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ORIGINAL ARTICLE

Case Fatality Proportion

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Abstract A precise definition of case fatality proportion for compartmental disease transmission models with disease induced mortality rate is given. This is applied in classical epidemic modeling frameworks to models with multiple infectious stages, with multigroups, with spatial patches, and with age of infection. It is shown that the case fatality proportion is the sum over all stages of the product of the probability of dying from the disease at a given stage and the probability of surviving to that stage. The derived expressions for case fatality can be used to estimate the disease induced death rates from more readily available data.

Keywords Case fatality · Differential mortality · Epidemic model · Survival probability

1. Introduction

The case fatality proportion (sometimes called case fatality ratio, case mortality, or case fatality rate) is an important epidemic parameter for a disease that causes mortality. It measures the proportion of those who acquire an infection that eventually die from the disease (see, e.g., MedicineNet.com, 2003; Anderson et al., 2004), and is often given as a percentage. For example, Nandy et al. (2006) counted 92 deaths among 945 cases of measles in an outbreak in eastern Niger in 2003, and gave the case fatality proportion as 9.7%. Estimates of the case fatality proportion for many human infectious diseases are given in Chin (2000).

Dietz and Heesterbeek (2002) discussed a case fatality model, in which they studied the probability that an individual is alive at age a given a force of infection $\lambda(a)$. In their model, they assume that an infective individual (who does not die naturally) dies from the disease with probability $\tilde{c}$. Such models assume that infected individuals die from the disease *after* they go through the infectious stage. The same idea can be applied to a population model. Safan et al. (Submitted) consider such a model with standard incidence and input proportional to the population number. For most epidemics, the population can

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be regarded as approximately constant. Thus, we consider a model with mass-action incidence and constant input. For simplicity, we ignore the latent stage. The compartmental model can be written as

$$S' = \lambda - \mu S - \beta SI, \tag{1a}$$

$$I' = \beta SI - \mu I - \gamma I, \tag{1b}$$

$$R' = (1-\tilde{c})\gamma I - \mu R, \tag{1c}$$

where S, I, and R are the number of individuals who are susceptible, infectious, and recovered, respectively. The susceptible class S is assumed to have a constant input $\lambda > 0$; μ is the natural death rate; taking mass-action incidence, β is the transmission rate. For $\gamma > 0$, $1/\gamma$ is the mean infectious period; if $\gamma = 0$, then no individuals recover from the disease. Here, $\tilde{c}$ is usually called the case fatality proportion parameter. In fact, it can be interpreted as the fraction of disease induced deaths among the infected individuals who becomes noninfectious. If $\mu \approx 0$, i.e., the vital dynamics can be ignored, then $\tilde{c}$ is indeed, the case fatality proportion. However, for diseases in which the vital dynamics cannot be ignored, e.g., most childhood diseases (where birth is the dominant source of new susceptibles), and HIV (which has a long progression time), $\tilde{c}$ is different from the case fatality proportion because it ignores the natural deaths in class I.

One important feature of the case fatality model (1) is that $\tilde{c}$ does not affect the basic reproduction number,

$$\mathcal{R}_0 = \frac{\lambda\beta}{\mu(\mu+\gamma)} > 1,$$

because the disease induced deaths are assumed to occur after individuals leave class I. Biologically, $\mathcal{R}_0$ is the average number of secondary infections caused by an infectious individual in a completely susceptible population. The case fatality model is able to model deaths in class I if $\tilde{c}\gamma$ is interpreted as the death rate in class I, while $(1-\tilde{c})\gamma$ is the usual recovery rate (Safan et al., Submitted). However, this interpretation predicts that if $\tilde{c} \to 1$, then the time it takes to recover tends to ∞, which may be unrealistic.

Instead of employing the case fatality model, disease induced death is commonly modeled by an "excess death rate" caused by the disease. Such models are called differential mortality models. Day (2002) explored the relation between case mortality and differential mortality in the context of virulence evolution. In this paper, we discuss how to define the case fatality proportion in more complex differential mortality models.

In Section 2, we illustrate the definition of the case fatality proportion, along the lines of Day (2002), in a simple differential mortality model in which only infectious individuals may die from the disease. In Section 3, we extend the definition to multi-stage models, in which disease deaths may occur after an individual becomes noninfectious. We then further extend the definition to multi-group and patch models in Sections 4 and 5, respectively. In Section 6, we discuss the dependency of case fatality proportion on age of infection, and give some concluding remarks in Section 7.

2. Definition of case fatality proportion in a simple differential mortality model

In this section, we discuss the relationship of the case fatality proportion and excess death rate with a simple differential mortality model, in which it is assumed that disease-induced mortality occurs before individuals leave the infectious stage. As in (1), we ignore the latent stage. The model can be written as

$$S' = \lambda - \mu S - \beta SI, \tag{2a}$$

$$I' = \beta SI - \mu I - \gamma I - \delta I, \tag{2b}$$

$$R' = s\gamma I - \mu R, \tag{2c}$$

where δ is the excess death rate caused by the disease in class I. We assume that $\lambda > 0$ and $\mu > 0$.

By summing Eqs. (2a–2c), the total population number, $N = S + I + R$, is governed by:

$$N' = \lambda - \mu N - \delta I. \tag{3}$$

Note that the first octant is positively invariant, thus, $I < N$. It follows from (3) that

$$\lambda - \mu N - \delta N \le N' \le \lambda - \mu N.$$

Hence, the total population is positive and bounded.

We can follow the steps in Safan et al. (Submitted) and show that both (1) and (2) have a unique globally stable endemic equilibrium, and by mapping $(\tilde{c}\gamma, (1-\tilde{c})\gamma) \to (\delta, \gamma)$, the two systems are equivalent to each other. Because in our two models the population is finite, they do not differ in the extreme case of $\tilde{c} = 1$ as do the models in Safan et al. (Submitted). In that paper, the input is assumed to be proportional to N, standard incidence is taken, and proportions of susceptible and infectives are considered.

The disease free equilibrium (DFE) is

$$S^0 = \frac{\lambda}{\mu}, \qquad I^0 = 0, \qquad R^0 = 0.$$

The basic reproduction number $\mathcal{R}_0$ is given from the next generation matrix (van den Driessche and Watmough, 2002) as

$$\mathcal{R}_0 = \frac{\lambda\beta}{\mu(\mu + \gamma + \delta)}. \tag{4}$$

Note that in this model $\mathcal{R}_0$ decreases as the excess death rate δ increases, because the excess deaths in class I shorten the mean infectious period. In fact, as $\delta \to \infty$, $\mathcal{R}_0 \to 0$, because each infected individual dies before infecting any one else. Thus, the disease is driven to extinction. However, this effect of large mortality is due to the implicit assumption in the ordinary differential equation models that the time from infection to death is exponentially distributed; thus, the mean duration that an individual stays in class I goes to zero as $\delta \to \infty$. If we incorporate more realistic time-to-death distributions, the disease may not die out, as observed in the case of bird flu among domesticated birds (OIE, 2007).

Let D be the number of disease induced deaths, A be the total number of infected individuals. Then the case fatality proportion c can be defined as

$$c = \frac{D}{A}, \tag{5}$$

where

$$D = \int_0^\infty \delta I(t)\, dt,$$

and

$$A = \int_0^\infty (\mu + \gamma + \delta) I(t)\, dt.$$

This immediately leads to

$$c = \frac{D}{A} = \frac{\delta}{\mu + \gamma + \delta}. \tag{6}$$

Here c can be interpreted as the probability that an infected individual dies from the disease. Hence, $c \to 1$ if and only if $\delta \to \infty$, which leads to $\mathcal{R}_0 \to 0$. That is, if the excess death rate is very large, then every infected individual dies before recovering.

With this definition in (5), we revisit the case fatality model (1). There the disease deaths are

$$D = \tilde{c}\gamma \int_0^\infty I(t)\, dt,$$

and the total number of infected individuals is

$$A = \int_0^\infty (\mu + \gamma) I(t)\, dt.$$

The case fatality proportion is

$$c = \frac{D}{A} = \frac{\tilde{c}\gamma \int_0^\infty I(t)\, dt}{\int_0^\infty (\mu + \gamma) I(t)\, dt} = \frac{\tilde{c}\gamma}{\mu + \gamma}.$$

Thus, the case fatality proportion c is equivalent to the parameter $\tilde{c}$ only if $\mu = 0$. If $\mu > 0$, then $\tilde{c} > c$.

The definition of case fatality proportion in (5) can be applied to more complex models. Since the case fatality proportion is a measure of the disease virulence, intuitively, it should not depend on the transmission process. This can be illustrated by the following vector disease model. A typical vector disease model is the Ross–McDonald model (Anderson and May, 1991, Section 14.3), which describes the transmission of malaria among the human population via mosquitoes. The disease spreads by infected mosquitoes biting susceptible humans, while mosquitoes are infected when biting an infected human. Let S_H and I_H denote the number of susceptible and infectious humans, S_M and I_M represent the number of susceptible and infectious mosquitoes. Assume that the human and

mosquito populations have constant inputs, so that both populations remain bounded. It is assumed that, once infected, mosquitoes carry the pathogen and remain infectious until they die. For simplicity, we ignore any acquired immunity of infected humans. The model can be written as

$$S_H' = \lambda_H - \mu_H S_H - \beta_1 S_H I_M + \gamma I_H, \tag{7a}$$

$$I_H' = \beta_1 S_H I_M - \mu_H I_H - \gamma I_H - \delta I_H, \tag{7b}$$

$$S_M' = \lambda_M - \mu_M S_M - \beta_2 S_M I_H, \tag{7c}$$

$$I_M' = \beta_2 S_M I_H - \mu_M I_M, \tag{7d}$$

where β_1 is the transmission rate from mosquito to human, β_2 is the transmission rate from human to mosquito, γ and δ are the human recovery and excess death rates, respectively, λ_i are the human and mosquito population inputs, and μ_i are the natural death rates for $i = H, M$.

Considering only human case fatality, the total number of infected individuals is

$$A = \int_0^\infty (\mu_H + \gamma + \delta) I_H(t)\, dt,$$

and the total number of disease deaths is

$$D = \int_0^\infty \delta I_H(t)\, dt.$$

Hence,

$$c = \frac{D}{A} = \frac{\delta}{\mu_H + \gamma + \delta}.$$

Not surprisingly, this is equivalent to (6), and does not depend on the transmission process.

3. Disease deaths in multiple infectious stages

The simple differential mortality model (2) assumes that disease induced deaths occur in class I. However, an infected individual may die weeks after becoming noninfectious. For example, in the recent SARS epidemics, patients died on average 35.9 days after being admitted to hospital (Donnelly et al., 2003). In order to model deaths after an individual becomes noninfectious, we can keep track of excess deaths in class R. This leads to the model:

$$S' = \lambda - \mu S - \beta S I, \tag{8a}$$

$$I' = \beta S I - \mu I - \gamma I - \delta I, \tag{8b}$$

$$R' = \gamma I - \mu R - \theta R, \tag{8c}$$

where θ is the excess death rate in class R. But this model presents a problem: $1/\theta$ is the mean disease-induced time-to-death in class R, which for many diseases (e.g., SARS) is

magnitudes shorter than $1/\mu$, i.e., $\theta \gg \mu$. Since the probability that an individual exits class R because of disease induced death is $\frac{\theta}{\mu+\theta}$, this predicts that individuals in class R will die from the disease with a probability approaching 1.

To work around the problem, we introduce another class T, to which individuals enter when they stop being infectious. In this class, individuals are still affected by the disease (e.g., have disease complications), and thus have the possibility of dying from the disease. When they leave T, they are deemed fully recovered and enter the class R, where they will not die from the disease. The extended model can be written as

$$S' = \lambda + \mu S - \beta SI, \tag{9a}$$

$$I' = \beta SI - \mu I - \gamma I - \delta I, \tag{9b}$$

$$T' = \gamma I - \mu T - \rho T - \theta T, \tag{9c}$$

$$R' = \rho T - \mu R, \tag{9d}$$

where θ is the excess death rate in class T, and $1/\rho$ is the mean duration time in class T without counting deaths. The latter time period can sometimes be approximated by the hospitalization period.

System (9) is a special multi-stage model (a model with multiple infectious stages), where the class T can be considered an infectious stage with zero transmission rate. In addition to incorporating the T class, multi-stage models can be used to describe the dynamics of diseases such as HIV/AIDS. The standard *SEIR* model is also a special case of a multi-stage model, with zero transmission rate in the latent stage. In general, we consider a multi-stage model with n infectious stages (an SI^nR model):

$$S' = \lambda - \mu S - \sum_{k=1}^{n} \beta_k SI_k, \tag{10a}$$

$$I_1' = \sum_{k=1}^{n} \beta_k SI_k - \mu I_1 - \gamma_1 I_1 - \delta_1 I_1, \tag{10b}$$

$$I_k' = \gamma_{k-1} I_{k-1} - \mu I_k - \gamma_k I_k - \delta_k I_k, \quad 2 \le k \le n\,, \tag{10c}$$

$$R' = \gamma_n I_n - \mu R, \tag{10d}$$

where δ_k is the excess death rate in the infectious stage k, β_k is the transmission rate in the infectious stage k, and γ_k is the rate of passing from stage I_k to I_{k+1} (with stage I_{n+1} equal to class R). Summing (10) gives the population dynamics

$$N' = \lambda - \mu N - \sum_{k=1}^{n} \delta_k I_k. \tag{11}$$

As in the previous section, we can show that the population N is positive and bounded. The DFE is $(\frac{\lambda}{\mu}, 0, \ldots, 0)$. The basic reproduction number is

$$\mathcal{R}_0 = \frac{\lambda}{\mu} \sum_{k=1}^{n} \frac{\beta_k \nu_k}{\mu + \gamma_k + \delta_k}, \tag{12}$$

where

$$v_k = \prod_{i=1}^{k-1} \frac{\gamma_i}{\mu + \gamma_i + \delta_i}, \tag{13}$$

for $k \geq 2$, and $v_1 = 1$. Note that v_k is the probability that an infected individual survives to stage k. If $\mathcal{R}_0 > 1$, then the DFE is unstable.

In this model

$$D = \sum_{k=1}^{n} \int_0^\infty \delta_k I_k(t)\, dt.$$

Each infected individual has to pass through the first stage I_1, but not necessarily later stages (because of death). Thus, the total number of infected individuals is

$$A = \int_0^\infty (\mu + \gamma_1 + \delta_1) I_1(t)\, dt.$$

Hence,

$$c = \frac{D}{A} = \sum_{k=1}^{n} \frac{\delta_k \int_0^\infty I_k(t)\, dt}{(\mu + \gamma_1 + \delta_1) \int_0^\infty I_1(t)\, dt}. \tag{14}$$

Integrating (10c) gives

$$I_k(\infty) - I_k(0) = \gamma_{k-1} \int_0^\infty I_{k-1}(t)\, dt - (\mu + \gamma_k + \delta_k) \int_0^\infty I_k(t)\, dt,$$

which on dividing becomes

$$\frac{I_k(\infty) - I_k(0)}{(\mu + \gamma_k + \delta_k) \int_0^\infty I_{k-1}(t) dt} = \frac{\gamma_{k-1}}{\mu + \gamma_k + \delta_k} - \frac{\int_0^\infty I_k(t)\, dt}{\int_0^\infty I_{k-1}(t)\, dt}.$$

Assuming $I_k(0)$ is small, the left-hand side is zero (because either $I_k(\infty) = 0$ or $\int_0^\infty I_{k-1}(t)\, dt = \infty$). Thus,

$$\frac{\gamma_{k-1}}{\mu + \gamma_k + \delta_k} = \frac{\int_0^\infty I_k(t)\, dt}{\int_0^\infty I_{k-1}(t)\, dt}. \tag{15}$$

Hence, for $k \geq 2$,

$$\int_0^\infty I_k(t)\, dt = \prod_{i=2}^{k} \frac{\gamma_{i-1}}{\mu + \gamma_i + \delta_i} \int_0^\infty I_1(t)\, dt = \frac{\mu + \gamma_1 + \delta_1}{\mu + \gamma_k + \delta_k} v_k \int_0^\infty I_1(t)\, dt.$$

Substituting the above equations into (14) gives the case fatality proportion

$$c = \sum_{k=1}^{n} \frac{\delta_k}{\mu + \gamma_k + \delta_k} v_k\,. \tag{16}$$

Here c is the sum of the product of the probability of surviving to stage k and the probability of dying from the disease in stage k.

For model (9), since class T corresponds to I_2 in model (10), θ corresponds to δ_2, thus the case fatality proportion is

$$c = \frac{\delta}{\mu+\gamma+\delta} + \frac{\gamma\theta}{(\mu+\gamma+\delta)(\mu+\rho+\theta)}. \tag{17}$$

For model (8), class R corresponds to I_2 in model (10) with the corresponding $\gamma_2 = 0$, then the case fatality proportion for (8) is

$$c = \frac{\delta}{\mu+\gamma+\delta} + \frac{\gamma\theta}{(\mu+\gamma+\delta)(\mu+\theta)}. \tag{18}$$

This reveals the problem of model (8) that we mentioned at the beginning of this section, namely, if $\mu \approx 0$ (i.e., $\mu \ll \theta$ and $\mu \ll \gamma+\delta$), then $c \approx 1$.

Note that $\mu \approx 0$ is often assumed if we are interested in a single epidemic, as in the case of the recent SARS epidemic, where the vital dynamics can be neglected. In such a case, $\mu = \lambda = 0$, and the case fatality proportion becomes

$$c = \sum_{k=1}^{n} \frac{\delta_k}{\gamma_k+\delta_k} v_k, \tag{19}$$

where v_k becomes

$$v_k = \prod_{i=1}^{k-1} \frac{\gamma_i}{\gamma_i+\delta_i},$$

In this case, $c \to 1$ if there is a $\delta_k \to \infty$.

4. Multi-group models

In this section, we study fatality in multi-group models, where the population is divided into n groups (e.g., social groups). We assume individuals in group j can transmit the disease to group i with rate β_{ij}. Note that the contact matrix $B = [\beta_{ij}]$ need not be symmetric. The model can be written as

$$S_i' = \lambda_i - \mu_i S_i - \sum_{j=1}^{n} \beta_{ij} I_j S_i, \tag{20a}$$

$$I_i' = \sum_{j=1}^{n} \beta_{ij} I_j S_i - \mu_i I_i - \delta_i I_i - \gamma_i I_i, \tag{20b}$$

$$T_i' = \gamma_i I_i - \mu_i T_i - \theta_i T_i - \rho_i T_i, \tag{20c}$$

$$R_i' = \rho_i T_i - \mu_i R_i, \tag{20d}$$

where $1 \le i \le n$, λ_i, μ_i, γ_i, ρ_i are the input, natural death rate, removal rate, and recovery rate in group i, respectively, δ_i and θ_i are the disease induced death rates in class I_i and T_i, respectively. The removal rate γ_i may be different in each group because the effective infectious period can be shortened by various control measures, and these control measures can have different effectiveness in each group.

Summing the Eqs. (20) gives

$$(S_i + I_i + T_i + R_i)' = \lambda_i - \mu_i(S_i + I_i + T_i + R_i) - \delta_i I_i - \theta_i T_i.$$

Hence, S_i, I_i, T_i, and R_i are bounded in each group i. The DFE is given by $S_i = \lambda_i/d_i$, $I_i = T_i = R_i = 0$. The basic reproduction number $\mathcal{R}_0$ is given by the spectral radius of $\mathrm{diag}(\lambda_i/\mu_i)BV^{-1}$, where $V = \mathrm{diag}(\mu_i + \delta_i + \gamma_i)$. Our S_i, I_i, T_i system is a special case of the model of Guo et al. (2006). Assuming that $\mathcal{R}_0 > 1$, Guo et al. (2006) prove that the disease settles to a globally asymptotically stable endemic equilibrium with $I_i(t) = I_i(\infty)$ if $\mathcal{R}_0 > 1$.

In each group, a case fatality c_i can be defined as in previous sections. Let D_i be the disease induced deaths in group i, and A_i be the total number of infected individuals in group i, then

$$D_i = \int_0^\infty \delta_i I_i(t)\,dt + \int_0^\infty \theta_i T_i(t)\,dt,$$
$$A_i = \int_0^\infty (\mu_i + \gamma_i + \delta_i) I_i(t)\,dt.$$

Hence, c_i can be defined as

$$c_i = \frac{D_i}{A_i} = \frac{\delta_i \int_0^\infty I_i(t)\,dt + \theta_i \int_0^\infty T_i(t)\,dt}{\int_0^\infty (\mu_i + \gamma_i + \delta_i) I_i(t)\,dt}.$$

Integrating (20c) gives

$$T_i(\infty) - T_i(0) = \gamma_i \int_0^\infty I_i(t)\,dt - (\mu_i + \theta_i + \rho_i) \int_0^\infty T_i(t)\,dt. \tag{21}$$

As for the derivation of (15), Eq. (21) gives

$$\frac{\int_0^\infty T_i(t)\,dt}{\int_0^\infty I_i(t)\,dt} = \frac{\gamma_i}{\mu_i + \rho_i + \theta_i},$$

because $T_i(\infty)$ is bounded. This leads to

$$c_i = \frac{\delta_i}{\mu_i + \gamma_i + \delta_i} + \frac{\gamma_i \theta_i}{(\mu_i + \gamma_i + \delta_i)(\mu_i + \rho_i + \theta_i)}.$$

At the overall population level, however, the case fatality should be defined as

$$c = \frac{\sum_{i=1}^n D_i}{\sum_{i=1}^n A_i} = \frac{\sum_{i=1}^n c_i A_i}{\sum_{i=1}^n A_i} = \sum_{i=1}^n c_i \frac{A_i}{\sum_{j=1}^n A_j}.$$

Since

$$\frac{A_i}{\sum_{j=1}^n A_j} = \frac{(\mu_i + \gamma_i + \delta_i)\int_0^\infty I_i(t)\,dt}{\sum_{j=1}^n (\mu_j + \gamma_j + \delta_j)\int_0^\infty I_j(t)\,dt}.$$

Applying L'Hôpital's rule gives

$$\frac{A_i}{\sum_{j=1}^n A_j} = \frac{(\mu_i + \gamma_i + \delta_i) I_i(\infty)}{\sum_{j=1}^n (\mu_j + \gamma_j + \delta_j) I_j(\infty)}.$$

Hence,

$$c = \sum_{i=1}^n c_i \frac{(\mu_i + \gamma_i + \delta_j) I_i(\infty)}{\sum_{j=1}^n (\mu_j + \gamma_j + \delta_j) I_j(\infty)}. \tag{22}$$

Unlike the homogeneous models we discussed previously, in group models, the transmission process affects the case fatality proportion c through $I_i(\infty)$. This is intuitively easy to understand: a patch with a larger epidemic size has a larger weight in total excess deaths.

5. Patch model with travel

In this section, we study a modified patch model that takes the travel of individuals into account. For n patches, the model is given by the following $4n$ equations, which is similar to that considered by Salmani and van den Driessche (2006):

$$S_i' = \lambda_i - \mu_i S_i - \beta S_i I_i + \sum_{j=1}^n m_{ij} S_j - \sum_{j=1}^n m_{ji} S_i, \tag{23a}$$

$$I_i' = \beta S_i I_i - \mu_i I_i - \delta_i I_i - \gamma_i I_i + \sum_{j=1}^n m_{ij} I_j - \sum_{j=1}^n m_{ji} I_i, \tag{23b}$$

$$T_i' = \gamma_i I_i - \mu_i T_i - \theta_i T_i - \rho_i T_i + \sum_{j=1}^n m_{ij} T_j - \sum_{j=1}^n m_{ji} T_i, \tag{23c}$$

$$R_i' = \rho_i T_i - \mu_i R_i + \sum_{j=1}^n m_{ij} R_j - \sum_{j=1}^n m_{ji} R_i, \tag{23d}$$

where $i = 1, 2, \ldots, n$; and $m_{ij} > 0$ is the travel rate from patch j to patch i, which is assumed to be the same for each class.

Summing the Eqs. (23) gives

$$N_i' = \lambda_i - \mu_i N_i + \sum_{j=1}^n m_{ij} N_j - \sum_{j=1}^n m_{ji} N_i - \delta_i I_i - \theta_i T_i,$$

where $N_i = S_i + I_i + T_i + R_i$. This system is bounded above by the following system:

$$X_i' = \lambda_i - \mu_i X_i + \sum_{j=1}^{n} m_{ij} X_j - \sum_{j=1}^{n} m_{ji} X_i. \tag{24}$$

This can be written in matrix form:

$$X' = \Lambda - AX,$$

where $\Lambda = [\lambda_i]^T$, and $A = [a_{ij}]$ is an $n \times n$ matrix, where $a_{ii} = \mu_i + \sum_{j=1}^{n} m_{ji}$, and $a_{ij} = -m_{ij}$ for $j \neq i$. Note that (24) governs the dynamics of the population in the absence of the disease. Assuming $\mu_i > 0$, A is a nonsingular M-matrix (Horn and Johnson, 1991, Section 2.5), therefore, all eigenvalues of A have positive real parts, and also entries of A^{-1} are positive. Thus, assuming $\Lambda \neq 0$, (24) has a unique globally asymptotically stable equilibrium $X^* = A^{-1}\Lambda > 0$, which is indeed the DFE of the system (23). The DFE is unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is the spectral radius of FV^{-1}, with $F = \operatorname{diag}(\beta_i X_i^*)$, and $V = [v_{ij}]$ with $v_{ii} = \mu_i + \gamma_i + \delta_i + \sum_{j=1}^{n} m_{ji}$ and $v_{ij} = -m_{ij}$ for $i \neq j$ (see van den Driessche and Watmough, 2002). Also, $N_i \leq X_i$ implies that S_i, I_i, T_i, and R_i are bounded.

To define the case fatality proportion c in this model, let

$$D = \sum_{i=1}^{n} \left(\int_0^\infty \delta_i I_i(t)\, dt + \int_0^\infty \theta_i T_i(t)\, dt \right),$$

$$A = \sum_{i=1}^{n} (\mu_i + \gamma_i + \delta_i) \int_0^\infty I_i(t)\, dt.$$

Then

$$c = \frac{D}{A} = \frac{\sum_{i=1}^{n} \left(\int_0^\infty \delta_i I_i(t)\, dt + \int_0^\infty \theta_i T_i(t)\, dt \right)}{\sum_{i=1}^{n} (\mu_i + \gamma_i + \delta_i) \int_0^\infty I_i(t)\, dt}.$$

We assume that if $\mathcal{R}_0 > 1$, then the system converges to an endemic equilibrium, i.e., $I(t) \to I(\infty)$, $T(t) \to T(\infty)$. Applying L'Hôpital's rule gives

$$c = \frac{\sum_{i=1}^{n} \delta_i I_i(\infty) + \theta_i T_i(\infty)}{\sum_{i=1}^{n} (\mu_i + \gamma_i + \delta_i) I_i(\infty)}.$$

Summing the Eq. (23c) over all i gives

$$\sum_{i=1}^{n} T_i' = \sum_{i=1}^{n} \gamma_i I_i - \mu_i T_i - \theta_i T_i - \rho_i T_i.$$

Hence

$$\sum_{i=1}^{n} (\mu_i + \theta_i + \rho_i) T_i(\infty) = \sum_{i=1}^{n} \gamma_i I_i(\infty).$$

This leads to

$$c = \frac{\sum_{i=1}^{n}\left[\delta_i + \frac{\theta_i\gamma_i}{\mu_i+\rho_i+\theta_i}\right]I_i(\infty)}{\sum_{i=1}^{n}(\mu_i+\gamma_i+\delta_i)I_i(\infty)}.$$

We can see that in this case, there is no simple expression for c_i in each patch.

However, c_i can be explicitly found if we make the assumption that individuals do not move to other patches after they become infectious and before they fully recover. Under this assumption, a latent class E is needed to allow the cross-patch transmission of the disease. The model then becomes

$$S_i' = \lambda_i - \mu_i S_i - \beta_i S_i I_i + \sum_{j=1}^{n} m_{ij} S_j - \sum_{j=1}^{n} m_{ji} S_i, \tag{25a}$$

$$E_i' = \beta_i S_i I_i - \mu_i E_i - \sigma_i E_i + \sum_{j=1}^{n} m_{ij} E_j - \sum_{j=1}^{n} m_{ji} E_i, \tag{25b}$$

$$I_i' = \sigma_i E_i - \mu_i I_i - \gamma_i I_i - \delta_i I_i, \tag{25c}$$

$$T_i' = \gamma_i I_i - \mu_i T_i - \theta_i T_i - \rho_i T_i, \tag{25d}$$

$$R_i' = \rho_i T_i - \mu_i R_i + \sum_{j=1}^{n} m_{ij} R_j - \sum_{j=1}^{n} m_{ji} R_i, \tag{25e}$$

where $\frac{1}{\sigma_i}$ is the mean latent period in patch i without counting deaths.

In this model, the DFE is the same as the DFE of the system (23), with $E_i = 0$. The basic reproduction number $\mathcal{R}_0$ is the spectral radius of FV^{-1}, where

$$F = \begin{bmatrix} 0 & \beta_i X_i^* \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} V_{11} & 0 \\ V_{21} & V_{22} \end{bmatrix},$$

$V_{11} = [u_{ij}]$ with $u_{ii} = \mu_i + \sigma_i + \sum_{j=1}^{n} m_{ji}$ and $u_{ij} = -m_{ij}$ for $i \neq j$, $V_{21} = -\text{diag}(\sigma_i)$, and $V_{22} = \text{diag}(\mu_i + \gamma_i + \delta_i)$.

We can define the per patch case fatality proportion, by letting

$$D_i = \int_0^\infty \delta_i I_i(t)\,dt + \int_0^\infty \theta_i T_i(t)\,dt,$$

$$A_i = \int_0^\infty (\mu_i + \gamma_i + \delta_i) I_i(t)\,dt.$$

Then

$$c_i = \frac{D_i}{A_i} = \frac{\int_0^\infty \delta_i I_i(t)\,dt + \int_0^\infty \theta_i T_i(t)\,dt}{\int_0^\infty (\delta_i + \gamma_i + \mu_i) I_i(t)\,dt}.$$

Integrating (25d) gives

$$\frac{\int_0^\infty T_i(t)\,dt}{\int_0^\infty I_i(t)\,dt} = \frac{\gamma_i}{\mu_i + \rho_i + \theta_i}.$$

Thus

$$c_i = \frac{\delta_i + \frac{\gamma_i\theta_i}{\mu_i+\rho_i+\theta_i}}{\mu_i+\gamma_i+\delta_i} = \frac{\delta_i}{\mu_i+\gamma_i+\delta_i} + \frac{\gamma_i\theta_i}{(\mu_i+\gamma_i+\delta_i)(\mu_i+\rho_i+\theta_i)}.$$

Then, at the overall population level, we can define the case fatality proportion c as in (22). In this case, we still cannot deduce an analytical form of $I_i(\infty)$.

6. Case fatality proportion as a function of age of infection

The case fatality proportion is usually measured for individuals who die from the disease within a given period of time τ after infection (see, e.g., Nandy et al., 2006, Fig. 3). We denote this by c_τ. Note that this is usually expressed as a percentage associated with age of infection τ. In fact, the case fatality proportion c in previous sections is c_∞. The models of previous sections cannot be applied to compute c_τ, because the stage-age information is lacking in those models. To study c_τ, we need to explicitly model the stage-age. The common approach is to use a system of partial differential equations as formulated by Kermack and McKendrick (1932, in Eqs. (28–29)) for a model with both chronological age and age of infection. For simplicity, we ignore chronological age and vital dynamics (thus results are conditional upon the host not dying of natural causes), and consider the following system

$$S' = -S(t)\int_0^\infty \beta(a)I(t,a)\,da, \tag{26a}$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -\big[\gamma(a)+\delta(a)\big]I, \tag{26b}$$

$$I(t,0) = S(t)\int_0^\infty \beta(a)I(t,a)\,da, \tag{26c}$$

$$R' = \int_0^\infty \gamma(a)I(t,a)\,da, \tag{26d}$$

where a is the age of infection.

In this model, the number of individuals $D(a)$ that die at time a after infection is

$$D(a) = \int_0^\infty \delta(a)I(t,a)\,dt = \delta(a)\int_0^\infty I(t,a)\,dt.$$

Let A be the total number of infected individuals. Then, from (26a) and (26c),

$$A = \int_0^\infty I(t,0)\,dt = S(0) - S(\infty).$$

The case fatality proportion is

$$c_\tau = \int_0^\tau \frac{D(a)}{A}\,da = \frac{\int_0^\tau \delta(a)\int_0^\infty I(t,a)\,dt\,da}{A}. \tag{27}$$

Let $u(a,s) = I(s+a,a)$, where $t = s+a$ (see, e.g., Thieme, 2003), then

$$\frac{\partial u}{\partial a}(a,s) = \frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} = -\big[\gamma(a)+\delta(a)\big]I(s+a,a) = -\big[\gamma(a)+\delta(a)\big]u.$$

Integrating with respect to a gives

$$I(s+a,a) = u(a,s) = u(0,s)e^{-\int_0^a[\gamma(x)+\delta(x)]\,dx}.$$

Hence,

$$I(t,a) = I(t-a,0)e^{-\int_0^a[\gamma(x)+\delta(x)]\,dx}. \tag{28}$$

Substituting (28) into (27) gives

$$\begin{aligned} c_\tau &= \frac{1}{A}\int_0^\tau \delta(a)\int_0^\infty I(t-a,0)e^{-\int_0^a[\gamma(x)+\delta(x)]\,dx}\,dt\,da, \\ &= \frac{1}{A}\int_0^\tau \delta(a)e^{-\int_0^a[\gamma(x)+\delta(x)]dx}\int_0^\infty I(t-a,0)\,dt\,da. \end{aligned}$$

Assume that $\int_{-\infty}^0 I(t,a)\,dt \ll 1$, then

$$\int_0^\infty I(t-a,0)\,dt = \int_{-a}^0 I(t,0)\,dt + \int_0^\infty I(t,a)\,dt \approx A.$$

Hence, the case fatality proportion is approximately equal to

$$c_\tau = \int_0^\tau \delta(a)e^{-\int_0^a[\gamma(x)+\delta(x)]\,dx}\,da. \tag{29}$$

From (29)

$$c_\tau = \int_0^\tau \frac{\delta(a)}{\gamma(a)+\delta(a)}\big[\gamma(a)+\delta(a)\big]e^{-\int_0^a[\gamma(x)+\delta(x)]\,dx}\,da,$$

where $[\gamma(a)+\delta(a)]e^{-\int_0^a[\gamma(x)+\delta(x)]\,dx}$ is the probability density that an infected individual leaves class I at age of infection a, and $\frac{\delta(a)}{\gamma(a)+\delta(a)}$ is the probability that an individual dies when exiting class I at age of infection a. Thus, (29) has a similar interpretation to (16), i.e., it is the "sum" of the probability of disease induced death times the survival probability for the period of infection up to infection age τ. As $\tau \to \infty$, (29) for c_∞ agrees with Day (2002).

Fung and Yu (2003) use a different definition for the case fatality proportion for SARS that depends on the progression of epidemics. Specifically, they studied the ratio of the number of disease induced deaths to the sum of disease induced deaths and recoveries within a given period of time after the epidemic started. Mathematically, that is

$$\hat{c}_\tau = \frac{\int_0^\tau\int_0^\infty \delta(a)I(t,a)\,da\,dt}{\int_0^\tau\int_0^\infty[\gamma(a)+\delta(a)]I(t,a)\,da\,dt}. \tag{30}$$

This is not in general equivalent to (29). In fact, it is equivalent to (29) with $\tau \to \infty$ if and only if δ and γ do not depend on a. In this special case, they both reduce to (6) with $\mu = 0$. However, for most diseases the infectious and time-to-death period distributions are not exponential. Thus γ and δ usually depend on a, and thus $\hat{c}_\tau$ depends on $I(t, a)$ for $0 \le t \le \tau$. This means that the transmission process affects $\hat{c}_\tau$. Yet case fatality proportion describes the probability of an individual dying from the disease *after* becoming infected, which in general should be independent of the transmission process, as we have discovered in the homogeneously mixed models considered previously.

7. Conclusion

We have discussed how to compute the case fatality proportion using an excess death rate in models that describe disease induced deaths. Mathematically, it is the sum of the probability of dying from the disease at a given stage times the probability that an individual survives to the given stage. This formula gives us a relationship among the excess death rates and the case fatality proportion. Since the excess death rate is usually difficult to measure, while survival probability and case fatality are usually measurable, this formula can be used to estimate the excess death rates.

The case fatality proportion formulas derived give relationships between the case fatality proportion and the excess mortality rate. For example, from (6),

$$\delta = \frac{c(\mu + \gamma)}{1 - c}; \tag{31}$$

as Day (2002, Eq. (2.15)). The parameters c, μ, and γ can be estimated from data, thus giving an estimate of δ. This formula (31) is used by Chowell et al. (2006) to estimate the mortality rates for the 1918 pandemic influenza in Geneva, which were found to be 0.008 for the spring wave, and 0.02 for the fall wave.

For some diseases (e.g., SARS and influenza), the case fatality proportion depends on the chronological age of the patients. For SARS, it is reported (Donnelly et al., 2003; Anderson et al., 2004) that the case fatality proportion was 6.8% for patients younger than 60 years, and 55% for patients older than 60. Our multi-group model in Section 4, with $n = 2$ representing younger and older age groups, can be applied to this situation.

The case fatality proportion, by our definition, does not depend on the transmission process, if every infected individual has the same probability of dying from the disease, as demonstrated by the vector-transmitted disease model in Section 2. This means that the results hold for both $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$. However, it may depend on the age of infection and/or chronological age. As stated above, the chronological age dependence can be handled by our multi-group model. Its dependence on age of infection can be handled as in (29).

For simplicity, we have not discussed compartmental models with loss of immunity, or more general force of infection. But for homogeneously mixed models, the same techniques can be applied, and the case fatality formulas are identical, since these do not depend on the flow rate from susceptible to the first infectious stage.

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