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THE TYPE-REPRODUCTION NUMBER, THE SERIAL INTERVAL AND THE INTRINSIC GROWTH RATE: THE BASIC EPIDEMIOLOGICAL INDICES FOR ASYMPTOMATIC TRANSMISSION

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1. INTRODUCTION

During the last two decades in mathematical epidemiology of infectious diseases, the basic reproduction number R_0 has been developed to become a central quantity to discuss the infectious disease dynamics as well as the control strategy. Recently R_0 has come to be used more widely and frequently than in previous days, mainly we believe because statistical estimations of R_0 could be performed reasonably (*e.g.* assuming a homogeneous pattern of spread or approximately addressing some heterogeneity) ([7], [1], [3]).

Although the definition and theoretical implications of R_0 in heterogeneous populations were successfully formulated ([5], [6], [11], [20]), we cannot necessarily always rely only on R_0 to deal with infectious disease control in heterogeneous populations, apart from the fact that to estimate R_0 precisely, it has been necessary to collect very detailed data to quantitatively address various heterogeneities of hosts ([8], [4], [15]).

In fact, if our disease intervention can only be applied to a specific host type, R_0 for the multistate host population cannot offer the threshold condition for eradication by controlling a specific host type, because R_0 for the multistate population is the asymptotic ratio (growth factor) of the size of vectors describing the successive generations of infected individuals. Besides, when a public health intervention is conducted for a specific subpopulation only, it is of practical importance to understand its ripple effects on the dynamics of infectious disease spread. As a potential improvement on this issue, recent studies by Heesterbeek and Roberts proposed a type-reproduction number, T ([12], [18]). The type-reproduction number for a specific host type is the number of secondary cases of that specific host type produced by the primary cases of the same host type during its entire period of infectiousness. Here, an important point is that T takes into account not only the secondary cases "directly" transmitted from the specific host but also the cases "indirectly" transmitted by way of other type hosts who were infected from the primary cases of the specific host. Roberts and Heesterbeek [18] have shown that T is a useful measure when a particular single host type is targeted to disease control effort in a community with various types of host, because under appropriate assumption eradication threshold of the disease can be formulated as $T < 1$, referring only to the

target host type. In particular, the "control relation", $1 - 1/T$, can be extremely useful to determine the critical value of eradication, by means of control effort only for a specific type host in a heterogeneous infected population, implying the broad applicability to designing disease control policy.

The type-reproduction number theory has been so far based only on the next generation matrix K and the generation perspective, and the real time dynamical system formulation has been lacking. However, it is often crucial to formulate the real time dynamics (renewal process) of the target (infected) population. To identify the reproduction kernel based on model ingredients (parameters) is needed not only for obtaining the analytical expressions of the basic epidemiological indices as the type-reproduction number, the serial interval, the generation interval and the intrinsic growth rate but also for parameter estimation purpose. In the separate paper ([14]), we have established a general dynamical system for the epidemiological reproduction of the specific target population in a multistate population system.

As an interesting example to apply the dynamical system formulation of the type-reproduction number theory, we are motivated by a need to improve limited practical utility of previous epidemiologic models. Our major claim is, an event to acquire infectiousness is not directly observable. In reality, individuals in latent and infectious periods are not distinguishable without microbiological and contact-frequency information, while onset of an apparent disease is readily observed and reported. In addition, most infection events are not directly observable for a majority of directly transmitted diseases. These facts have lowered applicability level of previous epidemic models. That is, rather than a distinction of host types by acquisition of infectiousness, infectious disease data may be more reasonably analyzed if we separate host types by *onset* of a disease ([10]). Similarly, whereas the generation time (*i.e.* time since infection of a primary case to infection of the secondary case) is in general not directly observable, the serial interval (*i.e.* time since onset of a primary case to onset of the secondary case) can be partly recorded using detailed contact tracing data ([9], [19]). Accordingly, we propose an improved model to explicitly address these points, by assuming two specific types of host, *i.e.* asymptomatic and symptomatic individuals, which are distinguished by observable event; onset of a disease. Using such a practical distinction of host types, we introduce the type-reproduction numbers for each of the host types, discussing the eradication threshold offered by T and comparing different average lengths of interval between successive generations of infected individuals.

In this short note, we introduce a basic calculation of the type-reproduction number and related indices for initial invasion of an infectious disease with asymptomatic transmission. For expository purpose, we here only use a simple ordinary differential equation model. The reader may refer to Inaba and Nishiura [14] for more detailed definitions, general results and application to the structured population model for asymptomatically transmitted diseases.

2. The asymptomatic transmission model

Let $S(t)$ be the density of susceptible host population at time t, $E(t)$ the density of infected (exposed) population in the *incubation period* (the time elapsing between the receipt of infection and the appearance of symptoms), $C(t)$ the density of infecteds (cases) with onset of a disease and $R(t)$ the density of recovered population. We assume that the infecteds in the incubation period can have infectivity, that

is, the latent period (from infection to the development of infectivity) is shorter than the incubation period. Let γ_1 be the rate of onset, γ_2 the rate of recovery, β_1 the transmission rate between susceptibles and asymptomatic infecteds and β_2 the transmission rate between susceptibles and symptomatic infecteds.

Demographic factors of the host population such as birth, death and migration are neglected. Epidemiologically, the infecteds with onset are much likely to be observed, so they will be the target host of the disease prevention policy.

Then the asymptomatic transmission model with constant parameters is formulated as follows:

$$\begin{aligned}
\frac{dS(t)}{dt} &= -(\beta_1 E(t) + \beta_2 C(t))S(t), \\
\frac{dE(t)}{dt} &= (\beta_1 E(t) + \beta_2 C(t))S(t) - \gamma_1 E(t), \\
\frac{dC(t)}{dt} &= \gamma_1 E(t) - \gamma_2 C(t), \\
\frac{dR(t)}{dt} &= \gamma_2 I(t),
\end{aligned} \tag{2.1}$$

The reader will find that the above model is a special case ($n = 2$) of the SI^nR model introduced in [17].

First let us consider the linearized system, which describes the initial invasion of the infected population into the totally susceptible population:

$$\begin{aligned}
\frac{dE(t)}{dt} &= (\beta_1 E(t) + \beta_2 C(t))S_0 - \gamma_1 E(t), \\
\frac{dC(t)}{dt} &= \gamma_1 E(t) - \gamma_2 C(t),
\end{aligned} \tag{2.2}$$

where S_0 denotes the initial size of the susceptibles. Define a reproduction matrix M and a state transition matrix Q as follows:

$$M := \begin{pmatrix} S_0\beta_1 & S_0\beta_2 \\ \gamma_1 & 0 \end{pmatrix}, \quad Q := \begin{pmatrix} -\gamma_1 & 0 \\ 0 & -\gamma_2 \end{pmatrix}.$$

Then the next generation matrix K (see [6], p. 105) is calculated as

$$K = M(-Q)^{-1} = \begin{pmatrix} S_0\beta_1/\gamma_1 & S_0\beta_2/\gamma_2 \\ 1 & 0 \end{pmatrix}. \tag{2.3}$$

The basic reproduction number R_0 is defined as the spectral radius $r(K)$ of K, which is also a positive dominant eigenvalue (the Frobenius root) λ_d of the next generation matrix K. Hence we have

$$R_0 = r(K) = \lambda_d = \frac{1}{2}\left(R_1 + \sqrt{R_1^2 + 4R_2}\right), \tag{2.4}$$

where

$$R_1 := \frac{\beta_1 S_0}{\gamma_1}, \quad R_2 := \frac{\beta_2 S_0}{\gamma_2}. \tag{2.5}$$

Epidemiologically speaking, R_1 denotes the number of secondary cases produced by an exposed individual during its entire period of incubation, and R_2 is the number of secondary cases produced by an infective individual with onset during its entire period of infectiousness.

If the target host is the case population $C(t)$, the projection matrix with respect to the target host is given by

$$P = \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix}.$$

Then we have

$$(I - P)K = \begin{pmatrix} R_1 & R_2 \\ 0 & 0 \end{pmatrix}.$$

If we assume that $R_1 < 1$, we can apply the Roberts–Heesterbeek formula ([18]) to calculate the type-reproduction number for the case population, denoted by T_C, as

$$T_C = \langle e_2, (I - P)K(I - PK)^{-1}e_2 \rangle = \frac{R_2}{1 - R_1}, \tag{2.6}$$

where $e_2 = (0, 1)^{\mathrm{T}}$, while the type–reproduction number of the exposed population, denoted by T_E, is given by

$$T_E = \langle e_1, PK(I - (I - P)K)^{-1}e_1 \rangle = R_1 + R_2, \tag{2.7}$$

where $e_1 = (1, 0)^{\mathrm{T}}$. It is clear that under the assumption $R_1 < 1$, we have $T_C < 1$ if and only if $T_E < 1$. Moreover it is easy to see that $R_0 > 1$ if and only if $T_C > 1$ under the assumption $R_1 < 1$.

The assumption $R_1 < 1$ is biologically important. In fact, if $R_1 > 1$, the incubating population can reproduce themselves with its reproduction number being above unity, so the disease can always invade into the host population even though we do not observe the appearance of symptoms. If asymptomatic individuals produce substantial number of secondary cases before the onset of the disease, it would be a most dangerous situation to the public health. On the other hand, if $R_1 < 1$, we have a possibility to control the disease by isolating the case population. On the other hand, it is clear that the cases (the infecteds with onset) cannot be persistent without the incubating class.

3. Calculating epidemiological indices based on the renewal dynamics

Here we calculate the type-reproduction number T_C and T_E by using the dynamical system formulation in the real time ([14]). Different from the Roberts–Heesterbeek formula based on the next generation matrix, the dynamical system formulation makes it possible also to calculate the basic epidemiological indices as the serial interval, the generation time and the intrinsic growth rate.

By using the variation of constants formula, we can rewrite the linearized system (2.2) as

$$E(t) = E_0 e^{-\gamma_1 t} + \int_0^t e^{-\gamma_1(t-\sigma)}(\beta_1 S_0 E(\sigma) + \beta_2 S_0 C(\sigma))d\sigma, \tag{3.1}$$

$$C(t) = C_0 e^{-\gamma_2 t} + \int_0^t e^{-\gamma_2(t-\sigma)}\gamma_1 E(\sigma)d\sigma, \tag{3.2}$$

where E_0 and C_0 are given initial data.

Inserting the expression (3.2) into the equation (3.1), we obtain a renewal equation for the incubating class $E(t)$:

$$E(t) = g_-(t) + \int_0^t \psi_-(\sigma)E(t - \sigma)d\sigma, \tag{3.3}$$

where

$$g_-(t) := E_0 e^{-\gamma_1 t} + R_2 \int_0^t e^{-\gamma_1(t-\sigma)} q_2(\sigma) C_0 d\sigma, \tag{3.4}$$

$$\psi_-(\sigma) := R_1 q_1(\sigma) + R_2 \int_0^\sigma q_1(\zeta) q_2(\sigma - \zeta) d\zeta, \tag{3.5}$$

and

$$q_1(t) := \gamma_1 e^{-\gamma_1 t}, \quad q_2(t) := \gamma_2 e^{-\gamma_2 t},$$

that is, $q_1(t)$ is the probability of the onset at infection-age t and $q_2(t)$ denotes the probability of recovery at the disease-age (the time since the onset) t.

Then we know that the type-reproduction number of the exposed class is given by

$$T_E = \int_0^\infty \psi_-(\sigma) d\sigma = R_1 + R_2. \tag{3.6}$$

Moreover it is directly easy to see that under the assumption $R_1 < 1$, $T_E > 1$ if and only if $R_0 > 1$.

The average interval between the primary infection and the secondary infection, which is called the *generation time* and denoted by L_E, is calculated as

$$\begin{aligned} L_E :&= \frac{1}{T_E} \int_0^\infty \sigma \psi_-(\sigma) d\sigma = \frac{1}{\gamma_1} + \frac{R_2}{R_1 + R_2} \frac{1}{\gamma_2} \\ &= \frac{R_1}{R_1 + R_2} \frac{1}{\gamma_1} + \frac{R_2}{R_1 + R_2} \left(\frac{1}{\gamma_1} + \frac{1}{\gamma_2} \right), \end{aligned} \tag{3.7}$$

which tells us that the generation time is the weighted average of the interval between the primary case and the secondary case infected in the incubation period and the interval between the primary case and the secondary case infected after the onset.

Next let us calculate the renewal process of the target host $C(t)$. If we see $C(t)$ as a given function, the equation for $E(t)$ in (3.11) can be seen as a Volterra integral equation as

$$E(t) = h(t) + R_1 \int_0^t q_1(\sigma) E(t - \sigma) d\sigma, \tag{3.8}$$

where

$$h(t) := E_0 e^{-\gamma_1 t} + \int_0^t e^{-\gamma_1(t-\sigma)} \beta_2 S_0 C(\sigma) d\sigma. \tag{3.9}$$

If we define the resolvent kernel $\phi(t)$ corresponding to the integral kernel $R_1 q_1(t)$ by the solution of the resolvent equation:

$$\phi(t) = R_1 q_1(t) + R_1 \int_0^t q_1(\tau) \phi(t - \tau) d\tau, \tag{3.10}$$

then we can solve (2.15) as follows:

$$E(t) = h(t) + \int_0^t \phi(t - \sigma) h(\sigma) d\sigma. \tag{3.11}$$

Solving the resolvent equation (3.10), we have

$$\phi(t) = \beta_1 S_0 e^{(\beta_1 S_0 - \gamma_1)t} = \gamma_1 R_1 e^{-\gamma_1(1-R_1)t}, \tag{3.12}$$

which implies that

$$\int_0^\infty \phi(t)dt = \frac{R_1}{1-R_1}. \tag{3.13}$$

Inserting (3.11) into (3.2), we can arrive at the renewal equation for $C(t)$:

$$C(t) = g_+(t) + \int_0^t \psi_+(z)C(t-z)dz, \tag{3.14}$$

where

$$\begin{aligned} g_+(t) &:= e^{-\gamma_2 t}C_0 + \int_0^t e^{-\gamma_2(t-\sigma)}\left[q_1(\sigma) + \int_0^\sigma \phi(\sigma-\zeta)q_1(\zeta)d\zeta\right]d\sigma E_0, \\ \psi_+(z) &:= R_2\int_0^z q_2(\sigma)\left[q_1(z-\sigma) + \int_0^{z-\sigma}\phi(\zeta)q_1(z-\sigma-\zeta)d\zeta\right]d\sigma. \end{aligned} \tag{3.15}$$

Then the type-reproduction number of the infecteds with onset is calculated as

$$T_C = \int_0^\infty \psi_+(z)dz = \frac{R_2}{1-R_1}. \tag{3.16}$$

Again it is easy to see that under the assumption $R_1 < 1$, $T_C > 1$ if and only if $R_0 > 1$.

Suppose that we can immediately *isolate* infecteds who has just shown the onset. Let $\epsilon \in [0,1]$ be the proportion of isolation (the efficacy of isolation) from new cases with the onset. Then the type-reproduction number becomes $(1-\epsilon)T_C$, so the eradication condition is given by

$$\epsilon > 1 - \frac{1}{T_C}. \tag{3.17}$$

If we let θ be the proportion of transmission prior to symptoms by

$$\theta := \frac{R_1}{R_1+R_2} = \frac{R_1}{T_E}, \tag{3.18}$$

then the condition (3.17) can be written as

$$R_1 + (1-\epsilon)R_2 = T_E(1-\epsilon(1-\theta)) < 1. \tag{3.19}$$

The same kind of expression as (3.19) is given in [10].

Moreover the average interval between the primary onset and the secondary onset, denoted by L_C, is calculated as

$$L_C := \frac{1}{T_C}\int_0^\infty z\psi_+(z)dz = \frac{1}{\gamma_1}\frac{1}{1-R_1} + \frac{1}{\gamma_2}. \tag{3.20}$$

Traditionally the serial interval is defined as the period from the observation of symptoms in one case to the observation of symptoms in a second case "directly" infected from the first (see [2] p. 21). On the other hand, we can observe that L_C can be written as

$$L_C = \frac{1}{\gamma_2} + \frac{1}{\gamma_1}\sum_{n=0}^\infty R_1^n > \frac{1}{\gamma_2} + \frac{1}{\gamma_1} =: L, \tag{3.21}$$

where L is the serial interval in the traditional sense, $\sum_{n=1}^\infty R_1^n$ reflects the indirect reproduction of secondary cases by through the infection in the incubation period. Hence L_C is the mean interval from the primary case to the secondary case taking

into account all possible reproduction paths. From (3.7) and (3.21), we conclude that

$$L_C > L > L_E, \tag{3.22}$$

that is, the serial interval is longer than the serial interval in the traditional sense and the generation time.

Another possible observable parameter is the initial growth rate (the intrinsic rate of natural increase) of the cases with the onset. The Euler–Lotka characteristic equation for the intrinsic growth rate λ of the case population $C(t)$ is given by

$$\int_0^\infty e^{-\lambda z}\psi_+(z)dz = 1. \tag{3.23}$$

Using the expression (3.15), it is easy to see that (3.23) is reduced to a quadratic equation of λ:

$$\lambda^2 + [\gamma_2 + \gamma_1(1 - R_1)]\,\lambda + \gamma_1\gamma_2(1 - R_1) = \gamma_1\gamma_2 R_2. \tag{3.24}$$

The reader may confirm that the quadratic equation (3.24) is no other than the characteristic equation of the linearized system (2.2). Dividing the both sides of (3.24) by $\gamma_1\gamma_2(1 - R_1)$, we have

$$T_C = 1 + L_C\lambda + O(\lambda^2). \tag{3.25}$$

Then we know from the observables λ and L_C that the type-reproduction number of the target host is approximately given by $T_C \approx 1 + L_C\lambda$ as far as λ is not so large.

4. A REMARK AND COMMENT

Finally we give a remark. The next generation matrix (2.3) is based on the interpretation that the onset means a "birth" of symptomatic individual, which implies that the recovery process depends not on the infection-age but on the disease-age. On the other hand, if we assume that the recovery process depends on the infection-age, its reproduction matrix and the state transition matrix are given by

$$M = \begin{pmatrix} S_0\beta_1 & S_0\beta_2 \\ 0 & 0 \end{pmatrix}, \quad Q = \begin{pmatrix} -\gamma_1 & 0 \\ \gamma_1 & -\gamma_2 \end{pmatrix}. \tag{4.1}$$

Then we have $R_0 = r(M(-Q)^{-1}) = R_1 + R_2$. In this case, K is decomposable and the type-reproduction number of symptomatic individuals is not properly defined, because the onset is not interpreted as the reproduction of symptomatic individuals, but is state-transition. However, if we can immediately isolate the case population just after the onset and $\epsilon \in (0, 1)$ is the proportion of isolation, the transition matrix is changed into

$$\begin{pmatrix} -\gamma_1 & 0 \\ (1-\epsilon)\gamma_1 & -\gamma_2 \end{pmatrix}, \tag{4.2}$$

then the effective reproduction number is $R_e = R_1 + (1 - \epsilon)R_2$. The eradication condition $R_e = R_1 + (1-\epsilon)R_2 < 1$ is the same as (3.19). If we can take into account both the infection-age and the disease-age to characterize the symptomatic class by using the structured population model, the above two formulations would be unified.

Though here we have shown only one simple example, the reader may understand that our calculation method based on the dynamical system formulation could

be easily extended to more general situation, especially to multistate structured population models. A general formulation using the duration structured multistate demographic model is presented in Inaba and Nishiura ([14]).

In summary, a major point of our idea is that basic epidemiological indices (threshold values, serial interval, intrinsic growth rate, etc.) can be calculated from the renewal equation of the *observable* host type (symptomatic population), hence we can apply our model to real data. To formulate a theory based on *observables* is most crucial in order to apply the theory to the real world.

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