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Estimates of tuberculosis progression rate of children in China

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Estimates of tuberculosis progression rate of children in China

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In this paper, a discrete mathematical model is formulated to describe tuberculosis (TB) progression from latent infection to active disease. The data of national TB epidemiology surveys in China are taken to estimate the TB progression rate for children aged 0–14 years. The progression rate obtained in this paper gives a detailed and better estimate of TB progression rate among children.

Keywords: discrete TB model; children tuberculosis; progression rate; latent infection

AMS Subject Classification: 9A10; 92D30

1. Introduction

Tuberculosis (TB, mycobacterium tuberculosis) is a global public health problem that impacts one-third of the world's population and is a leading cause of death worldwide, especially in low-income and middle-income countries, such as those of sub-Saharan Africa and Asia. There were 5.8 million notified cases of TB in 2009, and the WHO estimated that there were 9.4 million incident cases and 14 million prevalent cases in 2009 [34].

TB spreads through air droplets which are expelled when infectious individuals cough, sneeze, speak, or sing. Close contacts are at the highest risk of becoming infected. After being infected, most people become latently infectious, with the bacteria being alive in the body but inactive. Latently infectious individuals do not have symptoms and cannot spread the infection to others. Most people are able to fight the infection with their immune system, but those people with latent infection are at a risk of developing active disease.

The chance of developing active TB is higher in children, older adults, and people with an impaired immune system. The risk of progression to active TB is highest immediately after the infection; subsequently, the risk follows approximately an exponential decline during the first 7 years and then levels off, apparently persisting for many years or even decades [6]. It is believed that the risk of progression to active TB depends on age and age of infection (the time since

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infection). Young children and elderly adults have the highest risk of progression to active TB after infection.

It is estimated that the chance of people living with latent infection converting to active disease over their lifetime is approximately 10%. It is also estimated that about 5% of people who have latent infection will develop active TB in 2 years, and another 5% will develop active TB in their lifetime [2,26,32].

Knowledge of the progression rate from latent infection to active TB has great importance in TB epidemiology since there is an enormous reservoir of individuals living with latent infection, and a small variation in the progression rate may produce a large difference in TB incidence. The progression rate is also the key parameter in epidemiological modelling since this rate is very sensitive in determining the case number of active TB patients. The TB progression rate can be estimated through a cohort study by following tuberculin converters for several years. For example, the observation from the Missouri Rehabilitation Center study in 1950s and 1960s found that 54% of the 243 cases had developed TB within a year and nearly 80% within 2 years following the infection [23,25]. There are difficulties in carrying out a cohort study since it is not easy to follow a cohort with a large population for a long time.

The estimated percentage of people with latent infection is one-third globally and even higher in southeast Asia. Although there are annual or monthly reports of TB cases from infectious disease surveillance systems, there is no regular survey of latent infections. What is more, it is very difficult, almost impossible, to determine the exact infection time for a individual with latent infection. For these reasons, we attack the challenging problem of estimating the TB progression rate by a modelling approach. Our estimate of the TB progression rate is restricted to childhood and is based on a TB transmission model as well as the data of national survey for the epidemiology of TB in China [14].

Other considerations for the study of childhood TB are that progression to active TB is likely to occur in young children, and childhood TB is a neglected aspect of the TB epidemic, despite constituting 20% or more of the TB cases in many countries with high TB incidence. There is relatively less research on the childhood TB progression rate because very few firm data are available. In countries with high TB prevalence, there are relatively few published data documenting the incidence of childhood TB, and childhood TB incidence rates may be more than 100 per 100,000 per year or even 200 per 100,000 per year. In South Africa in 1993, the national incidence of TB was 224 per 100,000 per year and children constituted 20% of the TB cases [33].

The advantage of estimating the childhood TB progression rate is that there is more cohort research on childhood screening and latent infection investigation. Minodiera *et al.* [12] evaluated a 10-year school-based latent TB infection screening programme, in which 4375 children were offered screening, 82.3% of them consented to have undergone the tuberculin skin test, and 22.8% were positive. One study concerning children aged 15 years and younger found a variable progression risk: the highest was in children between birth and 12 months of age, and the risk for children aged between 1 and 5 years and teenagers decreases [21].

The tuberculin skin test is widely used as a screening method and a diagnostic tool for TB. A volume of 0.1 ml, containing 5 tuberculin units of purified protein derivative (PPD), is injected intradermally into the forearm, and the reaction is read 48–72 h later by measuring the diameter of induration in millimetres. The measurement of the induration diameter is interpreted if a person has got TB exposure. The tuberculin skin test is regarded as positive if the induration diameter is greater than 5 mm in high-risk children or if the induration diameter is greater than 10 mm in all the other children. The tuberculin skin test is an easy and good test for finding a TB infection, which makes it possible for us to estimate the percentage of people with latent TB infection. A tuberculin skin test cannot tell us how long a person has been infected with TB. The results of a tuberculin skin test alone cannot confirm an active TB infection. Other tests, such as a chest X-ray and sputum culture, may be done to confirm an active TB infection when a skin test is positive.

Medical technology and tests provide the basis to distinguish latent TB and active TB infections. Public health assessment and projection of the TB epidemic require better estimation of the TB progression rate from latent infection to active disease, but insufficient data make direct estimation difficult. We hope that a modelling approach can make contributions to the estimation. In the next section, we give a brief introduction to the national sampling survey on TB epidemiology and TB epidemic in China. The estimation model and the result are presented in Section 3. Limitations and advantages are discussed in the last section.

2. The TB epidemic data in China

TB infection remains a serious public health challenge in China. According to the WHO estimates, China has the world's second largest TB epidemic, after only India, with more than 1.3 million new cases of TB being reported every year [31]. About 0.1% of the Chinese population developed TB for the first time in 2008, accounting for one in seven new cases worldwide [9]. Over the period 2001–2008, TB was the second largest cause of death among China's 39 notifiable communicable diseases, after HIV/AIDS [9].

In order to evaluate the national TB situation in China and to provide a scientific basis for effective TB control, four large-scale national sampling surveys of TB epidemiology were carried out in 1979, 1984/1985, 1990, and 2000, respectively. The multi-stratified grouping random sampling method was used and tuberculin testing was carried out among all children of the 0–14 age group. Children (aged 0–14 years) who were suspected of having TB were diagnosed by chest radiograph, sputum smear microscopy, and culture. The data regarding TB infection, prevalence, smear positive and bacteriological positive rates and other information were obtained. The sampling size, the sampling ratio, and the national population in the four surveys are listed in Table 1, demonstrating that this survey was a large-scale national survey.

The tuberculin PPD skin test is a widely used method to diagnose TB infection; it works by causing a mild, delayed allergic reaction in patients infected with TB or who have had a past infection. There are different tuberculin skin test data in China: a 1958 study of 6387 individuals in Hebei province indicated that the percentage of children with latent TB infection was over 15% [28]; the 4-year cohort study of 692 children under seven in Yiyang county, Hunan province, showed that 1.4% of children develop latent infection annually [27]; the 2003–2004 study of 43620 children at an elementary school in Jiaonan county, Shandong province, found that the PPD positive rate among elementary school children was 16.41% [29]. More uniform TB infection and prevalence data were also obtained in the national survey of TB epidemic.

In these four national sampling surveys, the tuberculin skin test reaction was studied in children who had no Bacille Calmette–Guerin scars and no inoculation to screen the latent TB infection. When the diameter of the induration was greater than 6 mm, the children were classified as PPD positive and the infection was considered as natural TB one. The data of the children aged 14 years and younger with natural TB infection, of the four national sampling surveys on TB epidemiology, are shown in Figure 1(a). The increasing trend with age is obvious, though there are some variations

Table 1. The data of national sampling survey of TB in China.

	Total population	Sampling	Ratio
1979	960,979,560	1,338,080	1:718
1984/1985	1,035,789,856	1,176,370	1:731
1990	1,133,682,501	1,539,451	1:787
2000	1,214,980,875	418,465	1:3152

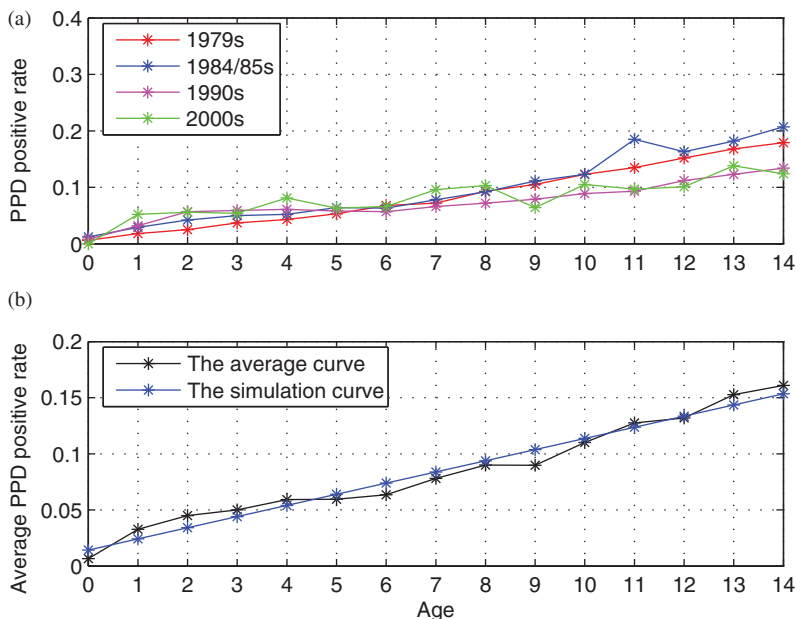


Figure 1. The age-dependent PPD positive rates of children aged 0–14 years in China.

in the PPD positive rates in the four sampling surveys. We used the averaged age-dependent PPD positive data of the four sampling surveys as the age-dependent latent TB infection rate though the sampling children were not in the same population cohort since the difference was not huge. From the averaged data, we obtained the curve of the PPD positive rate of children under 14 years (Figure 1(b)). The curve showed a linearly increasing tendency and we fit this curve by the least square method to get the equation of the simulation curve:

$$m_k = 0.009949k + 0.01419, \quad k = 0, 1, \dots, 14,$$

where m_k represents the PPD positive rate of children aged k , which is used as the latent TB infection rate in the next section to estimate the TB progression rate. The fitted curve is also shown in Figure 1(b). It was estimated that the annual risk of developing latent TB was 1.33% in 1985, 1.09% in 1990, 0.87% in 1995, and 0.72% in 2000, respectively [14]. The annual increase rate of latent TB infection in the expression of m_k is 0.99%, which is close to the estimated risk of 1992. The agreement of the risk and the increase rate indicates that our average and the fitting of the PPD positive rates are reasonable.

The prevalence in children aged 0–14 years was 242 cases, 178 cases, 172 cases, and 92 cases per 100,000 in 1979, 1984/1985, 1990, and 2000, respectively. The prevalence in children in the four sampling surveys broken down into three age subgroups is given in Table 2. However, data for the 1984/1985 survey are less detailed and are not included in Table 2. These surveys also showed that in China, TB cases in children continue to decline. The disease (TB) cases in children aged 0–14 years account for 13%, 9.9%, 9.7%, and 6.1%, respectively, of the total number of infectious cases for all ages in the four sampling surveys [14]. The subgroup aged 0–14 years had the second highest percentage of cases in the subject group, namely 24.5%, after only the subgroup aged 30–44 years. The sampling survey in 2000 shows that the number of TB cases in children aged 0–4 years is less than that in the other two subgroups, and the percentage of TB patients increases with age.

Table 2. TB prevalence in children in China.

	Age group	Sample size	TB cases	Prevalence (1/100,000)
1979	0–4	132,517	186	140
	5–9	174,618	476	273
	10–14	174,538	502	288
1990	0–4	132,558	101	76
	5–9	138,561	312	225
	10–14	130,878	279	213
2000	0–4	17,355	7	40
	5–9	29,080	27	93
	10–14	42,860	48	112

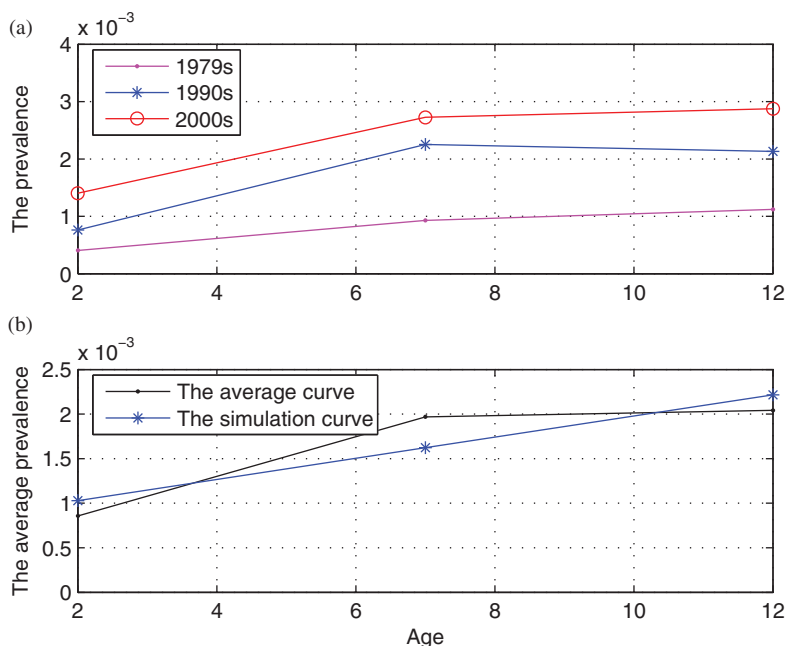


Figure 2. The age-dependent prevalence rates of children aged 0–14 years in China.

For the active TB cases, there were seven sets of data in the 1979 sampling survey, including those aged 0–4 years, age group 5–9, and age group 10–14. In the sampling survey of 1984/1985, prevalence was observed in children aged 0–14 years. The 1990 sampling survey showed prevalence in three age groups: 0–4, 5–9, and 10–14. The sampling survey of 2000 was the same as that of 1990. We used the prevalence in children aged 0–4 years to obtain the prevalence in children age group 0–4 in 1979. The prevalence data of these three sampling surveys in the 5-year age groups are shown in Figure 2(a). Then, we averaged these data in the three sampling surveys and fit these data with a linear function. The averaged and fitted curves of prevalence are shown Figure 2(b). The linear function of the fitted prevalence is

$$q_k = 0.0001186k + 0.0007921, \quad k = 0, 1, \dots, 14,$$

where q_k represents the prevalence in children aged k , which is used in the next section.

m_k and q_k are the fitted age-dependent PPD positive and TB prevalence rates. These two sets of parameters are used to estimate the TB progression rate from latent infection to active disease.

In an earlier TB survey in Hebei province, for children aged 0–14 years, the PPD positive rate and prevalence rate were higher than those in the four sampling surveys; however, both the PPD positive rate and prevalence rate were almost linear functions of age [28], and this trend is consistent with our simulation curves.

3. The TB model with age and infection age structures

Consider TB transmission in a stable society. We divide the population according to their epidemiological status: the susceptibles, the latent, and the active. Latent TB can be detected by the PPD test: the PPD-positive individuals without TB symptoms are classified as latent. Individuals in these epidemiological classes are further grouped according to their age and age of infection.

We consider only children aged 0–14 years in the stable state. Our general assumptions are as follows:

- (1) the population reaches a stable age distribution;
- (2) the proportions of latent and active individuals in children aged 0–14 years are independent of time; and
- (3) the progression rate from the latent to the active class depends only on the age of infection.

The following notations are used in our model. N_k denotes the total number of children aged k (whose ages are in the interval $[k, k + 1)$, $k = 0, 1, 2, \dots, 14$). E_k is the number of children aged k who are in the latent class. E_k is further divided into $k + 1$ subgroups according to the infection age, that is, the time from infection. Let $E_{k,j}$ be the number of children aged k with infection age j ($j = 0, 1, \dots, k$). Naturally, $k \geq j$, and the total number of latent children aged k satisfies $E_k = \sum_{j=0}^k E_{k,j}$. Let α_j be the annual progression rate of children whose infection age is j , m_j the fraction of children aged j who are PPD positive, and q_k the fraction of children aged k who have active TB. Let I_k be the number of children aged k who have active TB and d_k be the annual death rate of children aged k . Then, $p_k = 1 - d_k$ is the annual survival rate of children aged k . From the definition of m_k and q_k , we have $E_k = m_k N_k$ and $I_k = q_k N_k$.

We trace the children from age 0 to age 14 to investigate the progression rate from the latent class to the active class. In the initial year, as to the children aged 0, the number of children who are PPD positive is $m_0 N_0$ and the number of children with active disease is $q_0 N_0$. The TB infection and activation of children aged 0 years are just in the same year, which means $E_0 = E_{0,0} = m_0 N_0$ and $I_0 = q_0 N_0 = \alpha_0 E_{0,0}$. Furthermore, we obtain $\alpha_0 = q_0 N_0 / m_0 N_0 = q_0 / m_0$, which means that the progression rate of children with infection age 0 is $\alpha_0 = q_0 / m_0$.

As time passes, the ages of these children will increase with time. The total number of children aged k is given by

$$N_1 = N_0 - d_0 N_0 = p_0 N_0, \quad N_2 = p_1 p_0 N_0, \dots, N_k = p_{k-1} p_{k-2} \cdots p_1 p_0 N_0.$$

Similarly, we give the formula for $E_{k,j}$. According to our assumption (2), we know that the total number of children aged k in the latent class is $E_k = m_k N_k$. For children of age k with latent TB infection, the infection age may be $0, 1, \dots, k$. These children may become infected in any age from 0 to k and have not progressed from latent infection to active disease. Therefore,

$$E_{1,1} = E_{0,0} - d_0 E_{0,0} - \alpha_0 E_{0,0} = (p_0 - \alpha_0) E_{0,0},$$

$$E_{1,0} = m_1 N_1 - E_{1,1},$$

$$E_{2,j} = E_{1,j-1} - d_1 E_{1,j-1} - \alpha_{j-1} E_{1,j-1} = (p_1 - \alpha_{j-1}) E_{1,j-1}, \quad j = 1, 2,$$

$$\begin{aligned}
E_{2,0} &= m_2 N_2 - E_{2,1} - E_{2,2} \\
&\vdots \\
E_{k,j} &= E_{k-1,j-1} - d_{k-1} E_{k-1,j-1} - \alpha_{j-1} E_{k-1,j-1} \\
&= (p_{k-1} - \alpha_{j-1}) E_{k-1,j-1}, \quad j = 1, 2, \dots, k, \\
E_{k,0} &= m_k N_k - \sum_{j=1}^k E_{k,j}, \quad k = 1, 2, \dots, 14.
\end{aligned} \tag{1}$$

For those individuals having active TB, according to our assumption, in the first year, the number of children aged 0 in the active class is $I_0 = q_0 N_0 = \alpha_0 E_{0,0}$. In the second year, the number of children aged 1 in the active class is $I_1 = q_1 N_1 = \alpha_0 E_{1,0} + \alpha_1 E_{1,1}$. Based on the above idea, in the $(k+1)$ th year, the number of children aged k in the active class is

$$I_k = q_k N_k = \alpha_0 E_{k,0} + \alpha_1 E_{k,1} + \alpha_2 E_{k,2} + \dots + \alpha_j E_{k,j} + \dots + \alpha_k E_{k,k}, \tag{2}$$

where $k = 0, 1, \dots, 14$. From the expressions of I_1 , $E_{1,0}$, $E_{1,1}$, and $\alpha_0 = q_0/m_0$, we know that the progression rate of children with infection age 1 satisfies

$$\alpha_1 = \frac{q_1 N_1 - \alpha_0 E_{1,0}}{E_{1,1}}.$$

Similarly, the expressions of I_2 , $E_{2,0}$, $E_{2,1}$, $E_{2,2}$ and α_1 give the progression rate of children with infection age 2,

$$\alpha_2 = \frac{q_2 N_2 - \alpha_0 E_{2,0} - \alpha_1 E_{2,1}}{E_{2,2}}.$$

Based on the same idea, we obtain the progression rate of children with infection age j ,

$$\alpha_j = \frac{q_j N_j - \alpha_0 E_{j,0} - \alpha_1 E_{j,1} - \alpha_2 E_{j,2} - \dots - \alpha_{j-1} E_{j,j-1}}{E_{j,j}}, \quad j = 1, 2, \dots, 14. \tag{3}$$

From the expressions of N_k and $E(k, j)$, we know that N_0 can be cancelled from the numerator and denominator of Equation (3) and α_j depends only on $p_k, m_k, q_k (k, j = 0, 1, \dots, 14) (k \geq j)$.

Using the age distribution of China's population in 1982, the sampling survey data, and Equations (1)–(3), we can obtain an estimate of the TB progression rates α_j . These estimates are

$$\begin{aligned}
\alpha_0 &= 0.055821, & \alpha_1 &= 0.023144, & \alpha_2 &= 0.014357, & \alpha_3 &= 0.012035, & \alpha_4 &= 0.011428, \\
\alpha_5 &= 0.011269, & \alpha_6 &= 0.011225, & \alpha_7 &= 0.011213, & \alpha_8 &= 0.011211, & \alpha_9 &= 0.011209, \\
\alpha_{10} &= 0.011208, & \alpha_{11} &= 0.011208, & \alpha_{12} &= 0.011208, & \alpha_{13} &= 0.011208, & \alpha_{14} &= 0.011207.
\end{aligned}$$

The curve of the TB progression rate from latent infection to active disease is shown in Figure 3.

These detailed values show that for children in China, the risk of TB progression from latent infection to active disease is highest during the first year after infection, about 5.58%. From the second year, the risk declines rapidly, about 2.31%. In the third and fourth years, the risk continues to decline, about 1.43% and 1.2%, respectively. In the remaining years, the risk is lower, about 1.12%, and continues at this level for a long time. The value of α_j of our estimate implies that the risk of progression from latent infection to active disease decreases rapidly, and the risk of progression is greatest in the first 2 years following infection. On the whole, about 23% of children infected

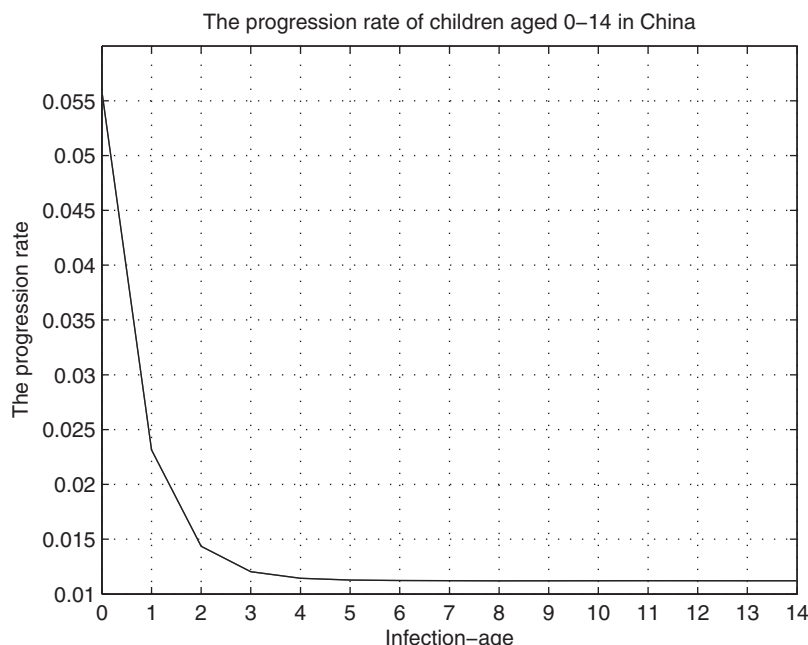


Figure 3. The TB progression rate from latent infection to active infection for children in China.

with the bacilli will develop active TB in China. The curve of the estimated progression rates is approximately an exponential curve for China. This trend is consistent with that given in [7,23].

The progression rates, estimated in [7], from latent infection to active disease in the first, second, third, fourth, and fifth years of latent infection are 0.06, 0.024, 0.009, 0.004, and 0.001, respectively. Although the definitions and the population cohort in [7,23] are different from ours, the decreasing tendency is similar. These data support our estimation of the progression rate. There is also other evidence to support our result [3,8].

If we assume that the progression is exponentially distributed in each year since infection, the progression rates that we have estimated suggest that the total progression in the first 2 years since infection is approximately 7.6%, which is large than the estimate of rapid progression, 5%, in [16]. The estimates also suggest that the progression rate is still 0.0112 after 10 years and the total progression rate in 15 years is 23%. These estimates are larger than the estimate that ‘5–10% of people who are infected with TB bacilli become sick or infectious at some time during their life’. We point out that our estimate of the progression rate includes the exogenous re-infections caused by contacts between latent and infectious individuals, a rate that cannot be estimated because of the absence of data. The other explanation is that the progression rate varies with different population cohorts. The progression rate of the population in developed countries with better economic conditions and medical care might be less than that of the population in developing countries. The progression rate of children might be larger than that of adults since children have an incomplete immune system and the latent infection may easily become active among children.

4. Discussion

Accurate epidemiological data are scarce for children with TB partly because of the lack of a standardized case definition, the difficulties in diagnosis, and the absence of a definitive diagnostic

test [1,4] and partly because most children with TB are sputum smear negative (more than 90%) [1, 4,15,17,30]. Furthermore, TB in children has received less attention from researchers, clinicians, and policy-makers. A relatively low public health priority has been given to TB in children relative to adults [1]. In fact, TB is a major cause of death in children worldwide, and it is also an important cause of morbidity. Based on age-specific data, the WHO estimated that 450,000 deaths from TB occur annually among children in developing countries [18]. If active TB is not diagnosed and treated, the estimated mortality rate from TB is 18 per 100,000 infected children aged 0–4 years and 9 per 100,000 for those aged 5–14 years [17,24]. In 2000, the global burden of TB among children below the age of 15 years was 884,019 cases, accounting for 11% of the total cases; 75% of these childhood cases occur annually in 22 high-burden countries [22].

Children become infected when they are exposed to infectious adults with smear-positive TB [5,13,19]. About 50% of children who are in close contact with an infectious case and 10% of children who are in casual contact with an infectious case become infected [5]. In developing countries with a high incidence of TB, the risk for infection among children in contact with adults with TB is 30–50% [13]. This implies that the infected children represent a pool from which a large proportion of future cases of adult TB will arise [18]. That is, we can use childhood TB as a marker that represents TB transmission within the group of adults. Therefore, it is important to discuss the progression rate of children. On the one hand, we can monitor the trend of childhood TB so that we can decrease the mortality in children. On the other hand, we can also obtain information about TB transmission in adults.

The risk of children becoming active after infection with TB is determined by various factors, which include age, recently acquired infection, nutritional and immune status, and genetic factors [17]. The risk is greatest in the first 2 years after infection and is much higher in the presence of HIV infection [5,11]. Children aged below 2 years have an increased risk of developing TB as well as an increased risk of serious disease [5]. Many experts agree that healthy adults infected with TB have a 5–10% lifetime risk of progression to disease if untreated [10,21]. However, for children, there is no similar affirmatory view. It is estimated that about 10–15% of children infected with the bacilli develop TB [20]. The estimated risk of progression from latent infection to active disease varies substantially in different studies [5,18,19,21].

Although China has the world's second largest TB epidemic and great efforts have been taken to control TB recently, there is little research on the progression rate from latent infection to active disease. The main goal of this paper is to use the data of four national TB epidemiology surveys in China to give the detailed progression rate of children aged 0–14 years with different infection ages. The estimate provides a good reference of parameter values in TB modelling and a basis to better prediction and control of the TB epidemic in China. The idea and method might be used to estimate the progression rate of adults if more data are available.

It is commonly recognized that 10% of latent TB cases will become active, and the active rate decreases with the latent period. There are no better statistical data or estimates on the progression rate. We have tried to give an infection age-dependent progression rate of children in China. Although the modelling approach, the data, and the result are not satisfactory now, our results make some progress regarding this challenging problem.

There are many difficulties in the estimation of the progression rate. The main obstacle is the lack of the exact infection time. The PPD test tells us if an individual has latent TB, but it cannot tell us when the infection actually occurred. We have not found any cohort research to determine the progression rate from latent infection to active disease for children in China to support our estimates, but we expect that the future cohort research on TB progression rate from latent infection to active disease can give better and accurate estimate of the vital rates.

Although the estimation of the TB progression rate has been carried out for children in China, the idea and the method are equally applicable to any population and age interval if the infection rates and the prevalence can be obtained.

A limitation of our paper is the variation in TB prevalence in the national sampling surveys. These variations may lead to a bias in TB progression rates, and the estimates would be improved if better data can be obtained. Since treatment in China normally does not begin before progression to active disease, our results are not affected by the treatment level. However, if latent TB cases are treated, progression rates would be much less than our estimates.

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