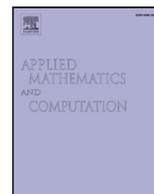




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Demography of sexually transmitted infections with vertical transmission



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ABSTRACT

Sexually transmitted infections (STIs) are an ongoing public health concern. Despite many efforts, STIs have not been eradicated. Most STIs are infected through “horizontal” sexual contact and “vertical” mother-to-child transmission. We therefore need to explore the mathematical relationship between horizontal and vertical transmissions, which is necessary for the strategic eradication of STIs. Here, we constructed a simple model to demonstrate the infection dynamics of STIs with vertical transmission. We proposed a new formulation of the basic reproduction number (R_0) for STIs over generations, and showed that vertical transmission exerts a smaller effect on the R_0 than horizontal transmission. We also performed agent-based simulations to validate our theoretical predictions.

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1. Introduction

Many sexually transmitted infections (STIs) have had a long history with human beings [1–6]. For instance, the symptoms of *Neisseria gonorrhoeae* infection were described in the Old Testament of the Bible (Leviticus 15: 1–3). This disease remains a global health concern, and approximately 106 million new cases are reported annually worldwide [6]. Chesson et al. [7] reported that in the United States, the lifetime cost of STIs acquired by individuals aged 15–24 years in 2000 was \$6.5 billion. Furthermore, nearly all STIs can affect newborns through vertical transmission from the mother [1–4]. Considering these concerns, STIs represent a substantial threat to public health and the well-being of human populations; therefore, preventing STIs is an urgent priority.

However, STIs are difficult to prevent due to the complex human sexual network, i.e., who contacts whom. Many studies have suggested that these networks are highly heterogeneous [8–14], indicating that the networks contain not only many people with very few sexual partners but also a few people with a multitude of sexual partners. Interviews and questionnaires administered by Liljeros et al. [9] in Sweden showed that the distribution of the number of sexual partners has an approximate power-law decay (scale-free). The scale-free trait is a common structure of various social networks, such as telephone calls, e-mail correspondence, paper citations, and internet service [12,15]. It is well known that scale-free networks

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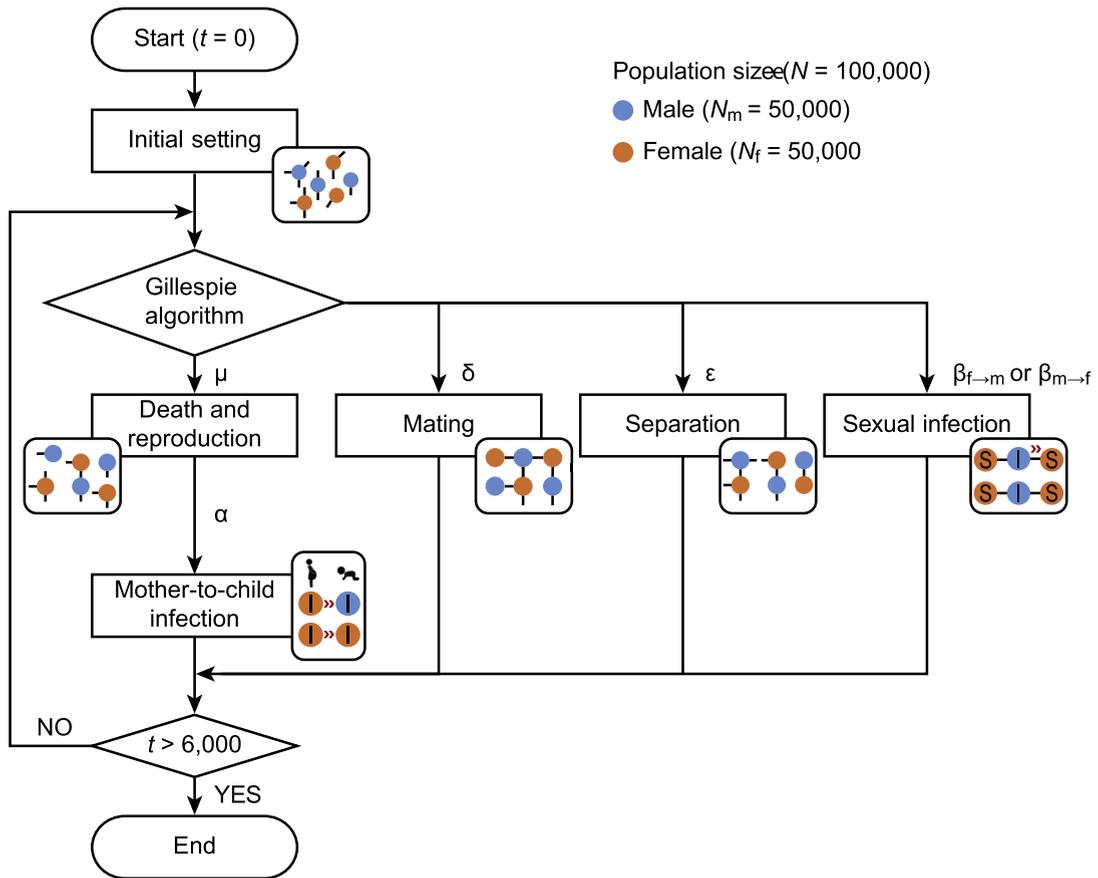


Fig 1. Illustration of the simulation scenario. Individuals are categorized as males (blue node) and females (orange node) and as susceptible (S) and infected (I). Using the initial setting, 50,000 males and 50,000 females are included. The following four types of events occur according to Poisson processes: (1) A person dies at rate μ , and then a new baby is born; the baby inherits the infection from the infected mother at probability α ; (2) a male and a female begin a sexual relationship at rate δ ; (3) a sexual relationship ends at rate ϵ ; and (4) sexual transmission between an infected female and a susceptible male who share a sexual relationship occurs at rate $\beta_{m \rightarrow f}$. Sexual transmission in the opposite direction occurs at rate $\beta_{f \rightarrow m}$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

have zero epidemic threshold; this means that STIs can spread on such networks regardless of how low the transmission rate is [12,16]. Note that, on the other hand, some studies suggest that the sexual network is not scale-free in the strict sense [17].

Although various mathematical models of STIs have been proposed [8,13,16,18–26], studies analyzing the long-term dynamics of endemic infection across generations are lacking. To characterize long-term endemic infectious behavior of STIs, we construct a simple model that includes vertical transmission. This model can be analyzed using approximation theory. We propose a new formulation of the basic reproduction number (R_0), which is defined as the average number of sexually infected females that a typical sexually infected female generates in a population that is totally susceptible. As with the usual basic reproduction number, the epidemic threshold of infectious diseases is represented by $R_0 = 1$, where $R_0 > 1$ indicates that the infection will spread in the population, and $R_0 < 1$ indicates that the infection cannot survive [27]. Therefore, the R_0 has a significant meaning and can indicate which control measures could be effective from a long-term public health perspective. We show that horizontal transmission influences the R_0 of STIs more strongly than vertical transmission if the sexual network is heterogeneous.

2. Model

2.1. Life history of population

We introduce a simple STI model that considers sexual networks and vertical transmission. Fig. 1 illustrates the proposed model. For simplicity, we assume that the sex ratio of males to females is one. We consider a population that includes $\frac{N}{2}$ females and $\frac{N}{2}$ males. We assign the identification numbers i_f and i_m ($i_f, i_m = 1, 2, 3, \dots, \frac{N}{2}$) to females and males, respectively. We assume that an individual has a potential degree k_{max} , which is defined as the maximum number of sexual partners that

an individual can have. To create heterogeneous sexual network, the potential degree is assumed to follow a power law distribution $p_{\max}(k_{\max}) \sim k_{\max}^{-\gamma}$ ($1 < k_{\max} < 200$). All individuals die at death rate μ . To ensure that the population size is constant, we assume that for every individual who dies, another individual reproduces. Therefore, the birth rate λ is identical to the death rate μ . These two individuals share the same identification number. In other words, the newborn individual takes over sex and potential degree of the dead one.

2.2. Mating and separating process

If the potential degree of an individual is larger than the number of its sexual partners, the individual seeks sexual partners as follows. A node in the sexual network has stubs whose number equals the potential degree minus the number of its links. At rate δ , a stub of a male node attempts to connect with a randomly chosen stub of a female node. If the male and female are not already sexual partners, they become sexual partners. If the male and female are already sexual partners, nothing occurs. In addition, a partnership ends at rate ε . When either member of a couple dies, the partnership ends. We do not consider homosexuality.

2.3. Infection process

We adopt a susceptibility-infection (SI) model on the abovementioned sexual network. Human immunodeficiency virus (HIV), human T-cell leukemia virus type 1 (HTLV-1), and other STIs are not spontaneously cured, and cannot acquire life-time immunity, even if the patients are treated with antibiotics for non-viral infections. Thus, we neglect the recovery in our model. For simplicity, the death rate μ is the same for both susceptible and infected individuals. When a susceptible individual has sexual contact with an infected individual, the disease can be transmitted. The rates of sexual transmission are $\beta_{m \rightarrow f}$ and $\beta_{f \rightarrow m}$ for male-to-female and female-to-male transmission, respectively. Moreover, we take mother-to-child transmission into account. A newborn individual is infected at a probability of vertical transmission rate α times the female infection rate. The numerical simulations are performed using the Gillespie algorithm [28].

3. Theory and results

To analyze the model, we perform a degree-based mean-field approximation. Here, the degree distributions for females and males are set as $p_f(k)$ and $p_m(k)$, respectively, where k is the time average number of sexual partners. These distributions $p_f(k)$ and $p_m(k)$ are calculated by the numerical simulation of the model, and have a similar form to the potential degree distributions. The average degrees of females and males are as follows:

$$k_f = \sum_{k=0} k p_f(k), \quad k_m = \sum_{k=0} k p_m(k).$$

Since the number of females is equal to the number of males, these average degrees coincide $\langle k \rangle_f = \langle k \rangle_m$ even if $p_f(k)$ and $p_m(k)$ differ. The fraction of infected individuals who have k sexual partners is denoted by $I_f(k)$ for females and $I_m(k)$ for males. Thus, the fractions of infected females and males are represented as follows:

$$I_f = \sum_{k=0} I_f(k) p_f(k), \tag{1}$$

$$I_m = \sum_{k=0} I_m(k) p_m(k). \tag{2}$$

By applying the approximation method used in Newman's textbook [12], the evolution equations of $I_f(k)$ and $I_m(k)$ are obtained as follows:

$$\frac{dI_f(k)}{dt} = \frac{\lambda}{2} \alpha I_f - \mu I_f(k) + \beta_{m \rightarrow f} k (1 - I_f(k)) \sum_{k'=0} q_m(k') I_m(k'), \tag{3}$$

$$\frac{dI_m(k)}{dt} = \frac{\lambda}{2} \alpha I_f - \mu I_m(k) + \beta_{f \rightarrow m} k (1 - I_m(k)) \sum_{k'=0} q_f(k') I_f(k'). \tag{4}$$

where $q_f(k)$ is the probability that a female partner of a male has k male partners other than the male, and $q_m(k)$ is the probability that a male partner of a female has k female partners other than the female. Note that, we express k' as the k in summation Sigma. This is often called excess degree distribution [12] and is represented as follows:

$$q_f(k) = \frac{(k+1)p_f(k+1)}{\langle k \rangle_f}, \quad q_m(k) = \frac{(k+1)p_m(k+1)}{\langle k \rangle_m}.$$

The first terms on the left-hand sides of Eqs. (3) and (4) correspond to the birth process, and represent an increase in the infected fraction due to maternal transmission; the second terms correspond to deaths; and the third terms represent an increase in the infected fraction due to sexual transmission.

The probability that a female partner of a male is infected is as follows:

$$v_f = \sum_{k=0} I_f(k) q_f(k), \quad (5)$$

and the probability that a male partner of a female is infected is as follows:

$$v_m = \sum_{k=0} I_m(k) q_m(k). \quad (6)$$

Using Eqs. (5) and (6), we can rewrite Eqs. (3) and (4) as follows:

$$\frac{dI_f(k)}{dt} = \mu \alpha I_f - \mu I_f(k) + \beta_{m \rightarrow f} k [1 - I_f(k)] v_m, \quad (7)$$

$$\frac{dI_m(k)}{dt} = \mu \alpha I_f - \mu I_m(k) + \beta_{f \rightarrow m} k [1 - I_m(k)] v_f. \quad (8)$$

By calculating Eqs. (7) and (8) for equilibrium conditions $\frac{dI_f(k)}{dt} = 0$ and $\frac{dI_m(k)}{dt} = 0$, the equilibrium state satisfies the following formulas:

$$I_f(k) = \frac{\mu \alpha I_f + v_m \beta_{m \rightarrow f} k}{\mu + v_m \beta_{m \rightarrow f} k}, \quad (9)$$

$$I_m(k) = \frac{\mu \alpha I_f + v_f \beta_{f \rightarrow m} k}{\mu + v_f \beta_{f \rightarrow m} k}. \quad (10)$$

By substituting Eqs. (9) and (10) into Eqs. (1), (5) and (6), we obtain self-consistent equations for the equilibrium:

$$I_f = \sum_{k=0} p_f(k) \frac{\mu \alpha I_f + v_m \beta_{m \rightarrow f} k}{\mu + v_m \beta_{m \rightarrow f} k}, \quad (11)$$

$$v_f = \sum_{k=0} \frac{(k+1) p_f(k+1)}{\langle k \rangle_f} \frac{\mu \alpha I_f + v_m \beta_{m \rightarrow f} k}{\mu + v_m \beta_{m \rightarrow f} k}, \quad (12)$$

$$v_m = \sum_{k=0} \frac{(k+1) p_m(k+1)}{\langle k \rangle_m} \frac{\mu \alpha I_f + v_f \beta_{f \rightarrow m} k}{\mu + v_f \beta_{f \rightarrow m} k}. \quad (13)$$

By calculating the nonzero root of the self-consistent Eqs. (11), (12) and (13), numerically substituting the root into Eqs. (9) and (10) and substituting these results into Eqs. (1) and (2), we obtain the equilibrium infected fraction. We easily show that in the equilibrium state, the ratio of maternally infected individuals to the total population is αI_f . Thus, the ratio of the number of maternally infected females to the total number of infected females is calculated as α , and the ratio of the number of maternally infected males to the total number of infected males is calculated as $\alpha I_f / I_m$.

In Fig. 2a–f, we show the results of a case in which the male-to-female transmission rate is greater than the female-to-male transmission rate $\beta_{m \rightarrow f} = 4\beta_{f \rightarrow m}$ (as is the case for HTLV-1). These graphs show good agreement between numerical simulations (marks) and theoretical results (curves). Here, we studied both cases without and with pair breakup ($\varepsilon = 0$ and 0.02 (1/y)). When $\beta_{f \rightarrow m} < \beta_{m \rightarrow f}$, the fraction of infected females is greater than the fraction of infected males (Fig. 2a–d). The ratio of maternally infected females to all infected females is smaller than the ratio of maternally infected males to all infected males (Fig. 2e and f). For the opposite case, i.e., $\beta_{m \rightarrow f} = \beta_{f \rightarrow m} / 4$, the effect of maternal transmission is smaller (not shown in the figure). For STIs, $\beta_{m \rightarrow f} > \beta_{f \rightarrow m}$ is more advantageous than $\beta_{m \rightarrow f} < \beta_{f \rightarrow m}$.

To derive the epidemic threshold (where the limit $I_f, v_f, v_m \rightarrow 0$ is realized), considering the first terms of $I_f, v_f, v_m \ll 1$, we can rewrite Eqs. (11)–(13) as follows [14]:

$$I_f = I_f \alpha + v_m \langle k \rangle_f \frac{\beta_{m \rightarrow f}}{\mu},$$

$$v_f = I_f \alpha + v_m \frac{\beta_{m \rightarrow f}}{\mu} \frac{\langle k \rangle_f^2 - \langle k \rangle_f}{\langle k \rangle_f},$$

$$v_m = I_f \alpha + v_f \frac{\beta_{f \rightarrow m}}{\mu} \frac{\langle k \rangle_m^2 - \langle k \rangle_m}{\langle k \rangle_m},$$

where

$$\langle k \rangle_f^2 = \sum_{k=0} k^2 p_f(k), \quad \langle k \rangle_m^2 = \sum_{k=0} k^2 p_m(k).$$

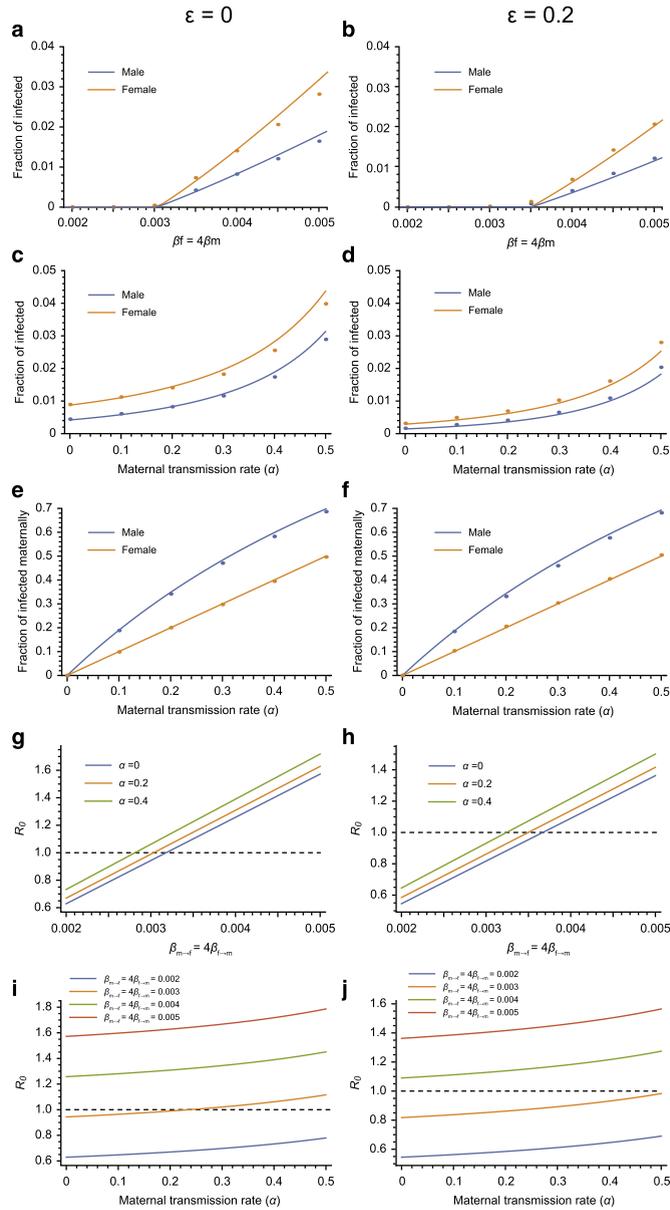


Fig 2. Numerical calculations and approximation predictions. The left panels ((a), (c), (e), (g), and (i)) represent mating only ($\varepsilon = 0$), and the right panels ((b), (d), (f), (h), and (j)) represent mating and break-ups $\varepsilon = 0.02$ (1/y), when $\gamma = 2.3$, $\mu = 0.02$ (1/y), and $\delta = 0.1$ (1/y). ((a), (b)) The fractions of infected females (orange) and males (blue) are plotted as a function of $\beta_{m \rightarrow f} = 4\beta_{f \rightarrow m}$ for $\alpha = 0.2$. ((c), (d)) The fractions of infected females (orange) and males (blue) are plotted as a function of maternal transmission rate α for $\beta_{m \rightarrow f} = 0.004$ (1/y) and $\beta_{f \rightarrow m} = 0.001$ (1/y). ((e), (f)) The ratios of maternally infected individuals to infected individuals are plotted as a function of α for $\beta_{m \rightarrow f} = 0.004$ (1/y) and $\beta_{f \rightarrow m} = 0.001$ (1/y). We performed simulations for 6000 simulated years as follows: First, we constructed a network without disease for the first 2000 years. Then, 5% of the population became infected, and the fractions of infected individuals were represented by the average during the final 2000 years. The standard error is smaller than the size of the symbols. The theoretical curves are derived by substituting the average values calculated numerically ($\langle k \rangle_f = \langle k \rangle_m = 1.61$, $\langle k^2 \rangle_f = \langle k^2 \rangle_m = 21.9$ for (g) and $\langle k \rangle_f = \langle k \rangle_m = 1.41$, $\langle k^2 \rangle_f = \langle k^2 \rangle_m = 16.8$ for (h)) into Eq. (14). The R_0 (the square root of Eq. (14)) is plotted as a function of $\beta_{m \rightarrow f} = 4\beta_{f \rightarrow m}$. Here, the maternal transmission rate is $\alpha = 0, 0.2$, and 0.4 from the bottom to the top. ((i), (j)) The R_0 is plotted as a function of α , where the sexual transmission rates are $\beta_{m \rightarrow f} = 4\beta_{f \rightarrow m} = 0.002, 0.003, 0.004$, and 0.005 (1/y) from the bottom to the top. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

By combining the three above-mentioned equations and delete I_f , v_f and v_m , we obtain the condition of the epidemic threshold as follows:

$$\frac{\beta_{m \rightarrow f}}{\mu} \frac{\beta_{f \rightarrow m}}{\mu} \frac{\langle k \rangle_m^2 - \langle k \rangle_m}{\langle k \rangle_m} \frac{\langle k \rangle_f^2 - \langle k \rangle_f}{\langle k \rangle_f} + \frac{\beta_{m \rightarrow f}}{\mu} \frac{\beta_{f \rightarrow m}}{\mu} \frac{\alpha \langle k \rangle_f}{(1 - \alpha)} \frac{\langle k \rangle_m^2 - \langle k \rangle_m}{\langle k \rangle_m} + \frac{\beta_{m \rightarrow f}}{\mu} \frac{\alpha \langle k \rangle_f}{(1 - \alpha)} = 1. \tag{14}$$

By tedious calculations, we can verify that the disease free solution ($I_f, v_f, v_m = 0$) is unstable if the left hand side is larger than one. As shown in the following (see also Figs. 3 and 4), the left-hand side of Eq. (14) represents the average number

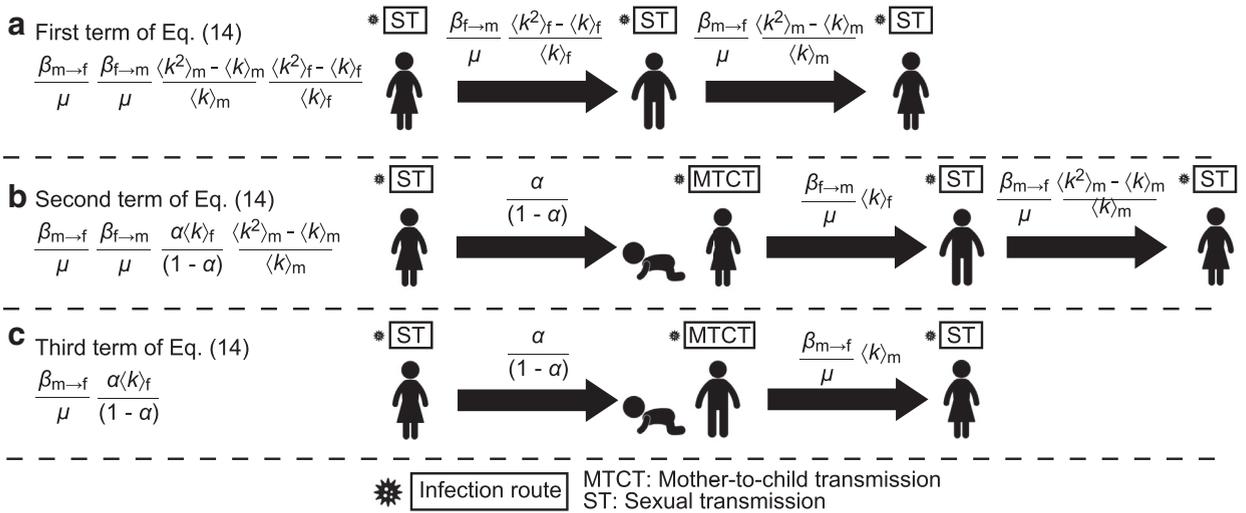


Fig 3. Explanation of Eq. (14). Eq. (14) yields the number of females with sexually transmitted infections (STIs). (a) The first term calculates the number of females with STIs who were infected through sexual transmission from males. (b) The second term calculates the number of females with STIs who were infected by sexually infected males and vertically infected females who were born to infected females. (c) The third term calculates the number of females who were infected by males infected vertically by their sexually infected mother.

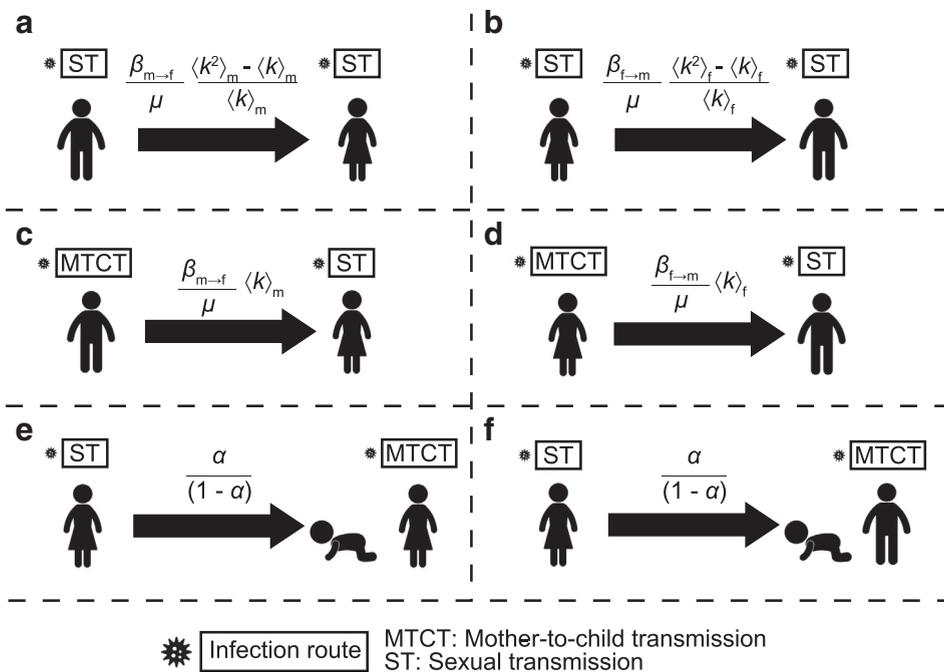


Fig 4. Explanation of the equations for each infection route. All infection patterns (cases) are expressed. The description in the overhead box indicates the infection route; i.e., ‘ST’ indicates sexual infection, and ‘MTCT’ indicates mother-to-child (vertical) transmission. The transmission events patterns of sexual transmission ((a), (b), (c) and (d)) and mother-to-child transmission ((e) and (f)). (a) An infected male who infected by ST transmit STIs to females by ST. (b) An infected female who infected by ST transmit to males by ST. (c) An infected male who infected by MTCT transmit to females by ST. (d) An infected female who infected by MTCT transmit to males by ST. (e) An infected female who infected by ST transmit to her female descendants by MTCT. (f) An infected female who infected by ST transmit to her male descendants by MTCT.

of sexually infected females that a sexually infected female generates; thus, we call this number the basic reproduction number R_0 over generations.

First,

$$\frac{\beta_{m \rightarrow f}}{\mu} \frac{\langle k^2 \rangle_m - \langle k \rangle_m}{\langle k \rangle_m}$$

represents the average number of females infected horizontally from a sexually infected male (Fig. 4a), and

$$\frac{\beta_{f \rightarrow m} \langle k^2 \rangle_f - \langle k \rangle_f}{\mu \langle k \rangle_f}$$

represents the average number of males infected horizontally from a sexually infected female (Fig. 4b) [10]. Thus, the first term on the left-hand side of Eq. (14) is the average number of females infected from a sexually infected female through two horizontal transmissions (Fig. 3a). Second, in our model, the average number of daughters a female gives birth to is 1. The average total number of females (or males) descendants infected vertically by a female infected horizontally is calculated as follows (Fig. 4e and f):

$$\alpha(1 + \alpha + \alpha^2 + \dots) = \frac{\alpha}{1 - \alpha}.$$

Since the average number of males infected horizontally by a female infected vertically is as follows (Fig 4d):

$$\frac{\beta_{f \rightarrow m}}{\mu} \langle k \rangle_f,$$

the second term on the left-hand side of Eq. (14) is the average number of infected females generated by a sexually infected female through two horizontal transmissions after a series of vertical transmissions (see Fig. 3b). Finally, in the same way, we obtain that the third term is the average number of infected females generated by a sexually infected female through a male-to-female horizontal transmission after a series of vertical transmissions (see Figs. 3c and 4c). In conclusion, the left-hand side of Eq. (14) provides the R_0 . Fig. 2g and h show the plot of the R_0 as a function of sexual transmission rate $\beta_{m \rightarrow f} = 4\beta_{f \rightarrow m}$, and Fig. 2i and j show the plot of the R_0 as a function of maternal transmission rate α . As shown in these figures, the effect of the maternal transmission rate is much smaller than that of the sexual transmission rate. This is because the second moments $\langle k^2 \rangle_f$ and $\langle k^2 \rangle_m$ are much larger than $\langle k \rangle_f$ and $\langle k \rangle_m$ for heterogeneous networks.

4. Discussion

We analyzed a simple model of STIs over generations in the context of maternal transmission. Using a degree-based approximation, we calculated the equilibrium solution of infection rate and the epidemic threshold. We formulated a new basic reproduction number R_0 , which is defined as the left-hand side of Eq. (14). In addition, we performed agent-based simulations to verify the theoretical calculations. The results of the numerical simulations closely match the theoretical predictions. Eq. (14) provides the following insights:

- (i) If the distributions of sexual contacts of both females and males are both equally heterogeneous ($\langle k^2 \rangle_f \gg \langle k \rangle_f$, $\langle k^2 \rangle_m \gg \langle k \rangle_m$, $\langle k^2 \rangle_m \cong \langle k^2 \rangle_f$), the first term on the left-hand side of Eq. (14) is dominant. Then, the effect of maternal transmission on the R_0 is negligibly small.
- (ii) If the heterogeneity of the distribution of sexual contacts of males is much higher than that of females ($\langle k^2 \rangle_m \gg \langle k^2 \rangle_f$), the second term may be comparable to the first term. This situation is realized when sexual activity is suppressed strictly in females, and there are only male spreaders. In this case, the effect of maternal transmission is not negligible.
- (iii) If the transmission rate from males to females is much greater than the transmission rate from females to males ($\beta_{m \rightarrow f} \gg \beta_{f \rightarrow m}$), then the third term may be comparable to the other terms. In this case, the effect of maternal transmission is not negligible.

Thus, except for special cases (ii) and (iii), sexual transmission has a greater effect on the R_0 than maternal transmission. Thus, to eliminate STIs, preventing horizontal infection is essential. As an example, we mention HTLV-1, where the rate of male-to-female transmission is four times greater than the rate of female-to-male transmission [29,30]. HTLV-1 is a retrovirus, which has been present in Japanese populations for more than 2300 years [31–34]. The eradication of HTLV-1 in Japan is expected to be possible through the prevention of mother-to-child transmission [35,36], but new cases remain a public health concern [37]. Although the microparameters, such as the rate of transmission per sexual contact, are unknown, our results suggest that safe-sex education is more important to eliminate HTLV-1 than prevention of mother-to-child transmission.

Notably, our model assumed a constant population. We believe that this assumption does not critically affect the dynamics of endemic STIs for the case that large population size N is large. Furthermore, we assume that females and males couple randomly. We must admit that this assumption is not realistic. However, what is essential is that the sexual network is heterogeneous. Our theoretical results indicate that lowering mother-to-child infection reduces the fraction of maternal infections but cannot eradicate STIs in heterogeneous sexual networks. Sexual behavior varies across cultures, religions, and time periods. Since the contact pattern in real human societies is excessively complex and mostly unknown, elaboration of the model is desired in the future.

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Author contributions

H.I., T.Y., and S.M. conceived the study and wrote the manuscript. H.I. and S.M. constructed the mathematical model. S.M. constructed the simulation model. T.Y. and S.M. assisted in the interpretation of the results. H.I. and S.M. generated the figures. H.I., T.Y., and S.M. revised the references and data.

Data availability

The authors declare that all data supporting the findings of this study are available within the article and its Supporting Information files or from the corresponding author upon reasonable request.

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