

Dynamic Characteristic Analysis of HIV Mother to Child Transmission in China¹

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Objective to explore dynamic characteristics of the HIV mother to child transmission (MTCT) epidemic in China. **Methods** A deterministic dynamic transmission model was used to determine the effect of key parameters on the likely long-term trends of the HIV MTCT epidemic in China. Matlab 7.0 was used to develop the model. **Results** The number of the susceptibles (S), the transmission rate (β), and the screening proportion (α) of HIV positive pregnant women have the greatest impact on the HIV MTCT epidemic in China. The growth of the MTCT epidemic in China could not be controlled only by decreasing the MTCT transmission rate. The prevalence of HIV positive women should be reduced and more pregnant women should be tested for HIV. **Conclusion** Prevention of MTCT (PMTCT) should focus not only on the reduction of HIV transmission rates and incidences of HIV among women but also on the increase of HIV testing for pregnant women. The most cost-effective PMTCT means for China should be investigated in future studies.

Key words: mother to child transmission, dynamic model, HIV, China

INTRODUCTION

The annual reported number of HIV positive women is on the rise in China^[1-3]. Factors related to the HIV epidemic, such as increase in sexual transmission and in the number of sex partners, poor HIV knowledge and migration to cities, increase the risk of HIV acquisition among women in China^[3-5]. According to the estimates in 2007, there were 1.8-3.8 million female sex workers (FSWs) in China^[6]. The yearly reported HIV positive male to female ratio decreased from 4:1 in 2000 to 2:1 in 2009^[3, 7]. Although there are relatively few cases of HIV due to mother to child transmission (MTCT) in China^[8], the possibility of increasing HIV prevalence through vertical transmission still exists. The

increasing number of HIV positive women of reproductive ages allows for the possibility of more cases of MTCT in China.

The first case of MTCT was reported in China in 1995^[9]. The proportion of reported cases of HIV/AIDS attributed to MTCT rapidly increased from 0.1% in 1997 to 1.6% in 2007^[3, 7, 10]. In some high risk areas in China, the HIV prevalence among pregnant women is as high as 2%^[3]. In 2004, the Chinese government initiated programs for the prevention of mother to child transmission (PMTCT)^[7]. PMTCT efforts mainly focus on the use of antiretroviral therapy (ART) for infected mothers during pregnancy and formula feeding for their infants after birth. PMTCT has been demonstrated to be able to reduce the transmission probability of MTCT^[11-12]. However,

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the cumulative number of HIV MTCT cases has been rising despite the PMTCT efforts.

It is still unknown how PMTCT efforts quantitatively impact the MTCT epidemic in China. Mathematical dynamic modeling based on differential equations has provided a means to evaluate the impact of the HIV/AIDS epidemic in some populations, such as injection drug users (IDUs), FSWs, and male clients of FSWs^[13-19]. A dynamic analysis of MTCT in China has not yet been carried out and thus, it is unknown how key parameters impact the epidemic trend of MTCT in China. The current study uses a dynamic model of MTCT transmission to analyze how the parameters related to key factors alter the the trend of this epidemic.

METHODS

A deterministic dynamic transmission model was used to explore the effect of key parameters on the likely long-term trends of the HIV MTCT epidemic in China. Matlab 7.0 was used to develop the model (Natick, MA, USA). Four divisions of the population between 0 and 14 years of age were considered: *S* (the susceptible) is the number of children born to HIV positive mothers and successfully delivered; *I*₁ is the number of HIV positive children who were born to HIV positive mothers who are unaware of their HIV positive status; *I*₂ is the number of HIV positive children who were born to HIV positive mothers who are aware of their HIV positive status; and *A* is the number of children in the AIDS stage. Among α of *S*, β_1 are infected and progressing to stage *I*₁. Among $(1-\alpha)$ of *S*, β_2 are infected and progressing to stage *I*₂. γ of *I*₁ and *I*₂ get developed to stage *A*. Fig. 1 illustrates the stages of the progress. It is assumed that 100% of tested HIV positive pregnant women receive PMTCT, that all births are uniparous, that one woman only bears one child based on China's one-child policy. If a child acquires HIV in utero, the infection is considered at age 0. Additionally, mothers are supposed to breastfeed their children for one year.

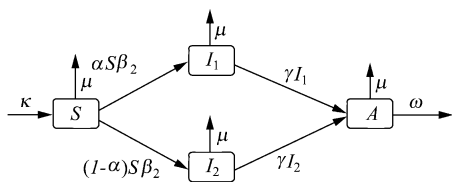


FIG. 1. Model for HIV mother to child transmission.

Parameter Setting

*S*₀: Baseline number of babies born to HIV positive mothers

(*I*₁+*I*₂)₀: Baseline number of HIV positive children

κ: The number of newborns born to infected mothers in the susceptible group (*S*) per year. κ is considered as the number of HIV positive pregnant women per year. Those fetuses that do not survive to birth are subtracted:

β₁: Variable rate of HIV transmission for tested HIV positive mothers

β₂: Variable rate of HIV transmission for untested HIV positive mothers

α: The proportion of tested HIV positive pregnant women in the total population of HIV positive pregnant women

γ: The rate of progression from acquisition of HIV infection to development of AIDS

μ: The natural mortality rate of children (aged 0-14)

ω: Removal rate of AIDS cases (from development of AIDS to death)

Differential Equations

$$\begin{cases} \frac{dS}{dt} = \kappa - \alpha S \beta_1 - (1-\alpha)S \beta_2 - \mu S \\ \frac{dI_1}{dt} = \alpha S \beta_1 - \gamma I_1 - \mu I_1 \\ \frac{dI_2}{dt} = (1-\alpha)S \beta_2 - \gamma I_2 - \mu I_2 \\ \frac{dA}{dt} = \gamma I_1 + \gamma I_2 - \omega A - \mu A \end{cases}$$

Equilibrium is considered (*S*⁰,0,0,0). From this equilibrium, the solutions for the equations are:

$$S = \frac{\kappa}{\alpha\beta_1 + (1-\alpha)\beta_2 + \mu}$$

$$I_1 + I_2 = \kappa \frac{\alpha\beta_1 + (1-\alpha)\beta_2}{[\alpha\beta_1 + (1-\alpha)\beta_2 + \mu](\gamma + \mu)}$$

According to the definition of the basic reproductive number (*R*₀), let

$$R_0 = \alpha\beta_1 + \beta_2 - \alpha\beta_2$$

because β₁ ∈ (0,1), β₂ ∈ (0,1), α ∈ (0,1), (αβ₁ + β₂ - αβ₂) ⊂ [0,1), that is 0 ≤ *R*₀ < 1. If an HIV positive woman of a reproductive age only bears one child, the basic reproductive number (*R*₀) is always smaller than 1 in the MTCT model. If an HIV positive woman of a reproductive age bears more than one child, then *R*₀ should be (αβ₁ + β₂ - αβ₂)*c*, where *c* is the total number of children born to HIV positive women of reproductive ages.

Data Sources

Data were collected from the Direct Reporting

Network for National HIV/AIDS in China, sentinel surveillance data, epidemiological surveys, mass screenings of target populations, and literature searches in scientific journals. As of the end of December 31, 2008, there were 3 964 HIV positive cases in those aged between 0 and 14. Among them, 2,814 (71.0%) were confirmed as MTCT. Of the remaining 1 149 (29.0%), 359 cases had HIV positive mothers, although it could not be conclusively determined that they acquired HIV from their mothers. The current study assumed that these 359

cases were all MTCT. For the remaining 791 cases that were not considered MTCT, mothers of 241 cases were untested and behavioral risk factors for their children were also not known; it could not be confirmed whether the mothers of 61 cases were tested, but other family members of 11 cases were HIV positive; and mothers in 516 cases were confirmed as HIV negative. The total cumulative number of HIV/AIDS MTCT cases by December 31, 2008 was 3 173 (Table 1).

TABLE 1

Cases of HIV/AIDS due to MTCT in China from 2003 to 2008

Year	Cumulative Number	Annual Number of Deaths	Cumulative Number of Survivors
2003*	286	46	240
2004	919	49	824
2005	1386	79	1212
2006	1907	94	1639
2007	2522	116	1707
2008	3173	93	2696

Note. *The cumulative number from 1995 to 2003.

Parameter Selection

Baseline: Although the first case of MTCT in China was discovered in 1995, PMTCT efforts had not been exerted in China until 2003. Since data from 2003 may more accurately reflect the MTCT epidemic in China, that year was chosen for the baseline study.

Input of S per year (κ): No data are available on the number of babies born to HIV positive mothers or on the number of HIV positive pregnant women per year, but the number of HIV positive MTCT children aged between 0-14 per year has been reported by the Chinese Centers for Disease Control (Table 1). From 2003 to 2008, the increase in MTCT had a linear trend with a slope of 564.7 (Table 1). This slope indicates that every year there would be 565 new cases of HIV from MTCT including both those that survive and those that do not survive. Based on the literature, in the absence of interventions, the MTCT rate would be 0.35^[20-24]. The number of babies born to HIV positive mothers would, therefore, be at least 1 614 per year.

Baseline number of babies born to HIV positive mothers (S_0): The reported number of HIV MTCT children in 2004 was 633 which is more than that reported in 2003. If the transmission rate is 0.35, the number of S at the end of 2003 would be 1 808.

Baseline number of HIV positive babies (I_1+I_2)₀: Based on case reports, there were 286 surviving children that acquired HIV through MTCT by the end of 2003. The baseline number of (I_1+I_2)₀ is,

therefore, 286. This number may be an underestimate since some cases may not have been found^[1, 7].

MTCT rate β_1 and β_2 : Varying transmission rates have been found in China in the presence of PMTCT interventions with 100% coverage. In the presence of PMTCT interventions, Wang, *et al.* reported a transmission rate of 0.13^[11]; however, Zhou, *et al.* reported a rate as low as 0.01^[12]. The current study assumed that β_1 fell between 0.01-0.15. Studies have reported transmission rates of 0.35-0.38 in the absence of interventions^[20-24]. The current study, therefore, assumed a MTCT rate, β_2 , of 0.35 in the absence of interventions.

α : The total proportion of positive pregnant women tested for HIV in the total population of HIV positive pregnant women in China. Ten percent of all pregnant women were tested for HIV in 2008^[25], but this is likely an underestimate of α .

γ and ω : These two parameters are determined by the lifespan of HIV positive children (from acquisition of HIV to death). If there were no ART, most HIV positive children would die in 5 years after acquisition^[1, 26-28]. Patel *et al.* reported that the median lifespan of HIV positive children was 6.3 years, although 70% of the participants of their study had initiated HAART^[29]. The parameter of $\gamma + \omega$ in one year should be the reciprocal of their expected lifespan. The longest life span was assumed to be 5 years and the shortest 1 year. In the current study, the parameter of $\gamma + \omega$ was considered to be between 0.1 and 0.5. ART prolongs the life span of HIV infected children and may, therefore, affect the parameters γ and ω .

μ : The natural mortality rate of children (aged between 0-14) in China is 6 deaths per 1 000 per year^[30].

RESULTS

Fig. 2 shows the reported number and the predicted number of HIV MTCT cases in China including both those that survive and those that do not survive. In this model, parameters were $\kappa=1614$, $S_0=1\ 808$, $(I_1+I_2)_0=286$, $\beta_1=0.13$, $\beta_2=0.35$, $\alpha=0.136$, $\gamma+\omega=0.3$, and $\mu=0.006$. Although these parameters were only derived from data during the six years (2003-2008), the modeling curve and the reported data curve fit well with a coefficient of determination of 0.99.

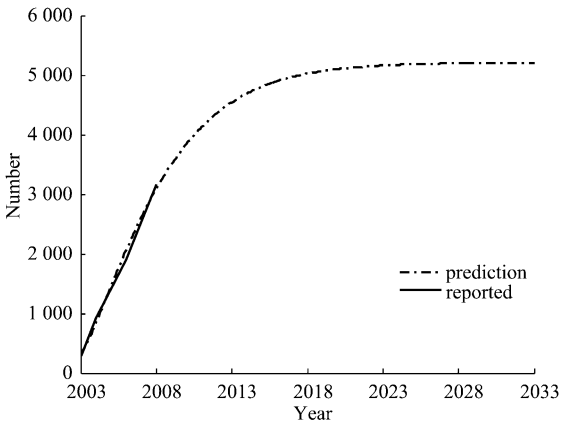


FIG. 2. Predicted and reported numbers of MTCT in China.

Fig. 3A. shows the impact of the input on the MTCT epidemic. When all other parameters are fixed ($S_0=1808$, $(I_1+I_2)_0=286$, $\beta_1=0.13$, $\beta_2=0.35$, $\alpha=0.136$, $\gamma+\omega=0.3$, and $\mu=0.006$) and κ is allowed to vary between 1 614, 3 228, and 4 842, it turns out that the larger the value of κ , the faster the epidemic increases.

Fig. 3B. shows the impact of the value of S_0 on the epidemic. When all other parameters are fixed ($\kappa=1614$, $(I_1+I_2)_0=286$, $\beta_1=0.13$, $\beta_2=0.35$, $\alpha=0.136$, $\gamma+\omega=0.3$, and $\mu=0.006$) and S_0 is allowed to vary between 1 808, 3 616, 7 232, and 1 0848, the epidemic curves differ greatly at the beginning of the epidemic and merge as the epidemic progresses.

Fig. 3C. shows the impact of I_0 on the epidemic. When all other parameters are fixed ($\kappa=1614$, $S_0=1808$, $\beta_1=0.13$, $\beta_2=0.35$, $\alpha=0.136$, $\gamma+\omega=0.3$, and $\mu=0.006$) and $(I_1+I_2)_0$ is allowed to vary between 286, 572, and 858, the epidemic curves overlap throughout the course of the epidemic.

Fig. 3D. shows the impact of transmission rate on the epidemic. When all other parameters are fixed ($\kappa=1614$, $S_0=10848$, $(I_1+I_2)_0=286$, $\beta_1=0.13$, $\alpha=0.136$, $\gamma+\omega=0.3$, and $\mu=0.006$) and the transmission rate β_2

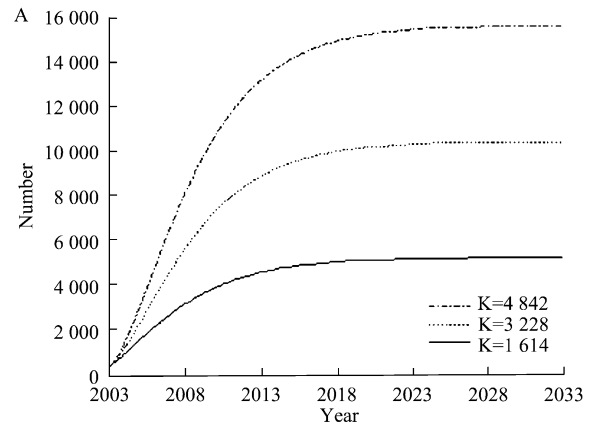
varies between 0.35, 0.25, 0.15, and 0.05, the epidemic curves differ at the beginning of the epidemic, but have little variation as the epidemic progresses. PMTCT can reduce the rapid growth of the initial epidemic, but has relatively little impact on the long-term epidemic trend.

Fig. 3E. shows the impact of α on the epidemic. When all other parameters are fixed ($\kappa=1614$, $S_0=10848$, $(I_1+I_2)_0=286$, $\beta_1=0.13$, $\beta_2=0.35$, $\gamma+\omega=0.3$, and $\mu=0.006$) and α is allowed to vary between 0.136, 0.50, and 0.70, the epidemic curves differ greatly at the beginning of the epidemic and merge as the epidemic progresses.

Fig. 3F. shows the impact of κ , β_2 , and α on the epidemic. All other parameters are fixed ($S_0=10\ 848$, $(I_1+I_2)_0=286$, $\gamma+\omega=0.3$, and $\mu=0.006$), but κ , β_2 , and α are allowed to vary between (1) $\kappa=1\ 614$, $\beta_1=0.13$, $\alpha=0.136$, (2) $\kappa=1\ 614$, $\beta_1=0.01$, $\alpha=0.70$, (3) $\kappa=807$, $\beta_1=0.01$, $\alpha=0.70$, (4) $\kappa=807$, $\beta_1=0.01$, $\alpha=0.50$ and (5) $\kappa=807$, $\beta_1=0.01$, $\alpha=1$. This figure indicates that the prevention of HIV in women can control the HIV MTCT epidemic in China by both lowering the MTCT rate and expanding HIV testing to pregnant women.

DISCUSSION

PMTCT focusing only on biological transmission cannot control the expansion of the MTCT epidemic in China, since the epidemic is also related to other factors, such as the increase in the number of S, demonstrated by Figs. 3A and 3F. The dynamic characteristics of HIV positive pregnant woman can have a great impact on the epidemic in children. With the increase in the number of HIV positive pregnant women, the epidemic in children will grow faster. If measures are not taken to prevent HIV in women^[31] despite strengthening of PMTCT measures, the rapid growth of the epidemic cannot be checked over the long term because of the prevalence of MTCT. Since 2003, at least 20 000 women have been infected by



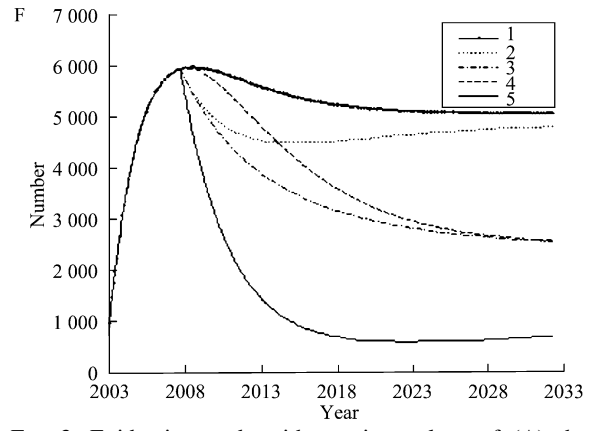
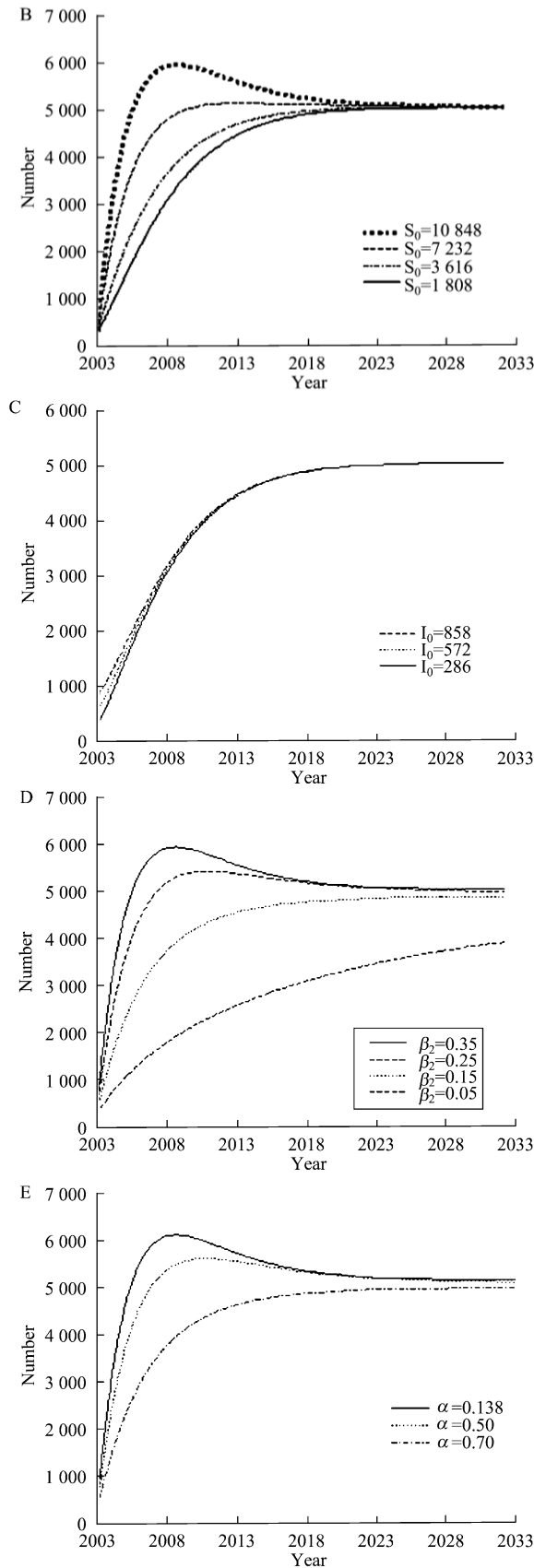


FIG. 3. Epidemic trends with varying values of (A) the number of HIV positive pregnant women per year, κ ; (B) baseline number of babies born to HIV positive mothers, S_0 ; (C) baseline number of HIV positive children (older than 1 year of age), I_0 ; (D) transmission rate, β_2 ; (E) testing proportion, α ; and (F) susceptibles, κ , transmission rate, β_1 , and testing proportion, α : 1) $\kappa=1614$, $\beta_1=0.13$, $\alpha=0.136$; 2) $\kappa=1614$, $\beta_1=0.01$, $\alpha=0.07$; 3) $\kappa=807$, $\beta_1=0.01$, $\alpha=0.70$; 4) $\kappa=807$, $\beta_1=0.01$, $\alpha=0.50$; 5) $\kappa=807$, $\beta_1=0.01$, $\alpha=1$.

HIV every year in China, mainly due to heterosexual transmission^[3].

The baseline number of S has a more significant impact on the epidemic of MTCT than the baseline number of I. This is consistent with the biology of the infection, because HIV positive mothers are the source of infection in our study. An increase in the number of HIV positive pregnant women will inevitably lead to more HIV positive children in the absence of PMTCT. Both S and I, however, have a significant impact on the epidemic of MTCT over a short period of time. The baseline number of S, in particular, may result in a rapid rise in HIV MTCT over the course of five years. The baseline year, however, is selected artificially and, if another year is selected as the baseline with a larger number of S, a larger-scale epidemic is predicted.

The current study's simulation indicates that the transmission rate has an impact on the beginning of the MTCT epidemic in China, but has relatively little impact on the long-term epidemic trend. PMTCT has a significant effect on the transmission rate^[32-33] and continued ART use during breastfeeding for HIV-positive mothers can reduce the transmission rate^[34]. Viral load, CD4 cell count, delivery method, and breastfeeding all affect MTCT probability^[35-38]. Chinese HIV MTCT rates are similar to those of other developing countries in Asia and Africa, but higher than those of developed countries. In developed countries with PMTCT programs, transmission rates can be lower than 0.02^[39].

Developing countries, however, often have difficulties in achieving transmission rates as low as those of developed countries^[40]. In developing countries, alternatives to breastfeeding may be problematic^[41-42], due to cultural norms^[43-44], unavailability of adequate nutritional substitutes, and poor water quality leading to high mortality from diarrheal diseases. A study in Yunnan Province of China, however, demonstrated that PMTCT could achieve a transmission rate of 0.01^[12].

When the screening proportion of HIV positive pregnant women is 13.6%, the MTCT number predicted from the model is similar to the reported number. From 2003 to 2008, there were approximately 16 million births per year, indicating that the number of pregnant women is, therefore, at least 16 million per year^[30]. In sentinel surveillance reports from 2003 to 2008, the HIV prevalence of pregnant women fluctuated between 0.02% and 0.08%^[3,7]. The HIV prevalence among common people in China is about 0.05%^[31]. The number of HIV positive pregnant women per year is, therefore, estimated to be between 3 200 and 12 800. The number of HIV positive pregnant women was considered to be the average of these estimates (8 000 per year). The number of HIV positive pregnant women who received PMTCT in 2008 was 980^[25]. The estimated proportion of HIV positive women who received PMTCT in all HIV positive women in 2008 was, therefore, 12%, which is similar to the result of 13.6% from the model. This indicates that the majority of HIV positive pregnant women and their newborns may have not received PMTCT in China. HIV screening of pregnant women should be therefore strengthened to improve the proportion of HIV positive pregnant women who receive PMTCT.

The overall HIV MTCT epidemic trend is also dependent on the total fertility rate (TFR). Despite China's one-child policy, some families have more than one child, especially those in rural areas and regions with high HIV prevalence^[37]. However, the TRF in HIV positive women may be lower than that in the general population. HIV positive women of reproductive ages could progress to AIDS before they have children and those women who are tested positive may decide to terminate their pregnancy. When the transmission rate is 0.35 and the TRF is higher than 2.86, the R_0 may be higher than 1. The R_0 is currently less than 1 at the national level because the TRF is lower than 2, but the MTCT epidemic in China continues to expand due to the increase in the number of HIV positive women.

This study has two limitations. First, only the reported number of MTCT was available, which may be an underestimate of the actual number of cases of MTCT in China. The data from the reported cases,

however, fit the epidemic well and it was assumed that this model could be used to analyze the dynamic characteristic of MTCT in China. Second, this study was conducted at the national level and its results cannot be generalized to regional levels. The HIV epidemic in China varies substantially with regions and the prevalence is particularly high in Yunnan, Xinjiang, and Guangxi provinces, which are home to a large proportion of ethnic minorities and have weaker economies compared to other Chinese provinces. In the absence of interventions, the transmission rate is 0.35, but PMTCT has been found to be able to reduce the transmission rate to as low as 0.01 in rural China^[12]. Low transmission rates are dependent on screening of pregnant women. In 2008, only 10% of pregnant women were tested for HIV in China and 980 HIV positive women received PMTCT^[25].

CONCLUSION

The dynamic model describes the characteristics of the HIV MTCT epidemic in China through simulation. Measures should be taken to prevent HIV incidence in women of reproductive ages, strengthen PMTCT interventions to reduce transmission rates and increase HIV testing of pregnant women to control the epidemic of MTCT in China. The most cost-effective PMTCT means for China should be investigated in future studies.

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