (des)	0.02	0.00	1.28	0.08	0.02	1.36
2012 (asc)	0.03	0.00	1.68	0.10	0.03	1.78
2012 (des)	0.02	0.00	1.25	0.06	0.02	1.31
2013 (asc)	0.03	0.00	1.84	0.09	0.03	1.93
2013 (des)	0.03	0.00	1.68	0.09	0.03	1.76
2014 (asc)	0.04	0.00	2.02	0.11	0.04	2.12
2014 (des)	0.02	0.07	1.54	0.05	0.10	1.59
2015 (asc)	0.04	0.00	2.04	0.10	0.04	2.13
2015 (des)	0.02	0.00	1.56	0.06	0.02	1.62
2016 (asc)	0.04	0.00	2.16	0.13	0.04	2.30
2016 (des)	0.03	0.00	1.58	0.06	0.03	1.64
2017 (asc)	0.03	0.00	2.02	0.09	0.03	2.11
2017 (des)	0.03	0.00	1.54	0.09	0.03	1.63
2018 (asc)	0.02	0.08	1.60	0.06	0.10	1.66
2018 (des)	0.02	0.00	1.48	0.11	0.02	1.59
2019 (asc)	0.00	0.40	1.40	0.09	0.40	1.49
2019 (des)	0.02	0.00	1.04	0.09	0.02	1.13
Median	0.07	0.03	1.57	0.09	0.09	1.66
P25	0.02	0.00	1.27	0.07	0.02	1.35
P75	0.03	0.00	1.77	0.11	0.05	1.89

R_{eff11} denotes the transmissibility of MTB from student cases to student cases. $R_{eff\,12}$ denotes the transmissibility of MTB from student cases to non-student cases. $R_{eff\,21}$ denotes the transmissibility of MTB from non-student cases to student cases. $R_{eff\,22}$ denotes the transmissibility of MTB from the non-student cases to non-student cases. R_{eff1} represents the transmissibility of the population of students with active TB cases (sum of R_{eff11} and $R_{eff\,12}$), whereas $R_{eff\,2}$ represents the transmissibility of the population of non-student active TB cases (sum of $R_{eff\,22}$ and $R_{eff\,21}$)

asc denotes the ascending R_{eff} ($R_{eff(asc)}$). des denotes the descending R_{eff} ($R_{eff(des)}$)

status of TB diagnostic capacity at county-level TB sentinel medical institutions in China [66]. To achieve the goal of "reaching a pathogenic positivity rate of more than 50% by 2022" as required by the Action Plan to Stop TB (2019–2022) [67], it is still necessary to continue to strengthen the quality of laboratory work [68].

Analysis of TB transmission dynamics characteristics

In this study, two mathematical models of TB were constructed according to the transmission characteristics of TB: Models A and B. Although there may be seasonal fluctuations in the actual incidence of TB in some areas, Model A fitted better than Model B. Therefore, we believe that the analysis results of Model A can better reflect the real situation of TB incidence.

Therefore, the following interpretations were made according to the results of the R_{eff} calculation of Model A and results of a knock-out analysis:

A) Overall, the average values of R_{eff} in the four regions showed that a single TB case could effectively spread to one or two people. TB transmissibility among non-students (R_{eff2}) was 23.30 times (IQR: 1.94–7.24) higher than among students (R_{eff1}). TB transmission remained dominant in the non-student population. This finding also existed in the knock-out analysis. Transmission among non-students increased the number of reported TB cases in all four groups (67% in non-students and 28% in students). The non-student population was large, and included 17 occupations, different locations with active cases, and a wide range of age groups. In high-burden

Table 5 R_{eff} of Model A between students and non-students (Chuxiong Prefecture)

Year	R_{eff11}	R_{eff12}	R_{eff22}	R_{eff21}	R_{eff1}	R_{eff2}
2008 (des)	0.01	0.00	0.80	0.02	0.01	0.82
2009 (asc)	0.02	0.01	1.96	0.02	0.03	1.98
2009 (des)	0.00	0.04	0.87	0.02	0.05	0.89
2010 (asc)	0.02	0.00	1.97	0.03	0.02	2.01
2010 (des)	0.00	0.00	1.04	0.02	0.01	1.06
2011 (asc)	0.01	0.00	1.52	0.04	0.01	1.56
2011 (des)	0.00	0.08	1.11	0.01	0.08	1.12
2012 (asc)	0.02	0.00	1.26	0.03	0.02	1.29
2012 (des)	0.01	0.05	1.72	0.02	0.06	1.74
2013 (asc)	0.00	0.01	0.24	0.05	0.02	0.29
2013 (des)	0.00	0.09	1.71	0.02	0.09	1.73
2014 (asc)	0.02	0.00	1.14	0.04	0.02	1.17
2014 (des)	0.00	0.09	1.78	0.04	0.09	1.82
2015 (asc)	0.03	0.02	2.82	0.13	0.05	2.95
2015 (des)	0.03	0.00	1.73	0.05	0.03	1.78
2016 (asc)	0.06	0.00	3.58	0.09	0.06	3.66
2016 (des)	0.00	0.13	1.52	0.02	0.13	1.54
2017 (asc)	0.00	0.16	1.80	0.00	0.16	1.80
2017 (des)	0.00	0.09	1.58	0.03	0.09	1.61
2018 (asc)	0.03	0.00	2.01	0.12	0.04	2.12
2018 (des)	0.00	0.09	1.26	0.04	0.09	1.30
Median	0.01	0.04	1.59	0.04	0.05	1.63
P25	0.00	0.00	1.14	0.02	0.02	1.17
P75	0.02	0.09	1.80	0.04	0.09	1.82

R_{eff11} denotes the transmissibility of MTB from student cases to student cases. R_{eff12} denotes the transmissibility of MTB from student cases to non-student cases. R_{eff21} denotes the transmissibility of MTB from non-student cases to student cases. R_{eff22} denotes the transmissibility of MTB from the non-student cases to non-student cases. R_{eff1} represents the transmissibility of the population of students with active TB cases (sum of R_{eff11} and R_{eff12}), whereas R_{eff2} represents the transmissibility of the population of non-student active TB cases (sum of R_{eff22} and R_{eff21})

asc denotes the ascending R_{eff} ($R_{eff(asc)}$). des denotes the descending R_{eff} ($R_{eff(des)}$)

areas, such as China, most TB transmission occurs outside the home (< 20% of household transmission) which is not necessarily attributable to known close contacts [69, 70]. The probability of TB transmission to others by a TB patient is determined by many factors, including socioeconomic, environmental, high or low regional disease burden, infectiousness of the case, MTB strain, and host susceptibility. Determining the specific site of TB transmission outside the home is difficult. The potential for airborne transmission even during brief contact, combined with variable incubation periods, makes it exceptionally difficult to establish a specific TB transmission link. Despite these challenges, certain specific settings have been identified as important contributors to TB risk, such as nasal transmission [71–74], hospital-associated transmission [75], homeless shelters [76], prisons [77, 78], public transportation [79], churches [80], schools [69, 81] and slums [82–84]. This is precisely because the places where students study and live are close, providing good conditions for the spread of TB; therefore, the implementation of TB control policies in schools is especially important. The presence of these factors has contributed to the high rates of acquired TB in this group over the years.

Furthermore, the concentration of TB transmission in certain settings and subpopulations also leads to heterogeneity of transmission, which can serve to increase R_{eff} and may make it more difficult to control transmission [85]. Moreover, adults in their most active age groups are more likely to be infected with TB due to their close contact with each other [86]. To explain why transmission among the non-student populations increased the number of infected patients among non-students, it may be assumed that household and unnoticed transmissions in the community contribute simultaneously [87].

B) The results from knock-out analysis indicated that non-student-to-student transmission increased the number of reported TB cases in the student group (either pathogen positive or negative), and transmission among non-students increased the number of reported TB cases

Table 6 R_{eff} of Model A between students and non-students (Xiamen City)

Year	R_{eff11}	$R_{eff\,12}$	$R_{eff\,22}$	$R_{eff\,21}$	R_{eff1}	R_{eff2}
2005 (asc)	0.04	0.00	2.21	0.03	0.04	2.24
2005 (des)	0.00	0.22	2.03	0.03	0.22	2.06
2006 (asc)	0.02	0.11	2.71	0.01	0.13	2.72
2006 (des)	0.02	0.00	1.77	0.05	0.02	1.83
2007 (asc)	0.04	0.00	1.81	0.04	0.04	1.84
2007 (des)	0.03	0.01	2.00	0.04	0.04	2.04
2008 (asc)	0.00	0.15	1.86	0.03	0.15	1.89
2008 (des)	0.03	0.00	1.54	0.03	0.03	1.57
2009 (asc)	0.00	0.09	1.75	0.02	0.09	1.77
2009 (des)	0.04	0.01	1.69	0.05	0.05	1.73
2010 (asc)	0.04	0.15	1.60	0.03	0.19	1.62
2010 (des)	0.03	0.01	1.33	0.02	0.04	1.36
2011 (asc)	0.03	0.00	2.01	0.05	0.03	2.06
2011 (des)	0.01	0.00	1.39	0.03	0.01	1.42
2012 (asc)	0.02	0.00	1.36	0.02	0.02	1.39
2012 (des)	0.00	0.12	1.31	0.03	0.12	1.34
2013 (asc)	0.06	0.00	1.79	0.08	0.06	1.87
2013 (des)	0.02	0.00	1.28	0.02	0.02	1.29
2014 (asc)	0.01	0.04	1.16	0.01	0.05	1.18
2014 (des)	0.01	0.02	1.19	0.03	0.03	1.22
2015 (asc)	0.02	0.00	1.48	0.02	0.02	1.50
2015 (des)	0.01	0.02	1.21	0.05	0.03	1.27
2016 (asc)	0.02	0.01	1.34	0.02	0.03	1.37
2016 (des)	0.00	0.10	1.11	0.01	0.10	1.12
2017 (asc)	0.02	0.00	1.38	0.02	0.02	1.40
2017 (des)	0.01	0.06	1.43	0.01	0.07	1.45
2018 (asc)	0.02	0.01	1.32	0.02	0.03	1.35
2018 (des)	0.02	0.00	1.22	0.02	0.02	1.25
Median	0.02	0.04	1.58	0.03	0.06	1.61
P25	0.01	0.00	1.32	0.02	0.03	1.35
P75	0.03	0.07	1.80	0.03	0.07	1.85

R_{eff11} denotes the transmissibility of MTB from student cases to student cases. $R_{eff\,12}$ denotes the transmissibility of MTB from student cases to non-student cases. $R_{eff\,21}$ denotes the transmissibility of MTB from non-student cases to student cases. $R_{eff\,22}$ denotes the transmissibility of MTB from the non-student cases to non-student cases. R_{eff1} represents the transmissibility of the population of students with active TB cases (sum of R_{eff11} and $R_{eff\,12}$), whereas $R_{eff\,2}$ represents the transmissibility of the population of non-student active TB cases (sum of $R_{eff\,22}$ and $R_{eff\,21}$)

asc denotes the ascending R_{eff} ($R_{eff(asc)}$). des denotes the descending R_{eff} ($R_{eff(des)}$)

in all the four groups. There may be several reasons for this. First, the home–school transmission route may be one of the reasons. TB is actively transmitted by household exposure [88], and a prospective case–control study found that previous exposure to TB in a household could cause an infected student to spread TB to their classmates [89]. Second, we believe that the school community transmission route is important due to increased exposure to other occupations during vacations.

C) Although TB transmission is spread mainly by non-students, the transmissibility of student-to-non-students in some years and in some regions, is particularly high, such as the R_{eff12} of Chuxiong Prefecture in 2016 (R_{eff12}: 0.13), 2017 (R_{eff12}: 0.16), and that of Wuhan City in 2006 (R_{eff12}: 0.36), etc. This could be due to TB outbreaks in schools [90]. Once TB transmission occurs in schools, the spread of TB will exceed beyond the public due to the frequent contact between students and cause widespread TB in schools. Due to this particularity of TB school transmission, the TB reporting system of China is more sensitive to the population of student occupation. A national single-case warning system is used to identify the student tuberculosis patients. When a student is diagnosed, close contacts screening, isolation and treatment of the TB patients are implemented in the shortest time. These measures make the control of student

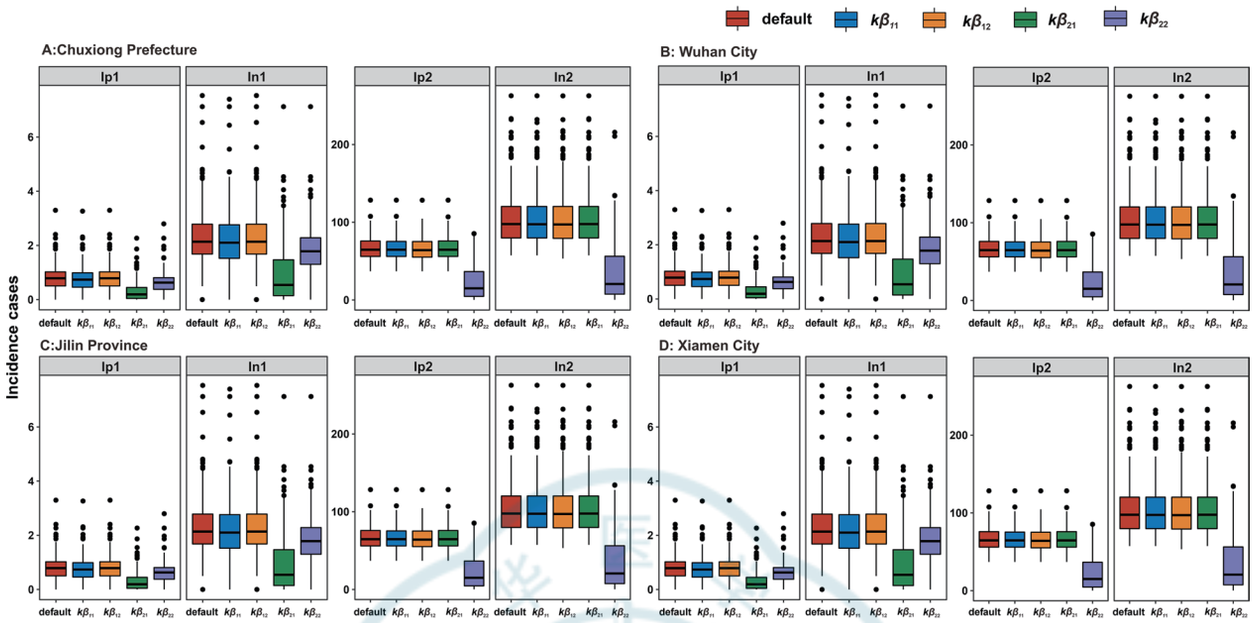

Fig. 10 Knockout analysis in the four study areas: **A** Wuhan City, **B** Jilin Province, **C** Xiamen City, and **D** Chuxiong Prefecture. The subscripts refer to the occupation of the students ($_1$ subscript) or non-students ($_2$ subscript). The initial state is denoted as the default. The performance of the knockout for each of the transmission pathway was determined by setting the beta value to zero. For example, k_{b11} stands for getting rid of the student-to-students' transmission pathway

TB outbreaks much more effective, and then reduce the tuberculosis cases of this outbreak. But in the real world, if the epidemic was not dealt with promptly, a widespread TB outbreak in schools will be inevitable.

Prevention and control of TB among students

The relevant authorities must continue to strengthen the prevention and control of TB in student populations in the future [91]. There are shortcomings at all levels, including schools, medical institutions and TB control institutions, and improvements are needed. For schools, the implementation of a system to trace the causes of absence from school to detect patients in a timely and proactive manner is effective. Medical institutions should keep the epidemic information channels open with schools and TB control institutions, and provide timely information about confirmed students to schools and TB control institutions. TB prevention and control institutions should perform timely information verification and close contact follow-up after the detection of the infected student.

In addition, we suggest that more attention should be paid to men, farmers, and young and middle-aged people; and the bacteriological diagnosis of TB should be strengthened. More data collection from social contact surveys is required to provide information on how individual behaviors drive disease dynamics at the population level.

In particularly, several limitations may have influenced the results obtained. The first is selection bias due to inconsistency at the administrative levels in our study areas, which includes three cities and one province. The second is that we only included cases that were diagnosed as "bacteriologically confirmed positive or negative" and excluded those that were diagnosed as "rifampicin resistant" when processing the initial data. The latter could also contribute to TB transmission. Furthermore, complete immunity does not occur in patients with TB after recovery. However, partial immunity has been observed in previously infected individuals, which can prevent reinfection (risk ratio = 0.5) [92]. The last limitation of our methodology is that it was not possible to subdivide the 17 non-student occupations to better articulate the mechanisms of transmission between different occupations and quantify the impact of different non-student occupations on the student population.

Conclusions

This study has the potential to improve our understanding of the features of TB transmission in different occupational groups. The transmission of MTB was high in non-student populations, and that in the non-student population was 23.30 times higher than in the student

population. It had the strongest influence among non-student groups. It not only increases the incidence of TB among non-students, but also among students. The incidence of TB among students has been on the rise and is the fourth highest in occupational distribution (especially in economically developed areas with a high number of students), despite the incidence of TB in China showing a downward trend annually. The TB outbreak among students can rapidly improve the transmissibility of TB in a short time, which will affect the prevalence of TB in other groups. TB screening should be performed rigorously at the beginning of the school semesters, when returning to school, to detect patients with LTBI. This implies the need for the implementation of more control measures such as strengthening the school TB management efforts and timely management of identified TB-infected students, after the academic year begins.

Abbreviations

SEIR: Susceptible-exposed-symptomatic-recovered; R_{eff}: Effective reproduction number; MTB: *Mycobacterium tuberculosis*; TB: Tuberculosis; PTB: Pulmonary tuberculosis; MDR-TB: Multidrug resistant tuberculosis; HIV: Human immunodeficiency virus; AIDS: Acquired immune deficiency syndrome; LTBI: Latent TB infections; NNDSS: National Notifiable Disease Surveillance System; IGRA : Interferon-gamma release assays; R_0: Basic reproduction number; DOTS: Directly observed treatment and short course chemotherapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40249-022-01046-z.

Additional file 1: Table S1. The basic information of the four regions.

Additional file 2: Table S2. Two different classifications of tuberculosis in National Notifiable Disease Surveillance System (NNDSS).

Additional file 3: Table S3. Estimation of transmissibility between students and non-students (Wuhan City).

Additional file 4: Table S4. Estimation of transmissibility between students and non-students (Jilin Province).

Additional file 5: Table S5. Estimation of transmissibility between students and non-students (Chuxiong Perfecture).

Additional file 6: Table S6. Estimation of transmissibility between students and non-students (Xiamen City).

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Author contributions

QC, SY, JR, YG, SY, GA, ZY, CL, LL, MW, ZL, QZ, LG, YN, RF, and TC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YN, RF, and TC were responsible for study conception and design. MW, and QZ collected the data. QC, SY, JR, YG, SY, GA, ZY, CL, LL, LG, and ZL were responsible for data analysis and interpretation. QC, SY and JR drafted the manuscript. YN, RF, and TC critically revised the manuscript for intellectual content. YN, RF, and TC contributed equally to this study. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the School of Medicine, Xiamen University. Consent requirement, either verbal or written, was waived by the thics Committee of the School of Medicine on the following grounds: (1) only anonymized records were used without the need for direct involvement nor active participation of patients; (2) neither medical intervention nor biological samples were involved; (3) study procedures and results would not affect clinical management of patients in any form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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