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Dynamic characteristic analysis of mother to child transmission of HIV in India

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ABSTRACT

In this study, a mathematical model of HIV/AIDS mother to child transmission to analyze the effectiveness of prevention of HIV mother to child transmission programmes has been presented. The result reveals that prevention of HIV mother to child transmission programmes focusing only on biological transmission cannot control the increase of the HIV mother to child transmission in India. Hence, to control the HIV MTCT epidemic in India, in spite of strengthening the PMTCT programmes to reduce transmission rates, effective measures should be taken to prevent HIV infection in women of reproductive ages. Since the overall HIV MTCT epidemic is dependent on the HIV incidence in women of reproductive age group, the integration of pediatric HIV model with a detailed model of adult HIV would be investigated in future studies in order to model these dynamics more accurately.

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INTRODUCTION

There are various modes of transmission of the HIV/AIDS epidemic, but two of the major modes of transmission are mother–to–child transmission (MTCT) and heterosexual transmission (HT).[1] The term mother–to–child transmission and heterosexual transmission of HIV, is described as Vertical and Horizontal transmission respectively.[2,3] As the epidemics move from the group's first affected to women of reproductive age, increasing numbers of infants are becoming infected with HIV through mother-to-child transmission. Infants of HIV-infected mothers are at great risk of becoming infected with HIV during childbirth. During this single event, between 10 and 20 percent will become infected if no steps are taken to prevent transmission. HIV is present in breast milk, although the viral concentrations in it are significantly lower than those found in blood. Between 10 and 20 percent of infants born to HIV-infected mothers become infected through sustained breastfeeding (18 months or longer).[4] Though India is a country with low HIV prevalence, it has the third largest number of people living with HIV/AIDS. As per HIV estimates 2008-09, there are an estimated 23.9 lakh people living with HIV/AIDS in India with an adult prevalence of 0.31 percent in 2009 of which, 39 percent are female and 4.4 percent are children. The heterosexual mode of HIV transmission is the major route of HIV transmission which accounts for 88.2% of HIV positive cases detected, followed by mother to child transmission and it accounts for 5.0% of HIV positive cases detected. By December 2012, among the 570620 total numbers of patients alive and on ART 34367 are found to be pediatric.[5]

In October 1987, first infant was born to seropositive woman in a hospital.[6] The free ART initiative in India was launched on 1st April 2004 and since then prevention of HIV from mother to child transmission

(PMTCT) programs were initiated.[7] PMTCT efforts mainly focus on the use of antiretroviral therapy (ART) for infected mothers during pregnancy and formula feeding for infants after birth. PMTCT programme has been exhibited to be capable to decrease the transmission probability of MTCT.[8] However, the cumulative number of HIV cases has been raising in spite of the PMTCT efforts. Mathematical dynamic modeling based on differential equations has provided to study the transmission dynamics of HIV/AIDS epidemic.[9] To explore the dynamic characteristics of the HIV mother to child transmission (MTCT) epidemic in China, a deterministic dynamic transmission model was and based on their result they have suggested some remedies to eradicate mother to child transmission of HIV/AIDS epidemic.[10] The current study uses a simple dynamic model of mother to child transmission which is mathematically solvable to analyze how the parameters related to key factors alter the trend of this epidemic. The result analysis carried out on basis of mathematical model reveals that prevention of HIV mother to child transmission programmes focusing only on biological transmission cannot control the increase of the HIV mother to child transmission in India, as the MTCT epidemic is related to other factors, like increase in the number of HIV infected women's in the child bearing age.

MATERIALS AND METHODS

Data Sources

Confirmed cases of infection with the HIV/AIDS virus and they are on ART in India were reported to the NACO through ART centers from different part of the country. Data were collected from the NACO annual reports, NACO website, literature searches in scientific journals and Karnataka Institute of Medical Sciences ART center Hubli. Karnataka has a population of around 61 million. Districts with the highest prevalence tend to be located in and around Bangalore in southern part of the state, or in northern Karnataka's "devadasi belt". Devadasi women have historically been dedicated to the service of gods. Despite being made illegal in 1988, the system has evolved into sanctioned prostitution, and as a result many women from this part of the country are moved to the sex trade in big cities such as Mumbai.[11] The Dharwad district is the center of this "devadasi belt" and Karnataka Institute of Medical Science ART center Hubli is the First ART center started in the Karnataka. As of the end of the December, 2012 there were 34,367 HIV positive paediatrics alive and on ART in India, among them 5,759 were from Karnataka and 410 from Dharwad district. The current study assumes that these cases were all MTCT. Although the first case of MTCT in India was discovered in 1987.[6]PMTCT efforts had not been exercised in India until 2004. Since the data from 2004 from the ART centers more accurately reflect the MTCT epidemic in India, that year was chosen for the baseline study.

Table 1Number of Adults Receiving ART, 2004-2012

	2004	2005	2006	2007	2008	2009	2010	2011	2012
India	5033	31009	54171	134445	180713	313130	345856	486173	570620
Karnataka	549	2736	4933	13145	19488	40320	45456	71019	82999
Dharwad District	128	639	1265	2043	2875	3650	4376	4902	5397

Table 2Number of Children Receiving ART, 2004-2012

	2004	2005	2006	2007	2008	2009	2010	2011	2012
India	235	1234	3410	9395	13106	16770	20730	28225	34367
Karnataka	21	81	324	1198	1928	2466	3112	4669	5759
Dharwad District	2	40	83	164	243	300	348	380	410

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Trends of HIV adults alive and receiving ART in India, Karnataka and Dharwad district have shown increasing trend and they have shown to be parallel with each other from 2004 to 2007, then from 2007 to 2012. The rate of increase of Dharwad district in the trend is minimum as compared to that of India and Karnataka (Fig. 1). This may be because of ART centers were started in other parts of the district by this time. The similar trend we can see in paediatrics also from 2007 to 2012 (Fig. 2). Also we can see that, from 2004 to 2007 the growth rate of paediatrics alive and receiving ART in Dharwad district is higher than that of India and Karnatka and then from 2007 to 2012 it is less than the India and Karnataka.

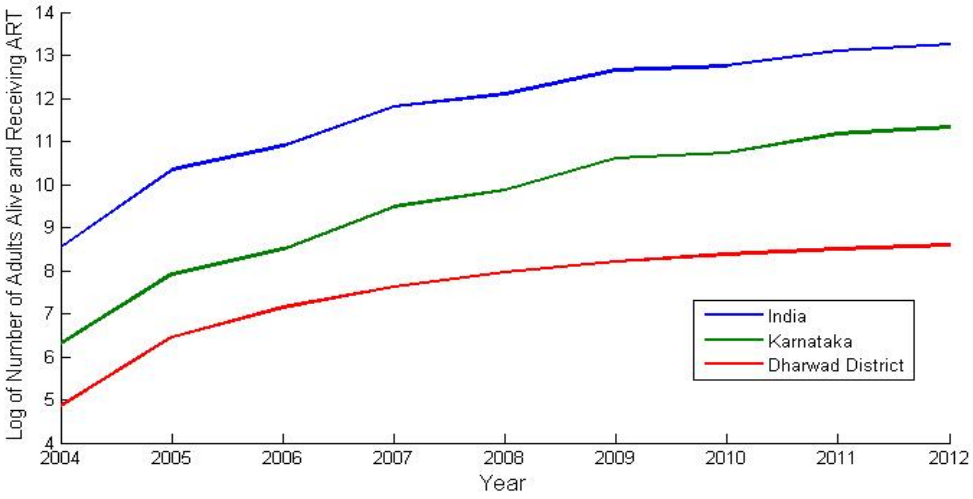

Figure 1 Log Plot of Number of Adults Alive and Receiving ART

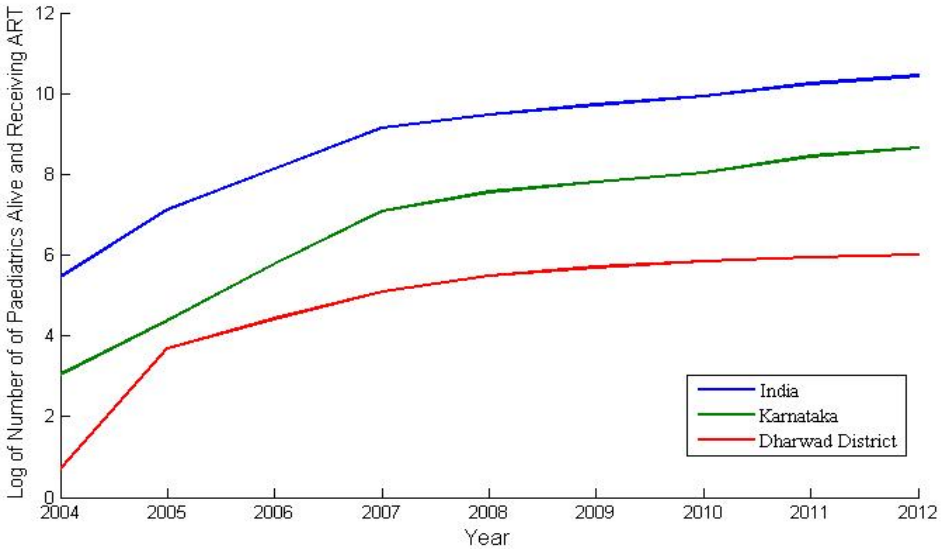

Figure 2Log Plot of Number of Pediatrics Alive and Receiving ART

Methods

A deterministic dynamic transmission model of HIV incidence in children was used explore the effect of key parameters on the likely long-term trends of the HIV MTCT epidemic in India. The children born to HIV infected mothers, based on their HIV infection progression were divided into three categories. $I(t)$, the number of HIV infected pediatrics at time t, who

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were born to HIV infected mothers and contracted the disease. $P(t)$, the number of pediatrics at time t, who have not contracted the disease from their HIV infected mothers. $A(t)$, the number of AIDS converted HIV infected pediatrics at time t and $M(t)$ be the number of female HIV infected individuals at time t. Number of HIV infected females are increasing at the rate $\propto$ and μ is the rate at which they die with disease or natural cause. The HIV infected pediatrics developed to the state of AIDS at the rate δ, where $\frac{1}{\delta}$ is the incubation period of HIV infected pediatrics. ρ is the birth rate (Total Fertility Rate) of pediatrics. The new born babies (pediatrics) contract the disease from their HIV infected mother with probability θ. Then the transmission dynamics of HIV incidence in children can be modelled using the following system of differential equations

$$\frac{dM(t)}{dt} = \propto M(t) - \mu M(t)$$

$$\frac{dI(t)}{dt} = \rho\theta M(t) - \delta I(t)$$

$$\frac{dP(t)}{dt} = \rho(1-\theta)M(t)$$

$$\frac{dA(t)}{dt} = \delta I(t)$$

with initial conditions $M(0) = m,\ I(0) = 0,\ P(0) = 0,\ and\ A(0)$. The solution of above system of differential equations can be obtained explicitly. By solving the first equation for $M(t)$ we obtain

$$M(t) = me^{(\alpha-\mu)t}.$$

By dividing second equation by first equation, then solving linear differential equation of first order and using the above result we obtain

$$I(t) = \frac{m\rho\theta}{\delta+\alpha-\mu}\left\{e^{(\alpha-\mu)t} - e^{-\delta t}\right\}.$$

Substituting the results of $M(t)$and $I(t)$ in equations three and four of the model respectively and then solving differential equations we obtain

$$P(t) = \frac{m\rho(\alpha-\mu)}{\alpha-\mu}\left\{e^{(\alpha-\mu)t} - 1\right\}$$

and

$$A(t) = \frac{m\delta\rho\theta}{\delta+\alpha-\mu}\left\{\frac{e^{(\alpha-\mu)t}}{\alpha-\mu} + \frac{e^{-\delta t}}{\delta}\right\}.$$

Fitting models to data

In the present paper we will attempt to obtain some of the parameters of the disease model (α, β, γ and θ) by fitting model predictions with different parameters to the disease data. Two main methods for fitting models to data are least squares statistic and Pearson chi-squared statistic. Both statistics measure the distance between data points and model predictions at the same time points. The least squares statistic is one of the most commonly used goodness of fit statistics. It is defined as the sum of the squared point-by-point distances between the model prediction and the data:

$$S = \sum_{i=1}^{N}(M_i - D_i)^2,$$

where *N* is the number of time points, M_i is the model prediction for disease incidence at time point *i* and D_i is the data for that time point. The best fitting model across many runs with different parameter sets is one that minimizes the least squares statistic. However, one potential issue is that in the least squares method we assume that each data point has the same amount of stochastic variation, which can be an issue for example due to the fact periods of low disease incidence carry relatively large stochasticity. The Pearson chi-squared statistic deals with this issue by weighting the distances and thus taking the stochasticity into account. The Pearson chi-squared statistic is defined as

$$S = \sum_{i=1}^{N}\frac{(M_i - D_i)^2}{M_i}$$

We use it to select a best fitting model in the same fashion as the least squares.

Parameter setting

In this study we made use of parameter choices reported in the literatures for HIV mother to child transmission. As per NACO HIV estimates 2008-09, 39 percent are female, hence 39 percent of the reported HIV adults alive and on ART in 2004 are taken as baseline number of HIV infected mothers*M(o)*, baseline number of HIV positive pediatrics are chosen from the 2004 NACO, Karnataka Institute of Medical Science ART center Hubli reported cases and remaining states of the model are assumed to zero at the baseline time point.The HIV infected pediatrics developed to the state of AIDS at the rate δ, where $\frac{1}{\delta}$ is the incubation

period of HIV infected pediatrics is taken as 0.1739 as an average incubation period of HIV infected pediatrics in the literature reported is 5 years 9 months.Total Fertility Rate is considered to fix the parameter ρ the birth rate of pediatrics and μ= 0.1087 the rate at which HIV infected mothers die with disease or natural cause. The dynamic characteristics of HIV infected women in the child bearing age can have a great impact on the epidemic in children as the biology of epidemic, the HIV infected mothers are the main source of HIV infection in children. Hence the parameter α is estimated by using the Pearsons Chi-square test for goodness of fit for model generated data with reported cases. The analysis of effectiveness of prevention of mother to child transmission programme is done by varying the parameter θ, the probability that new born babies (pediatrics) contract the disease from their HIV infected mother. In this study we estimate the parameter α by fixing all other parameters, because the HIV epidemic in pediatrics is mainly depends on HIV infected women.

RESULTS

Fig. 3a shows the predicted number and the reported number of HIV pediatrics cases in India when the prevention of HIV mother to child transmission programme is in force with θ=0.7 and Fig. 3b depict the same state of affairs when the prevention of HIV mother to child transmission programme is not in force (ie., when θ=1). The estimated rate of number of HIV infected females is $\propto = 0.5799$ (with goodness of fit statistics Pearson's chi-square = 1.3604×10^4 and 2.5299×10^4 respectively when θ=0.7 and θ=1). The analysis of these figures illustrates that the number HIV paediatrics might have increased to 59090 as against 41363 when θ=0.7 and it shows HIV mother to child transmission programme effective in controlling the HIV/AIDS in paediatrics, this is not only due to the PMTCT programme but also due to the increasing trend of the epidemic in the adult (See, Fig. 1).

The similar trend we can see from the model analysis (See, Fig. 4a,b and Fig. 5a,b for Karnataka and Dharwad district HIV pediatrics epidemic, but the estimated rate of number of HIV infected females for karnataka and Dharwad districts are $\propto = 0.6385$ and $\propto = 0.4877$ respectively (with goodness of fit statistics Pearson's chi-square $=2.1133\times10^3$ and 4.3669×10^3 respectively when θ=0.7 and θ=1 for Karnataka and 314.62 and 519.62 respectively when θ=0.7 and θ=1 for Dharwad district.

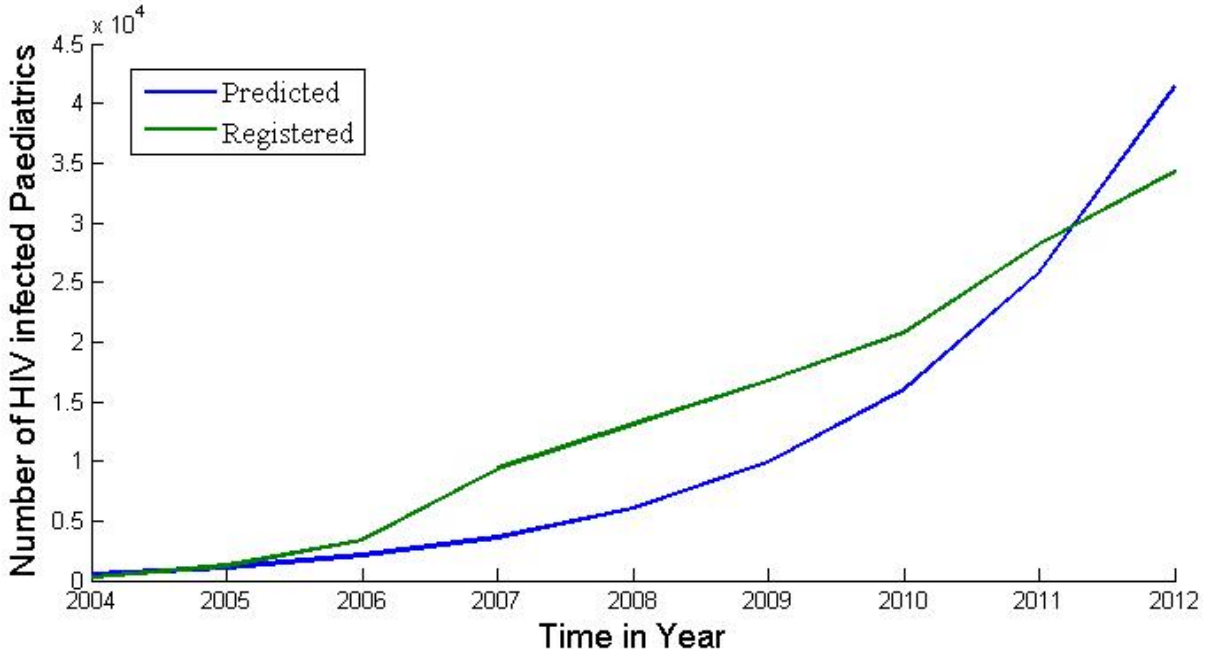

Figure 3aModel Predicted HIV MTCT Trend for the Parameter Choice α= 0.5799, μ= 0.1087, ρ= 0.2804, δ= 0.1739 and θ=0.7 versus Registered HIV Infected Pediatrics Who are Alive and on ART for India

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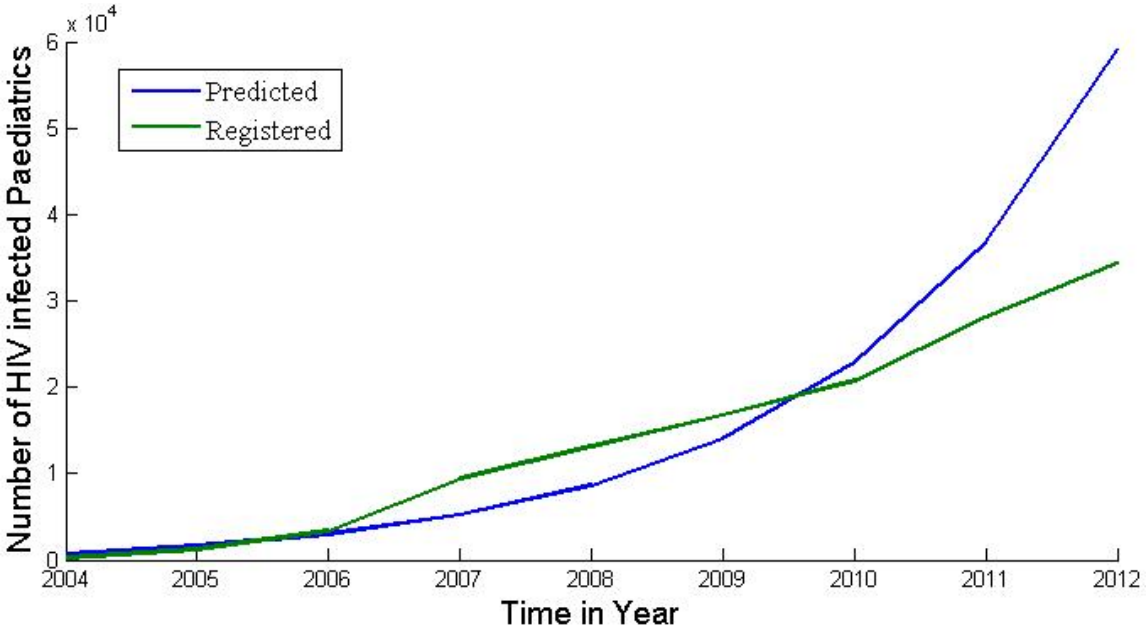

Figure 3b Model Predicted HIV MTCT Trend for the Parameter Choice α= 0.5799, μ= 0.1087, ρ= 0.2804, δ= 0.1739 and θ=1 (Prevention of HIV MTCT Programme is not in Force) versus Registered HIV Infected Pediatrics Who are Alive and on ART for India

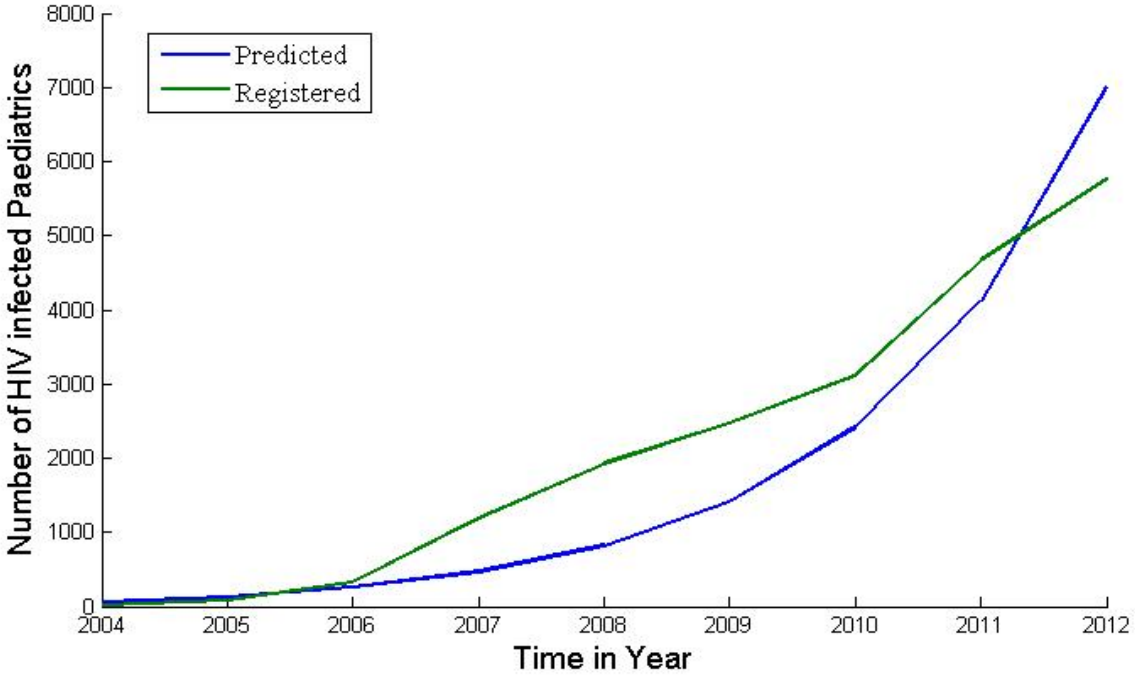

Figure 4a Model Predicted HIV MTCT Trend for the Parameter Choice α= 0.6385, μ= 0.1087, ρ= 0.2804, δ= 0.1739 and θ=0.7 versus Registered HIV Infected Pediatrics Who are Alive and on ART for Karnataka.

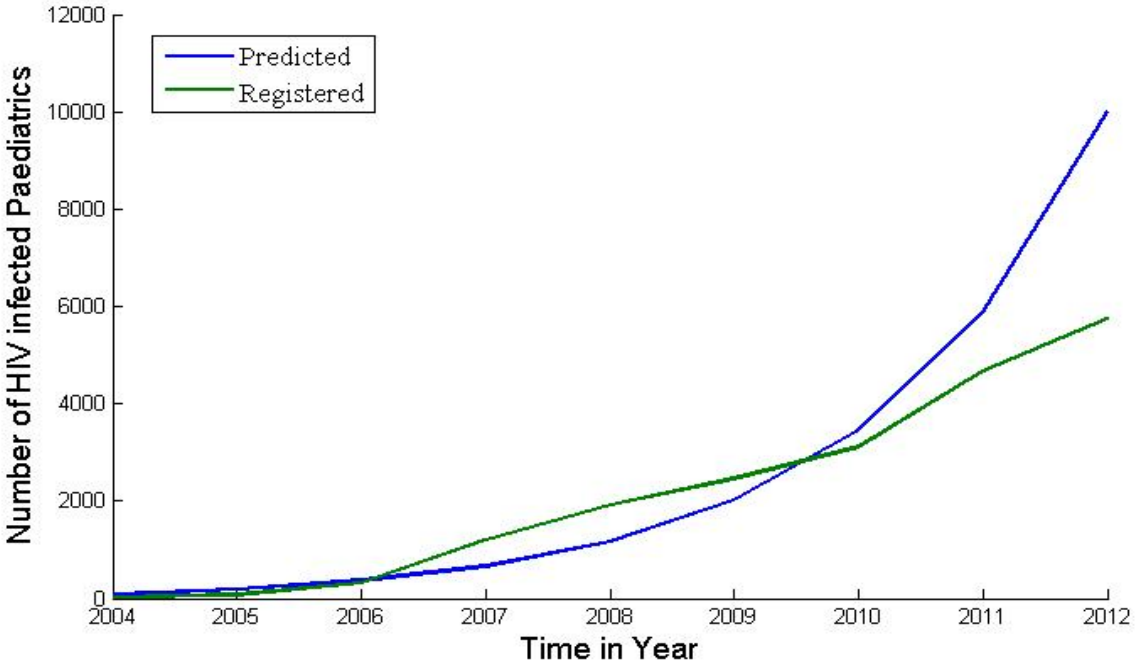

Figure 4b Model Predicted HIV MTCT Trend for the Parameter Choice α= 0.6385, μ= 0.1087, ρ= 0.2804, δ= 0.1739 and θ=1 (Prevention of HIV MTCT Programme is not in Force) versus Registered HIV Infected Pediatrics Who are Alive and on ART for Karnataka.

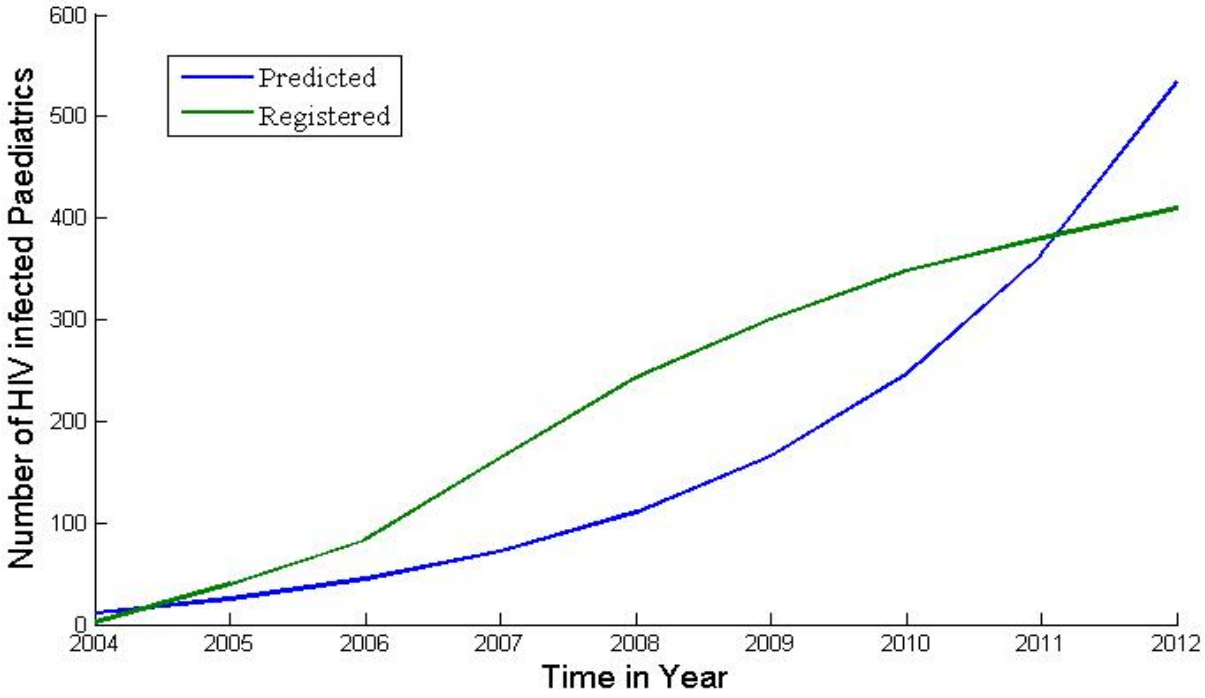

Figure 5a Model Predicted HIV MTCT Trend for the Parameter Choice α= 0.4877, μ= 0.1087, ρ= 0.2804, δ=0.1739 and θ =0.7 versus Registered HIV Infected Pediatrics Who are Alive and on ART for Dharwad District.

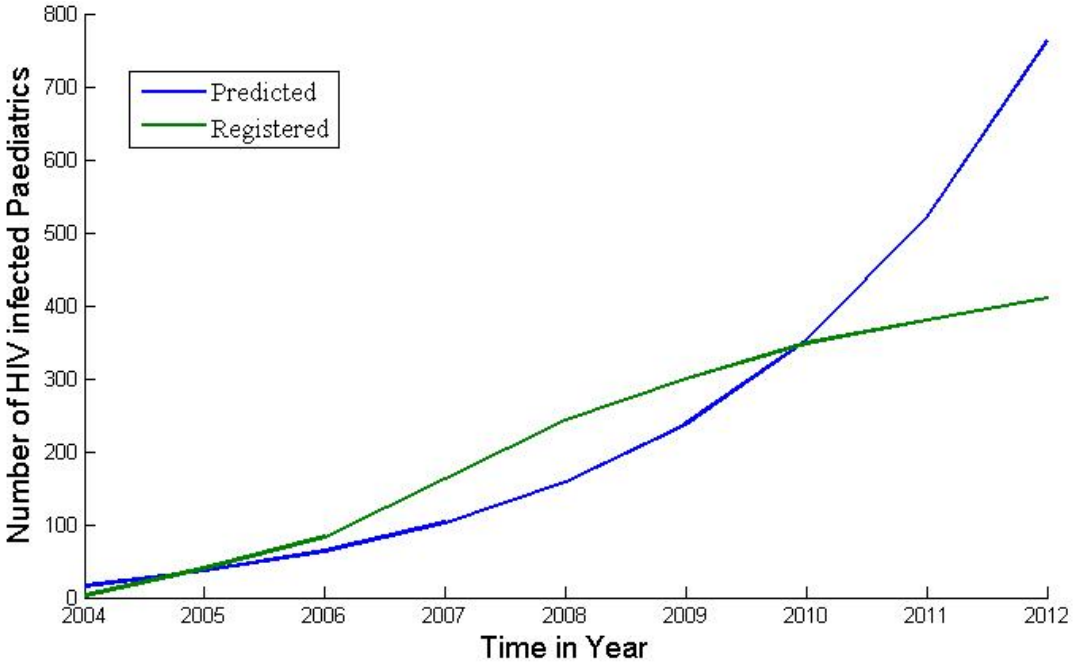

Figure 5bModel Predicted HIV MTCT Trend for the Parameter Choice α= 0.4877, μ= 0.1087, ρ= 0.2804, δ= 0.1739 and θ =1 (Prevention of HIV MTCT Programme is not in Force) versus Registered HIV Infected Pediatrics Who are Alive and on ART for Dharwad District.

DISCUSSION

In this study we presented a mathematical model of HIV/AIDS mother to child transmission to analyze the effectiveness of prevention of HIV mother to child transmission programmes. The result analysis carried out in Section 3 above reveals that prevention of HIV mother to child transmission programmes focusing only on biological transmission cannot control the increase of the HIV mother to child transmission in India, as the MTCT epidemic is related to other factors, like increase in the number of HIV infected women in the child bearing age, exhibited by Fig. 6 (The predicted HIV infected pediatrics by the 2012 are 42143, 46357 and 63215 respectively for having 2000, 2200 and 3000 HIV infected mother at the initial time 2004). Thus the dynamic characteristic of HIV infected women in the child bearing age can have enormous impact on the HIV epidemic in children. Trends analysis in Section 1 (Fig. 1 and 2) of HIV adults alive and receiving ART and HIV pediatrics alive and receiving ART shows that after 2006 increasing rate HIV adults is moderate, accordingly after 2007 increasing rate HIV pediatrics is also moderate. Thus despite strengthening of HIV PMTCT measures, if control measures were not taken to prevent HIV in women, the rapid growth of HIV epidemic in pediatrics cannot be verified over the long term because of the prevalence of MTCT.

The overall HIV MTCT epidemic trend is also dependent on the total fertility rate (TFR).[10] However, the TFR in HIV infected women may be lower than that of in the general population. When the probability of HIV MTCT transmission is θ=0.7 and TFR is 2.9[12] in 2004, the R_o the basic reproduction number may be higher than 1. The current value of Ro is at most 1.75 at the national level because the TFR is lower than 2.4. Also we know from the other studies that, the reported percentage of estimated HIV infected pregnant women in India who received anti-retrovirals for PMTCT was only 10 per cent.[13,14] Thus unless we make prevention of MTCT programme more effective (probability of HIV MTCT transmission, θ should be at least 0.41), R_o cannot be reduced to less than 1. Even then the HIV MTCT epidemic in India persists to increase due to the increase in the number of HIV infected women. The

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HIV MTCT analysis presented here has certain limitations. According to the World Bank report on HIV/AIDS in 2004[15] an estimated 54,000 HIV–infected children are born in India each year and as per WHO estimates there are between 22,000 and 61,000 HIV pregnant women living HIV in India[16], but as per NACO ART registered data number of children alive and receiving ART in 2012 is 34,367. Since the time of data collection for this study, the ART programme in India has expanded considerably (from 10 ART centers in December 2004 to 355 ART centers in March 2012), even then the access to treatment still remains a challenge as ART centers are not present in low prevalence areas. Therefore our model based analysis of the HIV MTCT limited to registered HIV infected persons who are alive and on ART treatment.

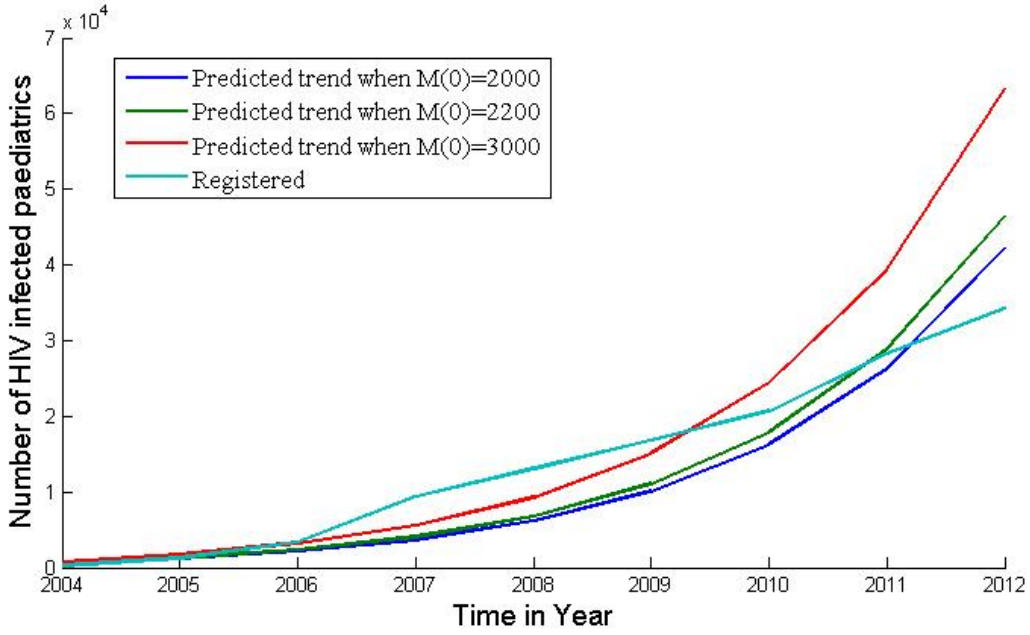

Figure 6 HIV MTCT Epidemic Trend with Varying Baseline Number of HIV Infected Women M(0) = 2000, 2200 and 3000 and Registered HIV Infected Pediatrics Who are Alive and on ART for India.

CONCLUSION

The study provides the important information about the characteristics of HIV MTCT in India through dynamic mathematical model simulation. To control the HIV MTCT epidemic in India, in spite of strengthening the PMTCT programmes to reduce transmission rates, effective measures should be taken to prevent HIV infection in women of reproductive ages. Since the overall HIV MTCT epidemic is dependent on the HIV incidence in women of reproductive age group, the integration of paediatric HIV model with a detailed model of adult HIV would be required in order to model these dynamics more accurately.

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