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Mathematical models of Ebola—Consequences of underlying assumptions

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ABSTRACT

Mathematical models have been used to study Ebola disease transmission dynamics and control for the recent epidemics in West Africa. Many of the models used in these studies are based on the model of Legrand et al. (2007), and most failed to accurately project the outbreak's course (Butler, 2014). Although there could be many reasons for this, including incomplete and unreliable data on Ebola epidemiology and lack of empirical data on how disease-control measures quantitatively affect Ebola transmission, we examine the underlying assumptions of the Legrand model, and provide alternate formulations that are simpler and provide additional information regarding the epidemiology of Ebola during an outbreak. We developed three models with different assumptions about disease stage durations, one of which simplifies to the Legrand model while the others have more realistic distributions. Control and basic reproduction numbers for all three models are derived and shown to provide threshold conditions for outbreak control and prevention.

1. Introduction

Mathematical models have been very helpful in evaluating and identifying alternative strategies for infectious disease control and prevention. However, for the recent epidemics of Ebola in West Africa, the success of mathematical models has been very limited. As pointed out in Butler [2], "mathematical models have failed to accurately project the outbreak's course". Although various reasons may explain why "on-the-ground data contradict the projections of published models", including incomplete and unreliable data on Ebola epidemiology (especially in the hardest-hit areas) and lack of empirical data on how disease-control measures quantitatively affect Ebola transmission, it is important to examine the appropriateness of assumptions made in the models on which the projections are based. This is the objective of the current paper. There have been various modeling approaches, including deterministic and stochastic models, or relatively simple models consisting of ordinary differential equations (ODEs) and more complicated agent-based models, among others. Many of the ODE models are variations of the model studied by Legrand et al. [8], to which we refer as the Legrand model. It has been pointed out that some of the assumptions made in the Legrand model may not have clear justifications (see, for example, Rivers et al. [11]). Thus, it is important to examine the critical assumptions made in this model and better understand their possible impact on model outcomes.

It often happens that, when a model is formulated, certain assumptions are made without consideration of their consequences. One of the most common assumptions made in ODE models is the exponential waiting time in disease stages. That is, the survival probability is described by a negative exponential function. For example, if the model assumes that an infected individual will recover at a constant per-capita rate γ, then it implicitly assumes that the infectious period is exponentially distributed, and the probability that an individual is still infectious $s > 0$ units of time since onset is given by

$$P_I(s) = e^{-\gamma s}.$$

That is, if X_I denotes the random variable for the waiting time in the infectious class I before exiting, then

$$\mathbb{P}[X_I > s] = P_I(s) = e^{-\gamma s}.$$

In this case, the average waiting time before recovery (or the mean infectious period) is given by

$$\mathbb{E}[X_I] = \int_0^\infty P_I(s)ds = \frac{1}{\gamma}.$$

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Table 1
Definition of symbols commonly used in all models including arbitrary stage distributions.

Symbol	Definition
T_P, T_L, T_M	Random variables for the waiting times in I before moving to R, H, D, respectively
X_I	Random variable for the overall time spent in the I compartment
X_H	Random variable for the overall time spent in the H compartment
$P_i(s)$	Probability that a living individual remains infectious s units of time since onset for Models I, II, III when $i = 1, 2, 3$, respectively. That is, $\mathbb{P}[T_{P_i} > s] = P_i(s)$
$L_i(s)$	Probability of a living individual not being hospitalized s units of time since onset for Models I, II when $i = 1, 2$, respectively. That is, $\mathbb{P}[T_{L_i} > s] = L_i(s)$
$M_1(s)$	Probability of surviving the disease s units of time since onset for Model I. That is, $\mathbb{P}[T_{M_1} > s] = M_1(s)$
$Q_3(s)$	Probability of not having recovered s units of time after being hospitalized for Model III
$\mathbb{E}[T_P]$	Mean duration from onset to recovery (absent intervention or death)
$\mathbb{E}[T_L]$	Mean duration from onset to hospitalization (given hospitalized and not dead)
$\mathbb{E}[T_M]$	Mean duration between onset and death (absent intervention or recovery)
$\mathbb{E}[X_I]$	Mean duration in the I compartment (hospitalization and death included)
$\mathbb{E}[X_H]$	Mean duration in the H compartment (death included)
$\mathcal{D}_{HR}$	Mean duration from hospitalization to recovery
$\mathcal{D}_{HD}$	Mean duration from hospitalization to death
γ_{IR}	$= 1/\mathbb{E}[T_P]$,
γ_{IH}	$= 1/\mathbb{E}[T_L]$,
γ_{ID}	$= 1/\mathbb{E}[T_M]$,
ω_{HR}	$= 1/\mathcal{D}_{HR}$, per-capita rate of transition from H to R if the transition is exponential
ω_{HD}	$= 1/\mathcal{D}_{HD}$, per-capita rate of transition from H to D if the transition is exponential
p	Proportion hospitalized (dependent on control effort)
f	Probability of death (with or without hospitalization)
γ	$= 1/\mathbb{E}[X_I]$, per-capita rate of exiting I if X_I is exponential

Because of the memoryless property of exponential distributions, this leads to ODE models that are easy to analyze. However, when isolation of infectious individuals is considered as a control strategy, models with exponentially distributed infectious stages can lead to misleading or even incorrect evaluations of effectiveness (see, e.g., Feng et al. [4]). Similar results hold for discrete-time models, in which the analogue of the exponential distribution is geometric [5,6]. These findings demonstrate some of the drawbacks of ODEs models with exponentially-distributed disease stages.

It is not clearly specified in the Legrand model (see model (A.1) in Appendix A) what underlying assumptions have been made regarding the distributions of waiting times for epidemiological processes such as recovery (transition from I to R), hospitalization (transition from I to H), and death (transition from I to D). For ease of reference, we refer to these three transitions as IR, IH, and ID, respectively. In addition, the two possible transitions for hospitalized individuals, recovery or death, are denoted by HR and HD. Let T_P, T_L and T_M denote random variables for the waiting times associated with IR, IH and ID, and let the associated survival functions be denoted by $P(t)$, $L(t)$ and $M(t)$, respectively. The mean durations of these transitions are respectively $\mathbb{E}[T_P]$, $\mathbb{E}[T_L]$, $\mathbb{E}[T_D]$. Similarly, let $\mathcal{D}_{HR}$ and $\mathcal{D}_{HD}$ denote the mean durations from hospitalization to recovery or death, respectively. For ease of comparison between models presented in this paper, we list in Table 1 some of the quantities that play common roles and have clear biological meaning in these models. Several of these quantities should have values that are independent of model assumptions, including the mean duration (absent intervention) from onset to recovery $\mathbb{E}[T_P]$, the probability of hospitalization p, and the probability of death f.

At first glance (A.1) (see Appendix A), it may seem that the transitions IR, IH and ID are assumed to be independent in the Legrand model and the waiting times are all exponentially distributed with mean durations $1/\gamma_{IR}$, $1/\gamma_{IH}$ and $1/\gamma_{ID}$, respectively. If so, however, the mean overall rate of exiting the I compartment would not be given by Δ in (A.5) (see Table 2 and Appendix A). In fact, if we denote the survival functions by $P(t) = e^{-\gamma_{IR}t}$, $L(t) = e^{-\gamma_{IH}t}$ and $M(t) = e^{-\gamma_{ID}t}$, respectively, then the overall waiting time in I is

$$\begin{aligned}\mathbb{P}[\min\{T_P, T_L, T_M\} > t] &= \mathbb{P}[\{T_P > t\} \cap \{T_L > t\} \cap \{T_M > t\}] \\ &= \mathbb{P}[T_P > t]\mathbb{P}[T_L > t]\mathbb{P}[T_M > t].\end{aligned}$$

Thus, the mean overall time spent in the I compartment is

$$\mathbb{E}[\min\{T_P, T_L, T_M\}] = \int_0^\infty P(t)L(t)M(t)dt = \frac{1}{\gamma_{IR} + \gamma_{IH} + \gamma_{ID}}.$$

It follows that the overall rate of exiting I is $\gamma_{IR} + \gamma_{IH} + \gamma_{ID}$, which is not a weighted average, unlike Δ in (A.5) for the Legrand model.

To fully understand the underlying assumptions used in the Legrand model, we develop three models based on general distributions for the waiting times of key transitions and consider various assumptions about their relationships. We demonstrate that, when specific stage distributions are considered, one of these general models reduces to the Legrand model (A.1). The models that we develop in this paper under arbitrarily distributed disease stages consist of integro-differential equations. It has been asserted that, when the arbitrary distributions are replaced by Gamma distributions, the so-called "linear chain trick" can be applied to reduce the integral equations to ODEs (MacDonald [10], Hethcote and Tudor [7], Lloyd [9]). However, apart from a proof of the linear chain trick in a simpler setting by Smith [13, Section 7.1], a rigorous derivation of this fact for more complex epidemic models, such as the one in this paper, is lacking. In this paper, we provide a derivation (see Section 3).

We also provide a simpler (but equivalent) formulation of the Legrand model. In particular, we define the overall waiting time in the I class to be the weighted combination of waiting times $\mathbb{E}[T_P]$, $\mathbb{E}[T_L]$ and $\mathbb{E}[T_M]$ of the following form:

$$\mathbb{E}[X_I] = p\mathbb{E}[T_H] + (1-p)f\mathbb{E}[T_M] + (1-p)(1-f)\mathbb{E}[T_P], \tag{1}$$

where p and f denote the probability of hospitalization and case-fatality, respectively. Using this assumption, as shown in Section 2, we obtain a much simpler formulation of the Legrand model (A.1). This facilitates identification of its underlying assumptions, as illustrated in Sections 3 and 4.

Our paper is organized as follows. In Section 2, we present an equivalent Legrand model with a simpler formulation. Section 3 is devoted to the derivation of three models with arbitrarily distributed disease stages under various assumptions about the relationships between the overall waiting time in the I class and

Table 2
Connection between parameters in the Legrand model (A.1) and the equivalent model (2).

Symbol	Definition
γ_{IR} (γ_i)	$= 1/\mathbb{E}[T_P]$, per-capita rate of transition from I to R when T_P is exponential
γ_{IH} (γ_h)	$= 1/\mathbb{E}[T_L]$, per-capita rate of transition from I to H when T_L is exponential
γ_{ID} (γ_d)	$= 1/\mathbb{E}[T_M]$, per-capita rate of transition from I to D when T_M is exponential
ω_{HR} (γ_{ih})	$= 1/\mathcal{D}_{HR}$, per-capita rate of transition from H to R if the transition is exponential
ω_{HD} (γ_{dh})	$= 1/\mathcal{D}_{HD}$, per-capita rate of transition from H to D if the transition is exponential
p (θ_1)	Proportion hospitalized
f ($f_i = f_h, \delta$)	Probability of death (with or without hospitalization)
$\frac{1}{\gamma}$	$= \mathbb{E}[X_I] \triangleq p\mathbb{E}[T_H] + (1-p)f\mathbb{E}[T_M] + (1-p)(1-f)\mathbb{E}[T_P] = \frac{p}{\gamma_{IH}} + \frac{(1-p)f}{\gamma_{ID}} + \frac{(1-p)(1-f)}{\gamma_{IR}}$
(Δ)	$= \frac{1}{\mathbb{E}[X_I]} \triangleq \theta_1\gamma_h + (1-\theta_1)\delta_1\gamma_d + (1-\theta_1)(1-\delta_1)\gamma_i$
$\frac{1}{\omega}$	$= \mathbb{E}[X_H] \triangleq f\mathcal{D}_{HD} + (1-f)\mathcal{D}_{HR} = \frac{f}{\omega_{HD}} + \frac{1-f}{\omega_{HR}}$
(δ_1)	$= \frac{\delta\gamma_i}{\delta\gamma_i + (1-\delta)\gamma_{dh}}$

Note: The symbols in parentheses are those used in the Legrand model (A.1).

those for recovery, hospitalization and death. It is shown that these integro-differential equation models reduce to ODE models when the distributions are Gamma or exponential. One of these ODE models is shown to be equivalent to the Legrand model. Basic and control reproduction numbers for these general models are derived in Section 4. The three models and the Legrand model are compared in Section 5. Discussions of the results are included in Section 6. The Appendices collect the detailed proofs of results.

2. An equivalent and simpler formulation of the Legrand model

The Ebola model studied by Legrand et al. [8] has been widely cited. Their model consists of a system of ordinary differential equations with six compartments representing the epidemiological classes of susceptible (S), exposed (E), infectious (I), hospitalized (H), dead but not yet buried (D) and removed (R). For ease of presentation, the Legrand model is provided in Appendix A, and we provide in this section a simpler but equivalent formulation (with only a minor difference that dead individuals are removed from the population after being buried in our formulation, instead of entering the R class as in Legrand model). Let β_I, β_H and β_D denote the transmission rates in the I, H and D classes, respectively; $1/\alpha$ be the mean latent period; and $1/\gamma_f$ be the mean time between death and burial. We show in Appendix A that the Legrand model is equivalent to the following system

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D),\\
\frac{dE}{dt} &= \frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D) - \alpha E,\\
\frac{dI}{dt} &= \alpha E - \gamma I,\\
\frac{dH}{dt} &= p\gamma I - \omega H,\\
\frac{dD}{dt} &= (1-p)f\gamma I + f\omega H - \gamma_f D,\\
\frac{dR}{dt} &= (1-p)(1-f)\gamma I + (1-f)\omega H,
\end{aligned} \tag{2}$$

where $1/\gamma$ is the average overall time in the I compartment, and $1/\omega$ is the average overall time in the H compartment, which are *defined* as

$$\begin{aligned}
\frac{1}{\gamma} &:= p\mathbb{E}[T_H] + (1-p)f\mathbb{E}[T_M] + (1-p)(1-f)\mathbb{E}[T_P],\\
\frac{1}{\omega} &:= f\mathcal{D}_{HD} + (1-f)\mathcal{D}_{HR}.
\end{aligned} \tag{3}$$

In the case when the waiting time for all transitions IR, IH, ID, HR, and HD are exponential, the equations in (3) become (using the notation given in Table 1)

$$\begin{aligned}
\frac{1}{\gamma} &= p\frac{1}{\gamma_{IH}} + (1-p)f\frac{1}{\gamma_{ID}} + (1-p)(1-f)\frac{1}{\gamma_{IR}},\\
\frac{1}{\omega} &= f\frac{1}{\omega_{HD}} + (1-f)\frac{1}{\omega_{HR}}.
\end{aligned} \tag{4}$$

The Legrand model also imposes the following constraints to balance the times spent in related stages (e.g., the total time spent from I to R equals the summation of the times spent from I to H and from H to R):

$$\begin{aligned}
\frac{1}{\gamma_{IR}} &= \frac{1}{\gamma_{IH}} + \frac{1}{\omega_{HR}},\\
\frac{1}{\gamma_{ID}} &= \frac{1}{\gamma_{IH}} + \frac{1}{\omega_{HD}}.
\end{aligned} \tag{5}$$

We show in the Appendix that the model (2) with the conditions in (4) is equivalent to the Legrand model (A.1). However, the presentation of the model formulation (2) is much simpler and easier to follow than that of (A.1). Moreover, the system (2) facilitates derivation of the control reproduction number $\mathcal{R}_c$, which (based on the next generation matrix approach) is

$$\mathcal{R}_c = \frac{\beta_I}{\gamma} + p\frac{\beta_H}{\omega} + f\frac{\beta_D}{\gamma_f}. \tag{6}$$

We remark that the computation from model (2) does not require any of the γ_j in Table 1, or the intermediate parameters, such as θ_1, δ_1 and δ_2, used in Legrand model (A.1). Most importantly, the simpler structure and presentation of the equivalent model (2) provides added transparency for identifying the underlying assumptions in the Legrand model and three other ODE models considered in the following sections.

3. Models with general distributions for disease stages

To examine the underlying assumptions in the Legrand or equivalent model (2), and to provide more accurate evaluations of disease control strategies, we develop models using more realistic assumptions about the disease stage distributions. In this section, we formulate three models based on different assumptions about the relationship between the overall waiting time in the I class and the waiting times from onset to hospitalization, recovery without hospitalization, and death without hospitalization. We illustrate that these various assumptions lead to different models. We will adopt probabilistic terminology to facilitate the interpretation of our deterministic model, and focus on the following three scenarios:

(I) Assume that the three transitions IR, IH and ID are *independent* and the waiting times are described by the survival

functions $P_1(s)$, $L_1(s)$ and $M_1(s)$, respectively, where s represents the time-since-onset. It is also assumed that hospitalization does not affect the time from onset to recovery or death.

(II) The two transitions IR and ID are *combined* and described by a single survival function $P_2(s)$, with a fraction $1-f$ of the exiting individuals recovering (and the fraction f dying). The transition IH is independent of IR and ID and the waiting time is described by the survival function $L_2(s)$. Similar to Model I, it is also assumed that hospitalization does not affect the time from onset to recovery or probability of death.

(III) All three transitions (IH, IR, and ID) are combined and described by a single survival function $P_3(s)$, with a fraction p of the exiting individuals being hospitalized and a fraction $1-f$ (respectively, f) of the non-hospitalized individuals recovering (respectively, dying). The two transitions HR and HD are combined and the waiting time is described by a single survival function $Q_3(s)$ with a fraction $1-f$ (or f) of the exiting individuals recovering (or dying). P_3 and Q_3 are assumed to be independent. Unlike Models I and II, in which the time from onset to hospitalization is tracked due to the independent stage distributions, in Model III a constraint must be imposed so that the time between onset and hospitalization plus the time between hospitalization and recovery (or death) equals the time between onset and recovery (or death).

Because we focus on the general waiting time for the infectious stage and its influence on model formulation when hospitalization is considered, we assume simpler distributions for other stages including the latent stage and the interval between death and burial. That is, the E and D stages are assumed to have exponential distributions with constant rates α and γ_f. As the models are derived under arbitrary distributions for the waiting times of key disease stages, they consist of systems of integro-differential equations. We show that these systems reduce to ODE systems when the arbitrary stage distributions are replaced by Gamma or exponential distributions.

We introduce the following notation for two conditional probabilities, which will be used later in this section. Let s denote the time of onset. The conditional probability of being still infectious at time t, given that the individual was hospitalized at time τ ($s < \tau < t$), is given by:

$$P_1(t-s|\tau-s) := \frac{\mathbb{P}[T_{P_1} > t-s]}{\mathbb{P}[T_{P_1} > \tau-s]} = \frac{P_1(t-s)}{P_1(\tau-s)}. \tag{7}$$

Similarly, the assumption that hospitalization does not affect the time from onset to death implies that the conditional probability of being still alive at time t, given being alive and hospitalized at τ ($s < \tau < t$), is given by:

$$M_1(t-s|\tau-s) := \frac{\mathbb{P}[T_{M_1} > t-s]}{\mathbb{P}[T_{M_1} > \tau-s]} = \frac{M_1(t-s)}{M_1(\tau-s)}. \tag{8}$$

3.1. Model I

The model identified as (**I**) is described in this section. Let T_{P_1}, T_{L_1}, and T_{M_1} denote random variables for the independent waiting times of IR, IH, and ID, respectively, that are described by the following survival functions

- $P_1(s)$: Probability that a living individual remains infectious s units of time since onset (governing both IR and HR).
- $L_1(s)$: Probability of a living individual not being hospitalized s units of time since onset (governing the IH transition).
- $M_1(s)$: Probability of surviving the disease s units of time since onset (governing both ID and HD).

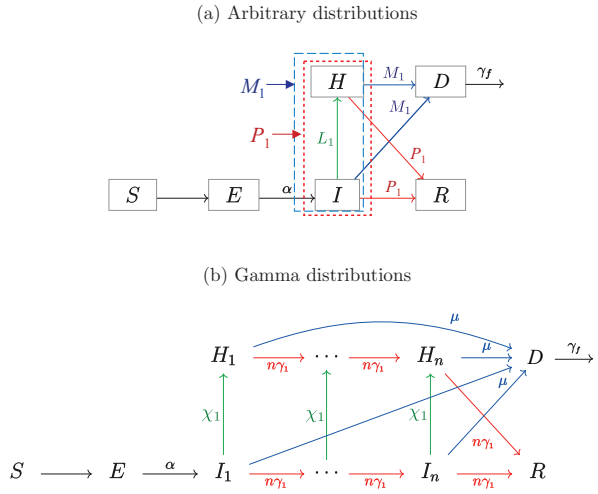


Fig. 1. Transition diagram for Model I when T_{P_1}, T_{L_1}, and T_{M_1} are (a) arbitrary, or (b) Gamma/exponential. The corresponding survival functions are $P_1(t)$ (red), $L_1(t)$ (green), and $M_1(t)$ (blue), respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 1 depicts the transitions between epidemiological classes for the model under scenario (I). All variables and parameters have the same meanings as before unless otherwise stated. The diagram in (a) depicts transitions between compartments when stage durations for the IR, IH, and ID transitions are described by the arbitrary survival functions $P_1(t)$, $L_1(t)$ and $M_1(t)$. The dotted rectangle around the I and H compartments indicates that individuals in these two compartments are being tracked for their time-since-onset using the same survival function $P_1(t)$; i.e., the time elapsed in I before entering H is taken into account when determining the time between entering H and recovery. The diagram in (b) illustrates the effect of the 'linear chain trick' when $P_1(t)$ follows a Gamma distribution, and $L_1(t)$ and $M_1(t)$ follow exponential survival functions. More details about the parameters for these distributions are given later (see also Remark 1 for explanations about the multiple compartments for the I and H classes).

The equations for the S and E classes are ODEs given by

$$\frac{dS}{dt} = -\lambda(t)S, \quad \frac{dE}{dt} = \lambda(t)S - \alpha E, \tag{9}$$

where $\lambda(t)$ denotes the force of infection (or hazard rate) given by

$$\lambda(t) = \frac{\beta_I I + \beta_H H + \beta_D D}{N}, \tag{10}$$

and $I = I(t)$ is the total number of infectious individuals given by

$$I(t) = \int_0^t \alpha E(s) P_1(t-s) L_1(t-s) M_1(t-s) ds + I(0) P_1(t) L_1(t) M_1(t). \tag{11}$$

The first term in (11) represents the total number of individuals at time t who became infectious $t-s$ units of time ago ($0 < s < t$) and have not recovered, been hospitalized or died by time t. The second term in (11) represents those individuals who were infectious at time 0 and are still in the I class at time t. Assume that the number of initially infected individuals $I(0)$ is small and, for simplicity, that these individuals all have stage age 0 in I.

Let $g_{P_1} = -P_1'$, $g_{L_1} = -L_1'$ and $g_{M_1} = -M_1'$ denote the probability density functions of P_1, L_1 and M_1, respectively. These functions also give the rates of entering the R, H and D classes, respectively. Detailed explanations of the probabilistic underpinnings of integro-differential equations are given in Feng and Thieme [3] and Feng

et al. [4]. Differentiating the I (Eq. (11)) will generate inflow terms from I to R, H and D classes:

$$\begin{aligned} I'(t) = \alpha E(t) &- \left[\int_0^t \alpha E(s)P_1(t-s)g_{L_1}(t-s)M_1(t-s)ds \right. \\ &\left. + I(0)P_1(t)g_{L_1}(t)M_1(t)\right] \\ &- \left[\int_0^t \alpha E(s)P_1(t-s)L_1(t-s)g_{M_1}(t-s)ds \right. \\ &\left. + I(0)P_1(t)L_1(t)g_{M_1}(t)\right] \\ &- \left[\int_0^t \alpha E(s)g_{P_1}(t-s)L_1(t-s)M_1(t-s)ds \right. \\ &\left. + I(0)g_{P_1}(t)L_1(t)M_1(t)\right]. \end{aligned} \tag{12}$$

If an infectious individual entered the H class $\tau - s$ ($0 < s < \tau < t$) units after becoming infectious, then based on our assumption regarding the conditional probabilities $P_1(t-s|\tau-s)$ and $M_1(t-s|\tau-s)$ defined in (7) and (8), the H equation can be written as

$$\begin{aligned} H(t) &= \int_0^t \left[\int_0^\tau \alpha E(s)P_1(\tau-s)M_1 \right. \\ &\quad \times(\tau-s)g_{L_1}(\tau-s)P_1(t-s|\tau-s)M_1(t-s|\tau-s)ds \\ &\quad \left. +I(0)P_1(\tau)M_1(\tau)g_{L_1}(\tau)P_1(t-\tau|\tau)M_1(t-\tau|\tau)\right]d\tau, \\ &= \int_0^t \left[\int_0^\tau \alpha E(s)P_1(t-s)M_1(t-s)g_{L_1}(\tau-s)ds \right. \\ &\quad \left. +I(0)P_1(t)M_1(t)g_{L_1}(\tau)\right]d\tau, \\ &= \int_0^t \alpha E(s)P_1(t-s)M_1(t-s)\int_s^t g_{L_1}(\tau-s)d\tau ds \\ &\quad +I(0)P_1(t)M_1(t)\int_0^t g_{L_1}(\tau)d\tau, \\ &= \int_0^t \alpha E(s)P_1(t-s)M_1(t-s)[1-L_1(t-s)]ds \\ &\quad +I(0)P_1(t)M_1(t)[1-L_1(t)]. \end{aligned} \tag{13}$$

For the inflows to the D class, in addition to the term from the I equation there is also a term from the H equation. Differentiating the H (Eq. (13)), we have

$$\begin{aligned} H'(t) = &\int_0^t \alpha E(s)P_1(t-s)M_1(t-s)g_{L_1}(t-s)ds \\ &+I(0)P_1(t)M_1(t)g_{L_1}(t) \\ &-\int_0^t \alpha E(s)P_1(t-s)g_{M_1}(t-s)[1-L_1(t-s)]ds \\ &-I(0)P_1(t)g_{M_1}(t)[1-L_1(t)] \quad \text{(to } D \text{ class)} \\ &-\int_0^t \alpha E(s)g_{P_1}(t-s)M_1(t-s)[1-L_1(t-s)]ds \\ &-I(0)g_{P_1}(t)M_1(t)[1-L_1(t)] \quad \text{(to } R \text{ class)} \end{aligned} \tag{14}$$

From Eqs. (12) and (14), we obtain the equations for D and R:

$$\begin{aligned} D(t) = &\int_0^t \left[\int_0^\tau \alpha E(s)P_1(\tau-s)g_{M_1}(\tau-s)L_1(\tau-s)ds \right. \\ &\left. +I(0)P_1(\tau)g_{M_1}(\tau)L_1(\tau)\right]e^{-\gamma_f(t-\tau)}d\tau \\ &+\int_0^t \left[\int_0^\tau \alpha E(s)P_1(\tau-s)g_{M_1}(\tau-s)[1-L_1(\tau-s)]ds \right. \\ &\left. +I(0)P_1(\tau)g_{M_1}(\tau)[1-L_1(\tau)]\right]e^{-\gamma_f(u-\tau)}du \\ = &\int_0^t \left[\int_0^\tau \alpha E(s)P_1(\tau-s)g_{M_1}(\tau-s)ds \right. \\ &\left. +I(0)P_1(\tau)g_{M_1}(\tau)\right]e^{-\gamma_f(t-\tau)}d\tau \end{aligned} \tag{15}$$

and

$$\begin{aligned} R(t) = &\int_0^t \left[\int_0^\tau \alpha E(s)g_{p_1}(\tau-s)M_1(\tau-s)L_1(\tau-s)ds \right. \\ &\left. +I(0)g_{p_1}(\tau)M_1(\tau)L_1(\tau)\right]d\tau \\ &+\int_0^t \left[\int_0^\tau \alpha E(s)g_{p_1}(\tau-s)M_1(\tau-s)[1-L_1(\tau-s)]ds \right. \\ &\left. +I(0)g_{p_1}(\tau)M_1(\tau)[1-L_1(\tau)]\right]d\tau \\ = &\int_0^t \left[\int_0^\tau \alpha E(s)g_{p_1}(\tau-s)M_1(\tau-s)ds + I(0)g_{p_1}(\tau)M_1(\tau)\right]d\tau \end{aligned} \tag{16}$$

Using the equations derived above, we obtain the system of integro-differential equations for Model I:

$$\begin{aligned} &\frac{dS}{dt} = -\lambda(t)S, \qquad \frac{dE}{dt} = \lambda(t)S - \alpha E, \\ &I(t) = \int_0^t \alpha E(s)P_1(t-s)L_1(t-s)M_1(t-s)ds \\ &\qquad +I(0)P_1(t)L_1(t)M_1(t), \\ &H(t) = \int_0^t \alpha E(s)P_1(t-s)M_1(t-s)[1-L_1(t-s)]ds \\ &\qquad +I(0)P_1(t)M_1(t)[1-L_1(t)], \\ &D(t) = \int_0^t \left[\int_0^\tau \alpha E(s)P_1(\tau-s)g_{M_1}(\tau-s)ds \right. \\ &\qquad \left. +I(0)P_1(\tau)g_{M_1}(\tau)\right]e^{-\gamma_f(t-\tau)}d\tau, \\ &R(t) = \int_0^t \left[\int_0^\tau \alpha E(s)g_{p_1}(\tau-s)M_1(\tau-s)ds + I(0)g_{p_1}(\tau)M_1(\tau)\right]d\tau, \end{aligned} \tag{17}$$

where $\lambda(t)$ is given in (10). The initial condition is $(S(0), E(0), I(0), H(0), D(0), R(0)) = (S_0, E_0, I_0, 0, 0, 0)$, where S_0 and E_0 are positive constants.

We remark that, in system (17), the probability distributions for T_{P_1}, T_{L_1} and T_{M_1} are arbitrary. We show in the next section that, when these general distributions are replaced by Gamma distributions, the integral equations can be reduced to ODEs.

3.1.1. Reduction of Model I (17) to ODEs

In this section, we show that the system of integro-differential Eq. (17) for Model I can be reduced to a system of ordinary differential equations when T_{P_1}, T_{L_1} and P_{M_1} follow Gamma distributions. Note that, for a Gamma distribution with shape and rate parameters $(n, n\alpha)$ (where $n \geq 1$ is an integer), the probability density function $g(t)$ and the survival function $G(t)$ are given, respectively,

by

$$g(t) = \frac{n\alpha(n\alpha t)^{n-1}}{(n-1)!}e^{-n\alpha t}, \quad G(t) = \sum_{j=1}^{n}\frac{(n\alpha t)^{j-1}e^{-n\alpha t}}{(j-1)!}. \tag{18}$$

A derivation for the survival function $G(t)$ in (18) can be found in Section 5.6.1 of Ross [12], in which the Gamma density $g(t)$ is given by the derivative of the cumulative distribution function $\mathbb{P}[T_n \le t]$, where T_n is Gamma distributed and can be expressed as a sum from n to ∞ of Poisson probabilities. Thus, the survival function $G(t) = \mathbb{P}[T_n > t]$ is the sum from 0 to $(n-1)$ (or in our notation it is a summation for $j-1$ from 1 to n) of Poisson probabilities.

Consider the case when T_{P_1} follows a Gamma distribution with shape and rate parameters $(n, n\gamma_1)$ (where $n \ge 1$ is an integer), and T_{L_1} and T_{M_1} follow exponential distributions with parameters χ_1 and μ, respectively (i.e., Gamma distributions with shape parameter 1),

$$\begin{aligned} P_1(t) &= G^n_{n\gamma_1}(t) = \sum_{j=1}^{n}\frac{(n\gamma_1 t)^{j-1}e^{-n\gamma_1 t}}{(j-1)!},\\ L_1(t) &= G^1_{\chi_1}(t) = e^{-\chi_1 t},\\ M_1(t) &= G^1_{\mu}(t) = e^{-\mu t}. \end{aligned} \tag{19}$$

In this case, the I equation in (17) becomes

$$\begin{aligned} I(t) &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi_1(t-s)}\sum_{j=1}^{n}\frac{(n\gamma_1(t-s))^{j-1}e^{-n\gamma_1(t-s)}}{(j-1)!}ds\\ &\quad + I(0)e^{-\mu t}e^{-\chi_1 t}\sum_{j=1}^{n}\frac{(n\gamma_1 t)^{j-1}e^{-n\gamma_1 t}}{(j-1)!}\\ &\doteq \sum_{j=1}^{n} I_j(t), \end{aligned}$$

where

$$\begin{aligned} I_j(t) &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi_1(t-s)}\frac{(n\gamma_1(t-s))^{j-1}e^{-n\gamma_1(t-s)}}{(j-1)!}ds\\ &\quad + I(0)e^{-\mu t}e^{-\chi_1 t}\frac{(n\gamma_1 t)^{j-1}e^{-n\gamma_1 t}}{(j-1)!}, \end{aligned}$$

for $j = 1, \ldots, n$. Similarly, the hospitalized class can be written as

$$H(t) = \sum_{j=1}^{n} H_j(t)$$

with $H_j(t)$ being the functions given by

$$\begin{aligned} H_j(t) &= \int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{(n\gamma_1(t-s))^{j-1}e^{-n\gamma_1(t-s)}}{(j-1)!}(1-e^{-\chi_1(t-s)})ds\\ &\quad + I(0)e^{-\mu t}\frac{(n\gamma_1 t)^{j-1}e^{-n\gamma_1 t}}{(j-1)!}(1-e^{-\chi_1 t}), \end{aligned}$$

for $j = 1, \ldots, n$.

Then we can show (see the detailed derivation in Appendix B) that the system (17) is equivalent to the following system of ODEs:

$$\begin{aligned} \frac{dS}{dt} &= -\frac{1}{N}S\left(\beta_I\sum_{j=1}^{n}I_j + \beta_H\sum_{j=1}^{n}H_j + \beta_D D\right),\\ \frac{dE}{dt} &= \frac{1}{N}S\left(\beta_I\sum_{j=1}^{n}I_j + \beta_H\sum_{j=1}^{n}H_j + \beta_D D\right) - \alpha E,\\ \frac{dI_1}{dt} &= \alpha E - (n\gamma_1 + \chi_1 + \mu)I_1,\\ \frac{dI_j}{dt} &= n\gamma_1 I_{j-1} - (n\gamma_1 + \chi_1 + \mu)I_j, \quad \text{for } j = 2, \ldots n,\\ \frac{dH_1}{dt} &= \chi_1 I_1 - (n\gamma_1 + \mu)H_1,\\ \frac{dH_j}{dt} &= \chi_1 I_j + n\gamma_1 H_{j-1} - (n\gamma_1 + \mu)H_j, \quad \text{for } j = 2, \ldots n,\\ \frac{dD}{dt} &= \mu\sum_{j=1}^{n}I_j + \mu\sum_{j=1}^{n}H_j - \gamma_f D,\\ \frac{dR}{dt} &= n\gamma_1 I_n + n\gamma_1 H_n. \end{aligned} \tag{20}$$

Remark 1. System (20) is consistent with the ODE system obtained by applying the linear chain trick to the system of integro-differential equations (17), which implies that the Gamma distributed stage can be considered as a sequence of n sub-stages with equal length, each of which follows an exponential distribution with parameter γ_1 (see, for example, MacDonald [10], Hethcote and Tudor [7], Lloyd [9]). However, a rigorous proof for the reduction of integral equations to ODEs has not been provided. Note that, in this case, the diagram in Fig. 1(a) becomes Fig. 1(b), where the I and H stages are divided into n sub-stages, each of which follows an exponential distribution with parameter $n\gamma_1$. Because of the memoryless property of exponential distributions, the period between H_i and H_{i+1} is the same as that between I_i and I_{i+1}. We observe that the recovery rates from both I_n and H_n, as well as the transition rates from I_j to I_{j+1} and from H_j to H_{j+1} $(j = 1, \ldots, n-1)$ are all the same and equal to $n\gamma_1$.

Remark 2. When $n = 1$ (i.e., when $P_1(t)$ is an exponential survival function), model (20) resembles the Legrand model. However, because the exiting rates from I and H due to recovery are the same (γ_1), model (20) differs from the Legrand model (see Section 5.1.1 for more details).

3.2. Model II

In Model I, the three transitions IR, IH and ID are assumed to be independent, in which case the three transitions 'compete' for individuals in the I class. Another scenario is to consider only two independent transitions, one being hospitalization and the other combining recovery and death for those who are not hospitalized. In this case, we have two survival probability functions:

- $P_2(s)$: Probability of still being infectious *and* alive s time units after onset (governing all four transitions IR, ID, HR and HD).
- $L_2(s)$: Probability of not being hospitalized s time units after onset (governing the IH transition).

Assume that, for those who exit I without being hospitalized, a fixed fraction $1-f$ (or f) will recover (or die), an assumption of Legrand model. Assume also that individuals in I and H classes have the same probability of death (f), also as assumed in the Legrand model. The transition diagram is depicted in Fig. 2(a).

Let $g_{P_2} = -P_2'$ and $g_{L_2} = -L_2'$. Note that the I equation in this case is

$$I(t) = \int_0^t \alpha E(s)P_2(t-s)L_2(t-s)ds + I(0)P_2(t)L_2(t).$$

Differentiation yields

$$\begin{aligned} I'(t) = \alpha E(s) &- \underbrace{\left[\int_0^t \alpha E(s)P_2(t-s)g_{L_2}(t-s)ds + I(0)P_2(t)g_{L_2}(t)\right]}_{to\ H}\\ &- \underbrace{\left[\int_0^t \alpha E(s)g_{P_2}(t-s)L_2(t-s)ds + I(0)g_{P_2}(t)L_2(t)\right]}_{to\ D,R}. \end{aligned}$$

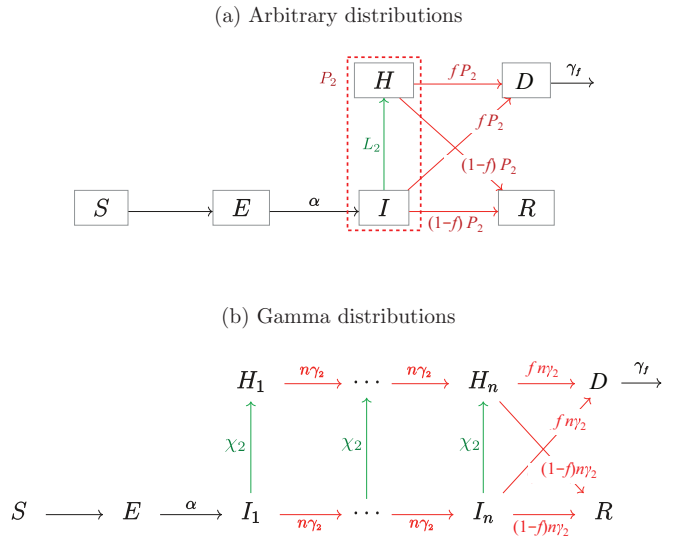


Fig. 2. A transition diagram for Model II (a) when T_{P_2} and T_{L_2} are arbitrary distributions and (b) when they are Gamma or exponential. In (a), the recovery/death (red) and hospitalization (green) transitions are governed by the survival functions P_2 and L_2. In (b), the recovery/death (red) and hospitalization (green) transitions are indicated by the same colors as in (a). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For the variable H, we have

$$\begin{aligned} H(t) &= \int_0^t \left[\int_0^\tau \alpha E(s) P_2(t-s) g_{L_2}(\tau - s) \right] ds d\tau \\ &\quad + \int_0^t I(0) P_2(t) g_{L_2}(\tau) d\tau \\ &= \int_0^t \alpha E(s) P_2(t-s)[1 - L_2(t-s)] + I(0) P_2(t)[1 - L_2(t)], \end{aligned}$$

and

$$\begin{aligned} H'(t) &= \int_0^t \alpha E(s) P_2(t-s) g_{L_2}(t-s) ds + I(0) P_2(t) g_{L_2}(t) \\ &\quad - \int_0^t \alpha E(s) g_{P_2}(t-s)[1 - L_2(t-s)] ds \\ &\quad - I(0) g_{P_2}(t)[1 - L_2(t)]. \end{aligned}$$

Then, using the assumption of fixed fraction of death (f), we arrive at the following system of equations for Model II:

$$\begin{aligned} \frac{dS(t)}{dt} &= -\lambda(t) S(t), \\ \frac{dE(t)}{dt} &= \lambda(t) S(t) - \alpha E(t), \\ I(t) &= \int_0^t \alpha E(s) P_2(t-s) L_2(t-s) ds + I(0) P_2(t) L_2(t), \\ H(t) &= \int_0^t \alpha E(s) P_2(t-s)[1 - L_2(t-s)] + I(0) P_2(t)[1 - L_2(t)], \\ D(t) &= f \int_0^t \left[\int_0^\tau \alpha E(s) g_{P_2}(\tau - s) ds + I(0) g_{P_2}(\tau) \right] e^{-\gamma_f (t-\tau)} d\tau, \\ R(t) &= (1-f) \int_0^t \left[\int_0^\tau \alpha E(s) g_{P_2}(\tau - s) ds + I(0) g_{P_2}(\tau) \right] d\tau. \end{aligned} \tag{21}$$

The function $\lambda(t)$ is the same as in Model I and given in (10).

3.2.1. Reduction of Model II to a system of ODEs

If T_{P_2} follows a Gamma distribution with parameters $(n, n\gamma_2)$ and T_{L_2} follows an exponential distribution with parameter χ_2, i.e., the survival functions are given by

$$\begin{aligned} P_2(t) &= G^n_{n\gamma_2}(t) = \sum_{j=1}^{n} \frac{(n\gamma_2(t-s))^{j-1} e^{-n\gamma_2(t-s)}}{(j-1)!}, \\ L_2(t) &= G^1_{\chi_2}(t) = e^{-\chi_2 t}, \end{aligned} \tag{22}$$

then, similar to the derivation of system (20) for Model I, we can reduce the integral equations in (3.2) to the ODEs given below:

$$\begin{aligned} \frac{dS}{dt} &= -\frac{1}{N} S(\beta_I \sum_{j=1}^{n} I_j + \beta_H \sum_{j=1}^{n} H_j + \beta_D D), \\ \frac{dE}{dt} &= \frac{1}{N} S(\beta_I \sum_{j=1}^{n} I_j + \beta_H \sum_{j=1}^{n} H_j + \beta_D D) - \alpha E, \\ \frac{dI_1}{dt} &= \alpha E - (n\gamma_2 + \chi_2) I_1, \\ \frac{dI_j}{dt} &= n\gamma_2 I_{j-1}(t) - (n\gamma_2 + \chi_2) I_j, \quad \text{for } j = 2, \ldots n, \\ \frac{dH_1}{dt} &= \chi_2 I_1 - n\gamma_2 H_1, \\ \frac{dH_j}{dt} &= \chi_2 I_j + n\gamma_2 H_{j-1} - n\gamma_2 H_j, \quad \text{for } j = 2, \ldots n, \\ \frac{dD}{dt} &= fn\gamma_2 I_n + fn\gamma_2 H_n - \gamma_f D, \\ \frac{dR}{dt} &= (1-f) n\gamma_2 I_n + (1-f) n\gamma_2 H_n. \end{aligned} \tag{23}$$

Because of the different assumptions made in Model II, the ODE reduction (23) differs from the ODE reduction (20) for Model I. This is more clearly illustrated in the transition diagram for (23) in Fig. 2(b). For example, we observe in Fig. 2(b) that transitions to R or D occur only to individuals in the last infectious and hospitalized compartments (I_n and H_n), whereas in Fig. 1(b), recovery and death can be from all the I_j and H_j ($j = 1, \ldots, n$) compartments. Observe also that the recovery rates from both I_n and H_n, as well as the transition rates from I_j to I_{j+1} and from H_j to H_{j+1} ($j = 1, \ldots, n-1$), are all the same and equal to $n\gamma_2$.

Remark 3. Note that the random variables T_{P_1} and T_{P_2} describe two very different transitions. Thus, the two parameters γ_1 and γ_2 in the Gamma survival functions $P_1 = G^n_{n\gamma_1}$ and $P_2 = G^n_{n\gamma_2}$ have very different meanings. That is, they have different connections with epidemiological parameters such as the infectious period. More detailed discussion of this point can be found in Section 5.

Remark 4. From the ODE model (23) or the transition diagram in Fig. 2(b), we observe that, in the case of $n = 1$, the rates from I to R and from H to R are the same. Therefore, as in the case of Model I, the ODE model (23) *cannot* be equivalent to the Legrand model. This suggests that the Legrand model does not assume that the hospitalization process is independent of the (combined) recovery and death processes.

3.3. Model III

Models I and II focus on the three exiting transitions from the I class. In Model III, both the transitions exiting the I and H classes are considered. Consider two independent distributions for the waiting times in I and H compartments, denoted by T_{P_3} and T_{Q_3}, with survival functions

- $P_3(s)$: Probability of remaining in the I class s units of time since onset (governing the transitions IR, IH and ID).
- $Q_3(s)$: Probability remaining in the H class s units of time after being hospitalized (governing the HR and HD transitions).

Let $p_3(t) = -P_3'(t)$ and $q_3(t) = -Q_3'(t)$ denote the probability density functions. P_3 describes the waiting time for the combined transitions, IR, IH and ID. Assume that among the individuals exiting the I class, fractions of p, $(1-p)f$, $(1-p)(1-f)$ will be hospitalized, non-hospitalized and dead, and non-hospitalized and recovered, respectively ($0 \le p, f < 1$). Q_3 describes the waiting time for the combined two transitions, HR and HD, and we assume that fractions $1-f$ and f of the hospitalized individuals recover and die, respectively.

In this case, Model III consists of the following system of integro-differential equations:

$$\begin{aligned}
&S'(t) = -\lambda(t)S(t), \qquad E'(t) = \lambda(t)S(t) - \alpha E(t),\\
&I(t) = \int_0^t \alpha E(s)P_3(t-s)ds + I(0)P_3(t),\\
&H(t) = \int_0^t p\left[\int_0^s \alpha E(\tau)p_3(s-\tau)d\tau + I(0)p_3(s)\right]Q_3(t-s)ds\\
&D'(t) = (1-p)f\left[\int_0^t \alpha E(s)p_3(t-s)ds + I(0)p_3(t)\right]\\
&\quad + f\int_0^t \left[p\int_0^s \alpha E(\tau)p_3(s-\tau)d\tau + pI(0)p_3(s)\right]q_3(t-s)ds - \gamma_f D(t),\\
&R'(t) = (1-p)(1-f)\left[\int_0^t \alpha E(s)p_3(t-s))ds + I(0)p_3(t)\right]\\
&\quad + (1-f)\int_0^t \left[p\int_0^s \alpha E(\tau)p_3(s-\tau)d\tau + pI(0)p_3(s)\right]q_3(t-s)ds.
\end{aligned} \tag{24}$$

Note that it is easier in this case to write equations for D' and H' than for D and H.

3.3.1. Reduction of Model III (24) to a system of ODEs

Assume that T_{P_3} and T_{Q_3} follow Gamma distributions with parameters $(n, n\gamma_3)$ and $(m, m\omega_3)$, respectively, i.e., the survival functions are given by

$$\begin{aligned}
P_3(t) &= G^n_{n\gamma_3}(t) = \sum_{j=1}^{n} \frac{[n\gamma_3(t-s)]^{j-1}e^{-n\gamma_3(t-s)}}{(j-1)!},\\
Q_3(t) &= G^m_{m\omega_3}(t) = \sum_{j=1}^{m} \frac{[m\omega_3(t-s)]^{j-1}e^{-m\omega_3(t-s)}}{(j-1)!}.
\end{aligned} \tag{25}$$

Then, the system (24) reduces to the following system of ODEs:

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{1}{N}S\left(\beta_I\sum_{j=1}^{n} I_j + \beta_H\sum_{j=1}^{m} H_j + \beta_D D\right)\\
\frac{dE}{dt} &= \frac{1}{N}S\left(\beta_I\sum_{j=1}^{n} I_j + \beta_H\sum_{j=1}^{m} H_j + \beta_D D\right) - \alpha E,\\
\frac{dI_1}{dt} &= \alpha E - n\gamma_3 I_1,\\
\frac{dI_k}{dt} &= n\gamma_3 I_{k-1} - n\gamma_3 I_k, \qquad k = 2,\dots,n\\
\frac{dH_1}{dt} &= pn\gamma_3 I_n - m\omega_3 H_1,\\
\frac{dH_k}{dt} &= m\omega_3 H_{k-1} - m\omega_3 H_k, \qquad k = 2,\dots,m\\
\frac{dD}{dt} &= (1-p)fn\gamma_3 I_n + fm\omega_3 H_m - \gamma_f D,\\
\frac{dR}{dt} &= (1-p)(1-f)n\gamma_3 I_n + (1-f)m\omega_3 H_m.
\end{aligned} \tag{26}$$

A transition diagram under the Gamma distributions for T_{P_3} and T_{Q_3}, for the ODE model (26) is shown in Fig. 3(b).We observe a major difference between this figure and Figs. 1(b) or 2(b) in the recovery rates from I_n and H_m, which have different values here. A similar difference exists in the transition rates from I_j to I_{j+1} ($j = 1,\dots,n-1$) and from H_j to H_{j+1} ($j = 1,\dots,m-1$).

Remark 5. As pointed out in Remark 3, the distributions T_{P_i} ($i = 1,2,3$) describe waiting times for three very different transitions. Thus, the three parameters γ_i ($i = 1,2,3$) in the Gamma survival functions $P_i = G^n_{n\gamma_i}$ have very different meanings and connections with epidemiological parameters such as the infectious period determined by γ_{IR}. More detailed discussion about this can be found in Section 5.

Remark 6. We observe from the ODE model (26) and diagram in Fig. 3(b) that, in the case of $n = m = 1$, the transition rates from I to R and from H to R can differ. This is a major difference between Model III and Models I and II. In fact, we show in Section 5.3 that, with an appropriate definition for γ_3 and ω_3 and the constraints (A.4), model (26) when $m = n = 1$ is the same as the model (2), which is equivalent to the Legrand model (A.1).

4. Reproduction numbers

In this section, we provide formulas for the control reproduction numbers for Models I, II and III. Both the general case of arbitrary distributions and special case of Gamma distribution are considered. These reproduction numbers are derived using two approaches, the next generation matrix and from biological interpretations. Denote the control reproduction numbers for Models I, II and III by $\mathcal{R}_{C1}$, $\mathcal{R}_{C2}$ and $\mathcal{R}_{C3}$, respectively.

4.1. Reproduction number $\mathcal{R}_{C1}$ for Model I

We derive the control reproduction number $\mathcal{R}_{C1}$ using two approaches, one using arguments based on the probabilistic transitions behind the integro-differential equations, which provide a formula for $\mathcal{R}_{C1}$ for general distributions. We present the formula under the specific distributions for T_{P_1}, T_{L_1} and T_{M_1} used in the ODE model (20). The other approach uses the next generation matrix for the ODE model (20).

Note that the expectations of T_j ($j = P_1, L_1, M_1$) represent mean times to recovery, hospitalization or death, respectively. The average time spent in the I compartment is $\mathbb{E}\left(\min\left\{T_{P_1}, T_{L_1}, T_{M_1}\right\}\right)$. Then

$$\begin{aligned}
\mathbb{P}[\min\{T_{P_1}, T_{L_1}, T_{M_1}\} > x] &= \mathbb{P}[\{T_{P_1} > x\} \cap \{T_{L_1} > x\} \cap \{T_{M_1} > x\}]\\
&= \mathbb{P}[T_{P_1} > x]\mathbb{P}[T_{L_1} > x]\mathbb{P}[T_{M_1} > x].
\end{aligned}$$

Thus,

$$\mathbb{E}(\min\{T_{P_1}, T_{L_1}, T_{M_1}\}) = \int_0^\infty P_1(t)L_1(t)M_1(t)dt.$$

Letting p_{M1} denote the probability of death for Model I, which includes two events, death before and during hospitalization, we have

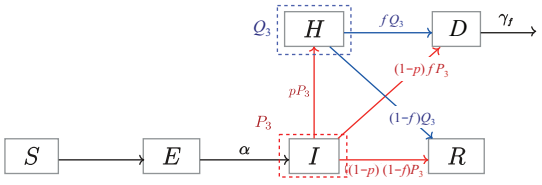
$$p_{M1} = \mathbb{P}[T_{M_1} = \min\{T_{P_1}, T_{L_1}, T_{M_1}\}] + \mathbb{P}[T_{L_1} < T_{M_1} < T_{P_1}].$$

Note that the average duration in the D compartment is $1/\gamma_f$. Then, based on the biological meaning of $\mathcal{R}_{C1}$, we obtain the following expression for $\mathcal{R}_{C1}$ under general stage distributions:

$$\begin{aligned}
\mathcal{R}_{C1} &= \beta_I\mathbb{E}(\min\{T_{P_1}, T_{L_1}, T_{M_1}\}) + \beta_H\mathbb{E}(\min\{T_{P_1}, T_{M_1}\})\\
&\quad -\mathbb{E}(\min\{T_{P_1}, T_{L_1}, T_{M_1}\})] + \beta_D\frac{1}{\gamma_f}p_M.
\end{aligned} \tag{27}$$

The formula (27) is convenient to use when specific survival functions for the waiting times T_j ($j = P_1, L_1, M_1$) are given. For example, consider the special case of Model I with $P_1(t) = G^n_{n\gamma_1}(t)$,

(a) Arbitrary distributions



(b) Gamma distributions

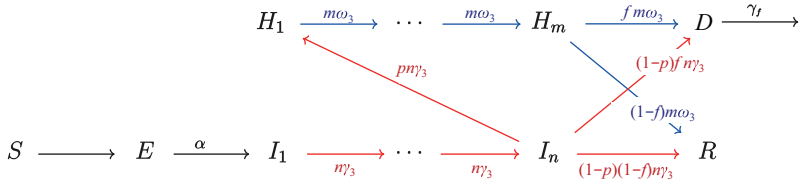


Fig. 3. A transition diagram for Model III (a) when T_{P_3} and T_{Q_3} are arbitrary distributions and (b) when they are Gamma or exponential.

$L_1(t) = e^{-\chi_1 t}$ and $M_1(t) = e^{-\mu t}$ (see (19)). Note that the average time in I is

$$\begin{aligned}\mathbb{E}(\min\{T_{P_1}, T_{L_1}, T_{M_1}\}) &= \int_0^\infty \sum_{k=1}^{n} \frac{(n\gamma_1 t)^{k-1} e^{-n\gamma_1 t}}{(k-1)!} e^{-\chi_1 t} e^{-\mu t} dt \\ &= \sum_{k=1}^{n} \int_0^\infty \frac{(n\gamma_1 t)^{k-1} e^{-(n\gamma_1+\chi_1+\mu)t}}{(k-1)!} dt \\ &= \frac{1}{\chi_1+\mu}\left[1 - \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^n\right], \end{aligned} \tag{28}$$

and the average total time in I and H is given by

$$\begin{aligned}\mathbb{E}(\min\{T_{P_1}, T_{M_1}\}) &= \int_0^\infty \sum_{k=1}^{n} \frac{(n\gamma_1 t)^{k-1} e^{-n\gamma_1 t}}{(k-1)!} e^{-\mu t} dt \\ &= \sum_{k=1}^{n} \int_0^\infty \frac{(n\gamma_1 t)^{k-1} e^{-(n\gamma_1+\mu)t}}{(k-1)!} dt \\ &= \frac{1}{\mu}\left[1 - \left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^n\right]. \end{aligned} \tag{29}$$

Thus, the average time spent in H is given by

$$\begin{aligned}\mathbb{E}(\min\{T_{P_1}, T_{M_1}\}) - \mathbb{E}(\min\{T_{P_1}, T_{L_1}, T_{M_1}\}) &= \frac{1}{\mu}\left[1 - \left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^n\right] \\ &- \frac{1}{\chi_1+\mu}\left[1 - \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^n\right]. \end{aligned} \tag{30}$$

Note also that

$$\begin{aligned} p_{M1} &= \mathbb{P}[T_{M_1} = \min\{T_{P_1}, T_{L_1}, T_{M_1}\}] + \mathbb{P}[T_{L_1} < T_{M_1} < T_{P_1}] \\ &= 1 - \left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^n. \end{aligned} \tag{31}$$

Substituting expressions (28)–(31) into (27), we arrive at the following expression

$$\begin{aligned}\mathcal{R}_{C1} &= \frac{\beta_I}{\chi_1+\mu}\left[1 - \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^n\right] \\ &+ \frac{\beta_H}{\mu}\left[\frac{\chi_1}{\chi_1+\mu} + \frac{\mu}{\chi_1+\mu}\left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^n \right. \\ &\left. - \left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^n\right] + \frac{\beta_D}{\gamma_f}\left[1 - \left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^n\right]. \end{aligned} \tag{32}$$

The next generation matrix approach for model (20) requires much more involved computations including the inverse of the transition matrix. The expression for $\mathcal{R}_C$ has the following form

$$\mathcal{R}_{C1} = \frac{\beta_I}{n\gamma_1+\chi_1+\mu}\sum_{j=1}^{n} q_{I_j} + \frac{\beta_H}{n\gamma_1+\mu}\sum_{j=1}^{n} q_{H_j} + \frac{\beta_D}{\gamma_f} p_{M1}, \tag{33}$$

where q_X denote the probabilities of being in compartment $X = I_j$ or H_j for $j = 1, \ldots, n$; i.e.,

$$\begin{aligned} q_{I_j} &= \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^{j-1}, \\ q_{H_j} &= \sum_{i=1}^{j}\left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^{i-1}\frac{\chi_1}{n\gamma_1+\chi_1+\mu}\left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^{j-i}, \\ & j = 1, \ldots, n, \end{aligned}$$

and p_{M1} denotes the probability of death for Model I, given by

$$p_{M1} = \frac{\mu}{n\gamma_1+\chi_1+\mu}\sum_{j=1}^{n} q_{I_j} + \frac{\mu}{n\gamma_1+\mu}\sum_{j=1}^{n} q_{H_j} = 1 - \left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^n. \tag{34}$$

In p_{M_1}, the first term corresponds to the probability of death without being hospitalized, whereas the second term corresponds to the probability of death after being hospitalized. Note that the average total times in I, H and D are

$$\sum_{j=1}^{n}\frac{q_{I_j}}{n\gamma_1+\chi_1+\mu}, \quad \sum_{j=1}^{n}\frac{q_{H_j}}{n\gamma_1+\mu}, \quad p_{M1}/\gamma_f,$$

respectively. Note also that

$$\begin{aligned}\sum_{j=1}^{n} q_{I_j} &= 1 + \frac{n\gamma_1}{n\gamma_1+\chi_1+\mu} + \cdots + \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^{n-1} \\ &= \sum_{j=1}^{n}\left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^{j-1} \\ &= \frac{n\gamma_1+\chi_1+\mu}{\chi_1+\mu}\left[1 - \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^n\right] \end{aligned}$$

and

$$\sum_{j=1}^{n} q_{H_j} = \sum_{j=1}^{n} \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^{j-1} \frac{\chi_1}{n\gamma_1+\chi_1+\mu}$$

(probability of path $I_1 \to I_j \to H_j$)

$$+\sum_{j=1}^{n}\sum_{i=1}^{j} \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^{i-1} \frac{\chi_1}{n\gamma_1+\chi_1+\mu} \left(\frac{n\gamma_1}{\gamma_1+\mu}\right)^{j-i}$$

(probability of path $I_1 \to I_i \to H_i \to H_j$)

$$= \sum_{k=1}^{n} \left(\frac{n\gamma_1}{n\gamma_1+\chi_1+\mu}\right)^{k-1} \frac{\chi_1}{n\gamma_1+\chi_1+\mu} \sum_{i=k}^{n} \left(\frac{n\gamma_1}{n\gamma_1+\mu}\right)^{i}.$$

Based on the biological meanings of the quantities involved in the expression for $\mathcal{R}_{C1}$ in (33), it is clear that the formula (33) describes the control reproduction number for the ODE model (20).

We repeat that the formula of $\mathcal{R}_{C1}$ for general distributions (27) is very helpful and convenient to use when specific stage distributions are considered. The derivation using probabilistic arguments also provides a contrast to the derivation of $\mathcal{R}_{C1}$ using the next-generation matrix approach, which requires intensive algebraic computations including the computation of the inverse of the transition matrix.

4.2. Reproduction number $\mathcal{R}_{C2}$ for Model II

As for Model I, we derive the formula for $\mathcal{R}_{C2}$ using two approaches.

For the derivation of $\mathcal{R}_{C2}$ using the a probabilistic processes, define two waiting times T_{P_2} and T_{L_2} corresponding to P_2 and L_2. The expectations of T_{P_2} and T_{L_2} are the infectious period and average time before hospitalization. Let $\mathbb{E}(T_{P_2})$ denote the expected total time spent in the I and H compartments and let $\mathbb{E}(\min\{T_{P_2}, T_{L_2}\})$ denote the expected time in the I compartment. Then the expected time spent in the H compartment is $\mathbb{E}(T_{P_2}) - \mathbb{E}(\min\{T_{P_2}, T_{L_2}\})$. Let $p_{H2} = \mathbb{P}[T_{L_2} < T_{P_2}]$, which denotes the probability of being hospitalized. Then, using these general notations, we can write the reproduction number $\mathcal{R}_{C2}$ as

$$\mathcal{R}_{C2} = \beta_I \mathbb{E}(\min\{T_{P_2}, T_{L_2}\}) + \beta_H[\mathbb{E}(T_{P_2}) - \mathbb{E}(\min\{T_{P_2}, T_{L_2}\})] + \beta_D \frac{1}{\gamma_f}[f(1-p_{H2}) + f p_{H2}]. \tag{35}$$

Consider the special case when $P_2 = G^n_{n\gamma_2}$ and $L_2 = G^1_{\chi_2}$ (see (22)). Note that

$$\begin{aligned}\mathbb{E}(\min\{T_{P_2}, T_{L_2}\}) &= \int_0^\infty \sum_{k=1}^{n} \frac{(n\gamma_2 t)^{k-1} e^{-n\gamma_2 t}}{(k-1)!} e^{-\chi_2 t} dt \\ &= \sum_{k=1}^{n} \int_0^\infty \frac{(n\gamma_2 t)^{k-1} e^{-(n\gamma_2+\chi_2)t}}{(k-1)!} dt \\ &= \frac{1}{n\gamma_2+\chi_2} \sum_{k=1}^{n} \left(\frac{n\gamma_2}{n\gamma_2+\chi_2}\right)^{k-1} \\ &= \frac{1}{\chi_2}\left[1 - \left(\frac{n\gamma_2}{n\gamma_2+\chi_2}\right)^{n}\right].\end{aligned}$$

The time spent in the H compartments is given by

$$\mathbb{E}(T_{P_2}) - \mathbb{E}(\min\{T_{P_2}, T_{L_2}\}) = \frac{1}{\gamma_2} - \frac{1}{\chi_2}\left[1 - \left(\frac{n\gamma_2}{n\gamma_2+\chi_2}\right)^{n}\right].$$

Note that $f(1-p_{H2}) + f p_{H2} = f$. Substituting these expressions into the general formula (35) for $\mathcal{R}_{C2}$, we obtain

$$\mathcal{R}_{C2} = \beta_I \frac{1}{\chi_2}\left[1 - \left(\frac{n\gamma_2}{n\gamma_2+\chi_2}\right)^{n}\right] + \beta_H\left[\frac{1}{\gamma_2} - \frac{1}{\chi_2}\left[1 - \left(\frac{n\gamma_2}{n\gamma_2+\chi_2}\right)^{n}\right]\right] + \beta_D \frac{f}{\gamma_f}. \tag{36}$$

When using the next generation matrix approach for the ODE model (23), we obtain

$$\mathcal{R}_{C2} = \beta_I \frac{1}{n\gamma_2+\chi_2} \sum_{k=1}^{n} q_{Ik} + \beta_H \frac{1}{n\gamma_2} \sum_{k=1}^{n} q_{Hk} + \beta_D \frac{1}{\gamma_f} p_{M2}, \tag{37}$$

where $p_{M2} = f$ and q_X is defined in the same way as in Section 4.1, although they have different expressions from those in Model I. It can be verified that the formula for $\mathcal{R}_{C2}$ is identical to (35).

4.3. Reproduction number $\mathcal{R}_{C3}$ for Model III

We can derive $\mathcal{R}_{C3}$ using the same two approaches as for Models I and II. Because the derivations are similar, we omit the details, and present the formula only for the special case when P_3 and Q_3 are both exponential, i.e., $P_3 = G^1_{\gamma_3}$ and $Q_3 = G^1_{\omega_3}$ (see (25)). In this case, the formula for $\mathcal{R}_{C3}$ for the ODE model (26) is *independent* of m and n, and is given by

$$\mathcal{R}_{C3} = \frac{\beta_I}{\gamma_3} + p\frac{\beta_H}{\omega_3} + f\frac{\beta_D}{\gamma_f}. \tag{38}$$

Remark 7. If we compare the $\mathcal{R}_{C3}$ formula with the $\mathcal{R}_C$ formula in (6), the two are identical when $\gamma_3 = \gamma$ and $\omega_3 = \omega$. This suggests again that model (26), as the reduction of Model III when $P_3(s)$ and $L_3(s)$ are exponential functions, is equivalent to the Legrand model.

5. Connections between the Legrand model and Models I, II and III

In this section, we compare the general Models I, II and III, particularly the ODE models (20), (23) and (26), which are their reductions when the distributions T_P, T_L, T_M, T_Q are Gamma or exponentially distributed. We investigate the key differences between these models and compare them with the Legrand model, which helps to identify its underlying assumptions.

The key difference between Models I, II and III (or between the ODE models (20), (23) and (26)) is in the parameters that define the stage distributions T_P, T_L, T_M and T_Q. Particularly, the parameters γ_j for the Gamma survival functions $P_j = G^n_{n\gamma_j}$ $(j = 1, 2, 3)$ have very different connections with other epidemiological parameters. Because the functions P_1, P_2 and P_3 describe different processes, γ_1, γ_2 and γ_3 have very different meanings. In fact, how the γ's are connected to other epidemiological parameters (e.g., the time between onset and recovery absent control, duration of hospitalization, time between onset and death, etc.) can play important role in model structure and outcomes, as well as the meaning of other parameters such as χ and μ.

5.1. Parameters in Model I and their connection to other parameters

When P_1, L_1 and M_1 are exponential with respective parameters γ_1, χ_1 and μ, because of the assumption in Model I that the three transitions IR, IH and ID are independent, the overall waiting time in the I compartment is also exponential with rate constant $\gamma_1 + \chi_1 + \mu$. From the definition of these parameters, we can link them to the general parameters (i.e., independent of model assumptions) in Table 1. For example,

$$\frac{1}{\gamma_1} = (1-p)(1-f)\frac{1}{\gamma_{IR}}, \tag{39}$$

where

$$\frac{1}{\gamma_{IR}} = \mathbb{E}[T_P].$$

Recall that $P(t)$ represents the marginal distribution for onset to recovery; and thus, $1/\gamma_{IR}$ is the mean time from onset to recovery for those who did not die or become hospitalized, a quantity independent of models. Similarly,

$$\frac{1}{\gamma_{IH}} = \mathbb{E}[T_L], \quad \frac{1}{\gamma_{ID}} = \mathbb{E}[T_M] \tag{40}$$

are the mean times from onset to hospitalization and death, respectively, which are independent of models.

The relation in (39) can also be written as

$$\gamma_1 = \frac{\gamma_{IR}}{(1-p)(1-f)}. \tag{41}$$

Note that the probability of death (see (31) with $n = 1$ and (41)) is given by

$$f = p_{M1} = 1 - \left(\frac{n\gamma_1}{n\gamma_1 + \mu}\right)^n = \frac{\mu}{\gamma_1 + \mu}. \tag{42}$$

From (41) and (42), we can solve for μ, i.e.,

$$\mu = \frac{\gamma_{IR} f}{(1-p)(1-f)^2}. \tag{43}$$

Notice also that the probability of hospitalization, which occurs before recovery or death, is (see Appendix C for a detailed derivation)

$$\begin{aligned} p &= p_{H1} \\ &= \mathbb{P}[T_{L_1} = \min\{T_{P_1}, T_{L_1}, T_{M_1}\}] \\ &= \int_{T_{P_1}, T_{M_1} > T_{L_1}} g_{P_1}(s) g_{M_1}(u) g_{L_1}(t) du dt ds, \\ &= \int_0^\infty \int_0^t \int_0^u g_{L_1}(s) ds\, g_{M_1}(u) du\, g_{P_1}(t) dt \quad (T_{P_1} \geq T_{M_1} \geq T_{L_1}) \\ &\quad + \int_0^\infty \int_0^u \int_0^t g_{L_1}(s) ds\, g_{P_1}(t) dt\, g_{M_1}(u) du \quad (T_{M_1} \geq T_{P_1} \geq T_{L_1}) \\ &= \frac{\chi_1}{\chi_1+\mu}\left[1 - \left(\frac{n\gamma_1}{\chi_1 + n\gamma_1 + \mu}\right)^n\right] = \frac{\chi_1}{\gamma_1+\chi_1+\mu} \quad (\text{for } n = 1). \end{aligned} \tag{44}$$

Using (41) and (44) we can solve for χ_1, i.e.,

$$\chi_1 = \frac{p\gamma_{IR}}{(1-p)^2(1-f)^2}. \tag{45}$$

Therefore, for Model I we can express the rates γ_1, χ_1, and μ in terms of only γ_{IR}, p and f.

In this case, the formula for $\mathcal{R}_{C1}$ in (27) simplifies to

$$\begin{aligned} \mathcal{R}_{C1} &= \frac{\beta_I}{\gamma_1+\chi_1+\mu} + \frac{\beta_H}{\gamma_1+\mu}\frac{\chi_1}{\gamma_1+\chi_1+\mu} + \frac{\beta_D}{\gamma_f}\frac{\mu}{\gamma_1+\mu} \\ &= \frac{\beta_I}{\gamma_1+\chi_1+\mu} + \frac{\beta_H p}{\gamma_1+\mu} + \frac{\beta_D f}{\gamma_f}. \end{aligned} \tag{46}$$

We remark that the formula for p_{H1} for Gamma distributions can also be calculated from the reduced ODE model (20) or by looking at all possible paths to enter any of the H_k (see Fig. 1(b)), which leads to

$$\begin{aligned} p_{H1} &= \sum_{k=1}^{n} \frac{\chi_1}{\chi_1 + n\gamma_1 + \mu}\left(\frac{n\gamma_1}{\chi_1 + n\gamma_1 + \mu}\right)^{k-1} \\ &= \frac{\chi_1}{\chi_1+\mu}\left[1 - \left(\frac{n\gamma_1}{\chi_1 + n\gamma_1 + \mu}\right)^n\right]. \end{aligned}$$

5.1.1. Comparison between Model I and the Legrand model

Consider the ODE formulation (20) of Model I. In the special case when P_1 is exponential (i.e., $P_1 = G^1_{\gamma_1}$), the ODE system reduces to

$$\begin{aligned} \frac{dS}{dt} &= -\frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D), \\ \frac{dE}{dt} &= \frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D) - \alpha E, \\ \frac{dI}{dt} &= \alpha E - (\gamma_1 + \chi_1 + \mu)I, \\ \frac{dH}{dt} &= \chi_1 I - (\gamma_1 + \mu)H, \\ \frac{dD}{dt} &= \mu I + \mu H - \gamma_f D, \\ \frac{dR}{dt} &= \gamma_1 I + \gamma_1 H. \end{aligned} \tag{47}$$

We can compare system (47) with system (2) (which is equivalent to the Legrand model).

First, note that in model (47) the per-capita transition rates from I to R and from H to R are both equal to γ_1, from which we have $\gamma_{IR} = \omega_{HR}$. This means that the constraints in (5) for model (2) cannot be satisfied. Thus, Model I cannot be equivalent to the Legrand model. This suggests that Legrand et al. did *not* assume that the three transitions of IR, IH and ID were described by independent exponential distributions and that the overall waiting time in the I compartment was the minimum of these three exponential waiting times.

Second, note that the exiting rate γ from I in (2) corresponds to the sum of rates $\gamma_1 + \chi_1 + \mu$ from the I compartment in (47). If we assume (based on the definitions of γ_1, p and f) that $\frac{1}{\chi_1} = p\frac{1}{\gamma_{IH}}$ and $\frac{1}{\mu} = f(1-p)\frac{1}{\gamma_{ID}}$, then the left- and right-hand-sides of the $1/\gamma$ equation in (4) are

$$\frac{1}{\gamma_1+\chi_1+\mu} \quad \text{and} \quad \frac{1}{\gamma_1} + \frac{1}{\chi_1} + \frac{1}{\mu},$$

respectively. Therefore, condition (4) does not hold for model (47).

Other discussions about the connections between parameters in the Legrand model and exiting rates from multiple infectious compartments are presented in Rivers et al. [11] and Browne et al. [1].

5.2. Parameters in Model II and their connection to other parameters

The key difference between Models I and II may become even more transparent by examining how the parameters such as γ_i and χ_i, which determine the stage duration functions $P_i(t)$ and $L_i(t)$ $(i = 1, 2)$, are connected to the common parameters listed in Table 1. For example, for Model I, when the stage durations are Gamma (P_1 and L_1) and exponential (M_1), the parameters γ_1, χ_1 and μ are linked to the common parameters as given in (41), (43), and (45). For Model II, consider model (23) in which $P_2(t) = G^n_{n\gamma_2}(t)$ and $L_2(t) = G^1_{\chi_2}(t) = e^{-\chi_2 t}$, with the fraction $1-f$ of the individuals exiting I recovering and the fraction f dying. Then, one way to link the parameter γ_2 to common parameters is to assume that the duration in I before recovery or death $(1/\gamma_2)$ is the weighted average of the durations $\mathcal{D}_{IR}$ and $\mathcal{D}_{ID}$ given not being hospitalized (see Table 1),

$$\frac{1}{\gamma_2} = (1-p)\left[(1-f)\frac{1}{\gamma_{IR}} + f\frac{1}{\gamma_{ID}}\right]. \tag{48}$$

From (48) and the fact that the probability of death is $\gamma_{ID}/(\gamma_{ID} + \gamma_{IR}) = f$, we can also solve for γ_2 and get

$$\gamma_2 = \frac{\gamma_{IR}}{2(1-p)(1-f)}. \tag{49}$$

From (41) and (49) we can observe the difference between γ_1 and γ_2 in terms of their connections with the common parameters listed in Table 1, particularly p, f and γ_{IR}.

Similar to the derivation of $p = p_{H1}$ for Model I, we can also get $p = p_{H2} = \chi_2/(\gamma_2 + \chi_2)$, from which we can compute χ_2:

$$\chi_2 = \frac{p\gamma_{IR}}{2(1-p)^2(1-f)}. \tag{50}$$

Then, for the ODE model (52), the formula for $\mathcal{R}_{C2}$ in (35) simplifies to

$$\mathcal{R}_{C2} = \frac{\beta_I}{\gamma_2 + \chi_2} + \frac{p\beta_H}{\gamma_2} + \frac{f\beta_D}{\gamma_f}. \tag{51}$$

5.2.1. Comparison of Model II with the Legrand model

In the special case when P_2 is exponential (i.e., $n = 1$), the ODE system (23) becomes

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D),\\
\frac{dE}{dt} &= \frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D) - \alpha E,\\
\frac{dI}{dt} &= \alpha E - (\gamma_2 + \chi_2)I,\\
\frac{dH}{dt} &= \chi_2 I - \gamma_2 H,\\
\frac{dD}{dt} &= f\gamma_2 I + f\gamma_2 H(t) - \gamma_f D(t),\\
\frac{dR}{dt} &= (1-f)\gamma_2 I + (1-f)\gamma_2 H.
\end{aligned} \tag{52}$$

For the same reason as in Model I (i.e., equal rates of recovery from I and H compartments in (52) and the constraint (A.4) in Legrand model), Model II or (52) cannot be the same as the Legrand model.

In addition, similar to the case of Model I, we can examine whether or not the condition (4) for γ in model (2) also holds for model (52). Note, from the I equations in the two models, that the γ in (4) corresponds to the sum of rates $\gamma_2 + \chi_2$ in (52) (total rate out of I), which implies that

$$\frac{1}{\gamma} = \frac{1}{\gamma_2 + \chi_2}. \tag{53}$$

However, from (48)) and $p = \chi_2/(\gamma_2 + \chi_2)$, we know that condition (4) does not hold in model (52).

5.3. Parameters in Model III and its equivalence to Legrand model

Recall that the ODE model (26), as the reduction of Model III, assumed that the distributions of overall times in the I and H compartments were two independent Gamma distributions with survival functions $P_3 = G^n_{n\gamma_3}$ and $Q_3 = G^m_{m\omega_3}$. Consider the special case when $n = m = 1$ (i.e., P_3 and Q_3 are exponential). The ODE model (26) simplifies to

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D),\\
\frac{dE}{dt} &= \frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D) - \alpha E,\\
\frac{dI}{dt} &= \alpha E - \gamma_3 I,\\
\frac{dH}{dt} &= p\gamma_3 I - \omega_3 H,\\
\frac{dD}{dt} &= (1-p)f\gamma_3 I + f\omega_3 H - \gamma_f D,\\
\frac{dR}{dt} &= (1-p)(1-f)\gamma_3 I + (1-f)\omega_3 H.
\end{aligned} \tag{54}$$

Notice that, if we ignore the last term in the R equation of the equivalent Legrand model (2) (this term indicates that the R class includes those buried), the model (54) is identical to the model (2) when the subscript "3" is dropped; that is, when γ_3 and ω_3 are defined as the follows:

$$\begin{aligned}
\frac{1}{\gamma_3} &= \frac{p}{\gamma_{IH}} + \frac{(1-p)f}{\gamma_{ID}} + \frac{(1-p)(1-f)}{\gamma_{IR}},\\
\frac{1}{\omega_3} &= \frac{f}{\omega_{HD}} + \frac{1-f}{\omega_{HR}},
\end{aligned} \tag{55}$$

together with the constraints

$$\frac{1}{\gamma_{IR}} = \frac{1}{\gamma_{IH}} + \frac{1}{\omega_{HR}}, \quad \frac{1}{\gamma_{ID}} = \frac{1}{\gamma_{IH}} + \frac{1}{\omega_{HD}}. \tag{56}$$

Remark 8. Note that the main difference between Models I, II and III lies in the assumptions on the underlying biological processes, particularly the sojourn distributions for various stage transitions, which are described by functions $L(t)$, $P(t)$, $M(t)$ and $Q(t)$. The fact that the Legrand model can only be obtained from Model III, not from Models I and II, identifies the specific assumptions made in the Legrand model in terms of these sojourn distributions. For example, our analyses suggest the following assumptions made in Legrand model:

(a) The overall sojourn in the I stage is assumed to be exponentially distributed with the average duration $1/\gamma$, which is further assumed to be the specific weighted average of $1/\gamma_{IR}$, $1/\gamma_{IH}$ and $1/\gamma_{ID}$ as given in (4), where $1/\gamma_{IR}$, $1/\gamma_{IH}$ and $1/\gamma_{ID}$ are the respective average stage durations of the IR, IH and ID transitions. However, from Model I we see that if the IR, IH and ID transitions follow independent exponential distributions with parameters γ_{IR}, γ_{IH} and γ_{ID}, then the overall sojourn in the I stage is exponentially distributed with the parameter $\gamma = \gamma_{IR} + \gamma_{IH} + \gamma_{ID}$ with the average duration
$$\frac{1}{\gamma} = \frac{1}{\gamma_{IR} + \gamma_{IH} + \gamma_{ID}},$$
which differs from (4).

(b) The distributions for the I and H stages are independent (see $P_3(t)$ and $Q_3(t)$). This implies that the average time spent in the H stage before recovery or death ($1/\omega_3$) does not depend on the average time spent in the I stage before recovery or being hospitalized or dying ($1/\gamma_3$). Under this assumption, the time spent in H before recovery ($1/\gamma_{HR}$) does not take into consideration the time spent in I before being hospitalized ($1/\gamma_{IH}$) . Because of this independence, the model needs to impose a constraint to link these two durations (see (A.4)).

6. Discussion

The objective of this paper is to investigate the underlying assumptions made in the Legrand model. Our approach is to develop models with generally distributed waiting times with general survival functions (e.g., $P(s)$, $L(s)$, $M(s)$ and $Q(s)$) for the processes associated with recovery, hospitalization, and death (referred to as transitions IR, IH and ID). Three models are considered under different assumptions about the connections between various transitions. These models (see Models I, II and III in Section 3.1–3.3) are systems of integro-differential equations, but we show that they can be reduced to systems of ordinary differential equations when sojourns are Gamma or exponential. Particularly, when these distributions are exponential, we can compare the resulting ODE models with the Legrand model, which allows us to identify the assumptions under which the general model reduces to the Legrand model.

Among the three ODE models (47), (52) and (54), which are reduced from the Models I, II and III with general distributions,

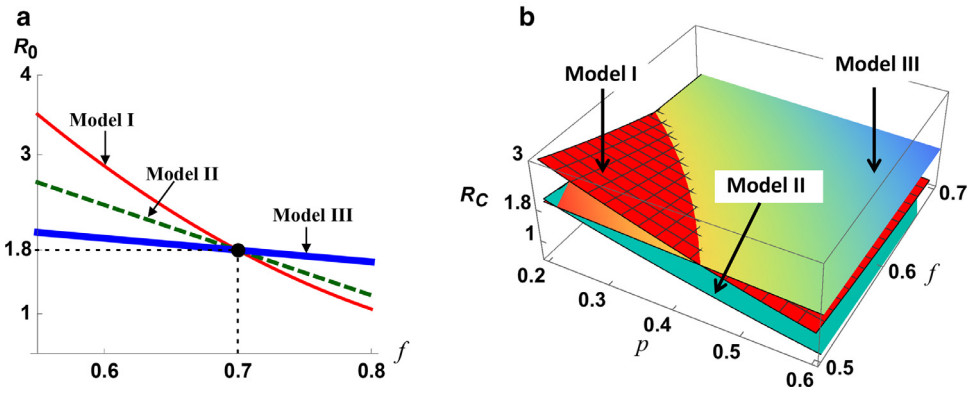


Fig. 4. Plots of the basic reproduction numbers (A) and control reproduction numbers (B) for the three models. In (A), $\mathcal{R}_0$ is plotted as a function of f for Model I (thin solid), Model II (thick dashed), and Model III (thick solid). The parameter values are chosen such that all three $\mathcal{R}_{0i}$ have the same value 1.8 at $f = 0.7$ (note that $p = 0$). In (B), $\mathcal{R}_{Ci}$ is plotted as a function of p and f for Models I, II, and III. Other parameter values are given in the text. .

the only model that can match the Legrand model is (54), for which the assumptions include: (i) The waiting times of the three transitions IR, IH and ID are *not* independent and (ii) the overall waiting time in the I compartment is a weighted average of the mean durations ($1/\gamma_{IR}$, $1/\gamma_{IH}$ and $1/\gamma_{ID}$) for the three transitions with weights determined by the probabilities of hospitalization p and death f, as described in (4) or (A.6). By examining ODE model (47), we found that, if the waiting times of the three transitions IR, IH and ID are independent and exponentially distributed (with parameters γ_1, χ_1 and μ), then the overall waiting time in I should be an exponential distribution with the parameter $\gamma_1 + \chi_1 + \mu$. That is, the average overall waiting time should be $1/(\gamma_1 + \chi_1 + \mu)$, *not* a weighted average such as the ones in (4) or (A.6).

Control reproduction numbers $\mathcal{R}_{Ci}$ $(i = 1, 2, 3)$ for the three general models are derived, as well as their expressions when the general distributions are replaced by Gamma or exponential distributions. These formulas for $\mathcal{R}_{Ci}$ provide a means of examining the influence of assumptions on model outcomes. For example, consider the three control reproduction numbers $\mathcal{R}_{Ci}$ $(i = 1, 2, 3)$, which are given in (46), (51), and (38) corresponding to the three ODE models (47), (52), and (54), respectively. In the absence of hospitalization (i.e., $p = 0$), these $\mathcal{R}_{Ci}$ reduce to the corresponding basic reproduction numbers $\mathcal{R}_{0i}$ $(i = 1, 2, 3)$. Fig. 4 illustrates the difference between the basic and control reproduction numbers of the three models for a given set of parameter values, most based on the Ebola outbreak in West Africa in 2014. We fix all parameters except β_i $(i = I, H, D)$ and f. Then, for a fixed value of $f_0 = 0.7$, we estimate β_i $(i = I, H, D)$ from a given value of $\mathcal{R}_0$ (assumed to be the same for all three models). If we further assume that ,$\beta_H = \beta_D = 0.3\beta_I$ then we can get a unique value for β_I for fixed $\mathcal{R}_0$. Once we have the values of β_i, we have three functions of f, $\mathcal{R}_{0i}(f)$ $(i = 1, 2, 3)$. For Fig. 4(A), we used the common value of $\mathcal{R}_0(f_0) = 1.8$. The three curves are for Model I (the thin solid curve), Model II (the thick dashed curve), and Model III (the thick solid curve). The decreasing property of these curves represents the fact that higher disease mortality decreases $\mathcal{R}_{0i}(f)$, which is expected because the assumption that $\beta_D < \beta_I$. An interesting observation is that the dependence of the basic reproduction number on disease death f is more dramatic in Model I than Models II and III, particularly for smaller f values. For smaller values of f, Model I tends to generate the highest $\mathcal{R}_0$, while for larger f values, Model III provides higher $\mathcal{R}_0$. Other parameter values used are (time in days): $1/\gamma_{IR} = 18, 1/\gamma_f = 2, 1/\alpha = 9$. Parameters such as μ, χ_i $(i = 1, 2)$ are calculated based on their relationships with the common parameters (e.g., (41), (43) and (45) for γ_1, μ and χ_1, respectively, (49) for γ_2). For Model III, additional parameter values include $1/\gamma_{IH} = 7$, $1/\gamma_{ID} = 8$, which can be used to determine γ_3 and ω_3 from (55).

When control is considered ($p > 0$), the dependence of $\mathcal{R}_{Ci}$ on p and f is illustrated in Fig. 4(B). We observe that, for the given set of parameter values, Model I (the darker surface with mesh) generates higher $\mathcal{R}_C$ values than Models II (the lighter surface) and III (the darker surface with no mesh) for smaller p and f, while Model III provides higher values for larger values of p and/or f. The differences in $\mathcal{R}_0$ and $\mathcal{R}_C$ between the three models indicates that model predictions about and evaluations of the effectiveness of control measures could be very different as well. Fig. 5 shows numerical simulation results of the three ODE models (47), (52) and (54), which are reduced from Models I, II and III, and presented in columns 1, 2, and 3, respectively. The A, B, and C panels correspond to three sets of (p, f) values: $(p, f) = (0, 0.7)$ (top panel), $(p, f) = (0.3, 0.5)$ (middle panel), $(p, f) = (0.2, 0.7)$ (bottom panel). The top panel (A1–A3) is for the case of no hospitalization ($p = 0$). We observe that the three models generate similar epidemic curves (fractions of infected individuals $(E + I + H)/N$), including peak sizes, times to peak, durations of epidemic (which lead to similar final epidemic sizes). From the middle panel (B1–B3), we observe that Model I has the highest peak size while Model II has the lowest. This is in agreement with the relative magnitudes of the control reproduction numbers $\mathcal{R}_{Ci}$, as the point $(p, f) = (0.3, 0.5)$ lies in the region where $\mathcal{R}_{C1} > \mathcal{R}_{C3} > \mathcal{R}_{C2}$ (see Fig. 4). For the bottom panel (C1–C3), because the point $(p, f) = (0.2, 0.7)$ lies in the region where $\mathcal{R}_{C3} > \mathcal{R}_{C1} > \mathcal{R}_{C2}$, we observe that Model III generates the highest peak size while Model II has again the lowest.

Another interesting observation from Fig. 5 is that Model 3 generates very similar epidemic curves for all three sets of (p, f) values (see A3, B3 and C3), whereas Model I (and II) produced vary different epidemic curves (A1, B1 and C1). This suggests that these three models may provide very different evaluations of the effects of control. To understand better these differences, we can examine in more detail the expressions for $\mathcal{R}_C$. Note that the reproduction numbers $\mathcal{R}_C$ of the three models (in the case when P, L and M are all exponential) with the rates γ_1 and γ_2 being defined by (39) and (48), respectively, can be written as (see (32), (36) and (38)):

$$\begin{aligned}
\mathcal{R}_{C1} &= \beta_I \frac{(1-p)^2(1-f)^2}{\gamma_{IR}} + \beta_H \frac{p(1-p)(1-f)^2}{\gamma_{IR}} + \beta_D \frac{f}{\gamma_f},\\
\mathcal{R}_{C2} &= \beta_I \frac{2(1-p)^2(1-f)}{\gamma_{IR}} + \beta_H \frac{2p(1-p)(1-f)}{\gamma_{IR}} + \beta_D \frac{f}{\gamma_f},\\
\mathcal{R}_{C3} &= \frac{\beta_I}{\gamma_3} + p\frac{\beta_H}{\omega_3} + f\frac{\beta_D}{\gamma_f},
\end{aligned} \tag{57}$$

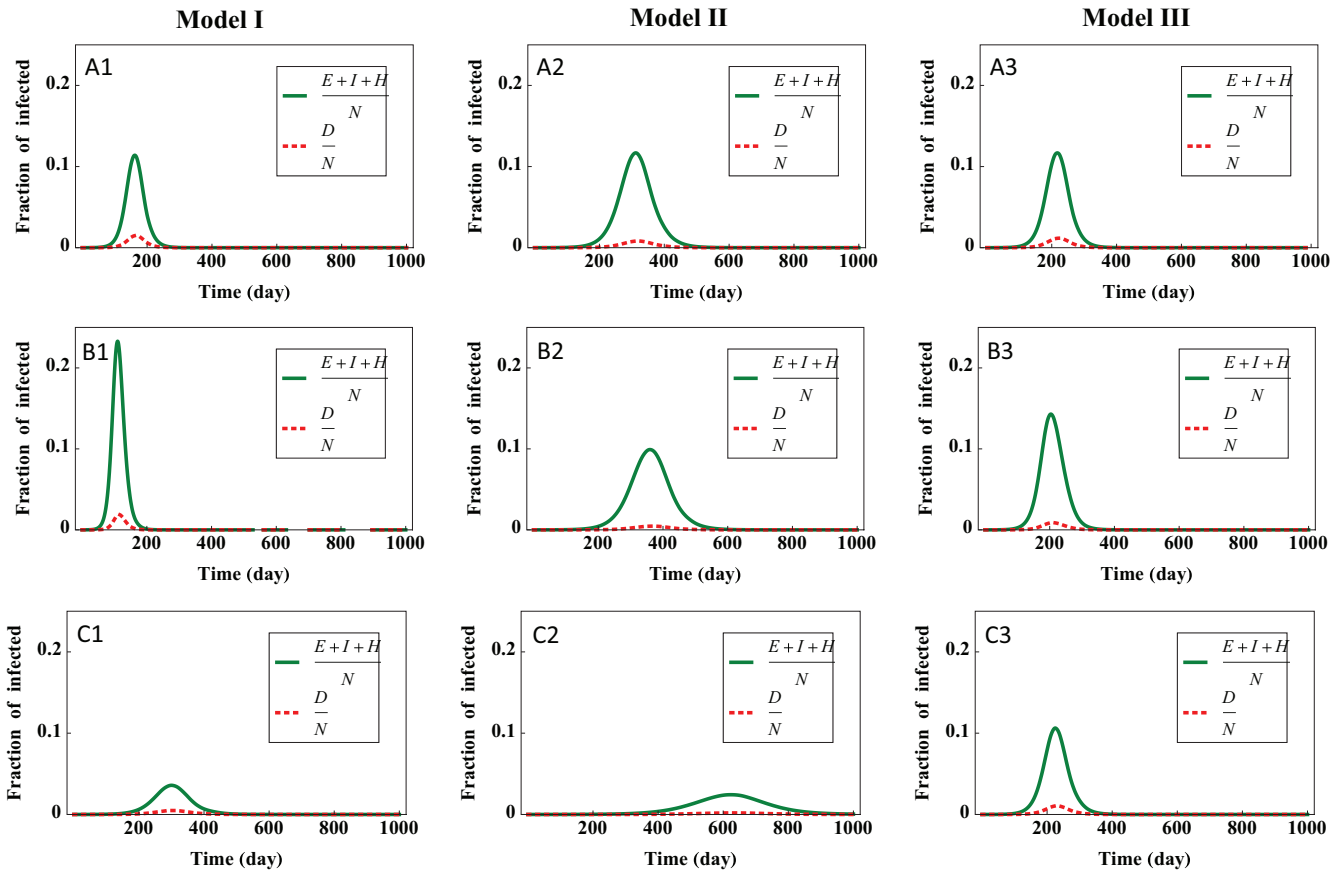


Fig. 5. Numerical simulations of the three ODE models (47), (52) and (54), which are reduced from the Models I, II and III, respectively. The fractions of infected individuals $(E+I+H)/N$ and death (D/N) are plotted over a time period of 1000 days. Three sets of (p, f) values are used: $(p, f) = (0, 0.7)$ (top row), $(p, f) = (0.3, 0.5)$ (middle row), $(p, f) = (0.2, 0.7)$ (bottom row). Parameter values are the same as in Fig. 4.

where γ_3 and ω_3 in $\mathcal{R}_{C3}$ are given in (55) and (56).

An important difference between the three $\mathcal{R}_{Ci}$ expressions is that for fixed β_I, β_H and β_D (these β values may not be the same for all three models), $\mathcal{R}_{C1}$ and $\mathcal{R}_{C2}$ depend only on γ_{IR}, f and p; whereas $\mathcal{R}_{C3}$ depends not only on these parameters, but also on γ_{IH} and γ_{ID} because of the constraints on γ_3 and ω_3 (see (55) and (56)). This apparently increases the uncertainty of results from the Legrand model and the potential misleading results that it may generate, as demonstrated in Fig. 6.

Fig. 6 plots contour curves of $\mathcal{R}_C$ for the three models to illustrate the dependence of $\mathcal{R}_{Ci}$ $(i = 1, 2, 3)$ on p and f. All parameters used in Fig. 6 are the same as Fig. 5, except that in Fig. 6(D) a different γ_{IH} value is used. The three sets of (p, f) values used in Fig. 5 are labeled by a triangle at (0, 0.7), a diamond at (0.2,0.7) and a circle at (0.3,0.5). All other parameter values are the same as in Figs. 4 and 5. The thick curve corresponds to $\mathcal{R}_C = \mathcal{R}_0 = 1.8$ (for $p = 0$ and $f = 0.7$) and the dotted curve corresponds to $\mathcal{R}_C = 1$. We observe that, when (p, f) is changed from (0,0.7) to (0.3,0.5), $\mathcal{R}_{C1}$ (Model I) increases from 1.8 to 2.5 (see A), while $\mathcal{R}_{C2}$ (Model II) decreases slightly from 1.8 to 1.7 (see B) and $\mathcal{R}_{C3}$ (Models III) increases slightly from 1.8 to 1.9 (see C). The more dramatic influence of p and f on $\mathcal{R}_C$ in Model I is reflected in the much higher peak of the epidemic curve shown in Fig. 5 (see the panels B1–B3). We observe also that when (p, f) changes from (0,0.7) to (0.2,0.7), $\mathcal{R}_{C3}$ decreases slightly from 1.8 to 1.7, while $\mathcal{R}_{C1}$ decreases from 1.8 to 1.4 and $\mathcal{R}_{C2}$ decreases a little more from 1.8 to 1.3 (with a significant delay in the timing of the epidemic peak, see Fig. 5(C2)).

Note from (57) that for Models I and II, $\mathcal{R}_{C1}$ and $\mathcal{R}_{C2}$ can be completely determined by γ_{IR}, p, f, and the β's, whereas for the Legrand model, $\mathcal{R}_{C3}$ depends also on γ_{IH}. Fig. 6(D) is similar to Fig. 6(C) except that the value of γ_{IH} is different. If $f = 0.7$ is fixed, we observe that for $1/\gamma_{IH} = 7$ (see Fig. 6C), $\mathcal{R}_{C3}$ remains above 1 for all $p \in [0, 1]$, but for $1/\gamma_{IH} = 3$ (see Fig. 6D), it is possible to reduce $\mathcal{R}_{C3}$ to below 1, although p is very close to 1 (see the dotted curve). However, Models I and II only require $p > 0.4$ to achieve $\mathcal{R}_C < 1$ (see the dotted curve in Fig. 6A and B). The changes shown in Fig. 6 in relative magnitudes of $\mathcal{R}_C$ among Models I, II and III are consistent with the changes in the epidemic curves shown in Fig. 5. Thus, different models may dramatically over- or underestimate the effect of hospitalization (p) in reducing the epidemic level (e.g., peak size and timing of the peak). This illustrates again the model assumptions can have important implications for the evaluation of control strategies. Another important point illustrated by comparing the three models is the identifiability issue in Model III (the Legrand model) regarding γ_{IH} and γ_{ID}. This also suggests that explicit examination of the underlying transition mechanism is critical to develop stochastic models for Ebola. In that situation, one needs to explicitly model these probability transfers.

One of the main contributions of this study is to provide an equivalent (but simpler) formulation of the Legrand model (see Section 2). This simpler formulation not only makes the presentation much clearer (due to a large reduction in the number of parameters involved), particularly when its extensions are considered, but also makes computation of $\mathcal{R}_C$ much easier. More importantly, the simpler formulation makes it possible to compare the Legrand model with our new models and to identify their underlying assumptions.

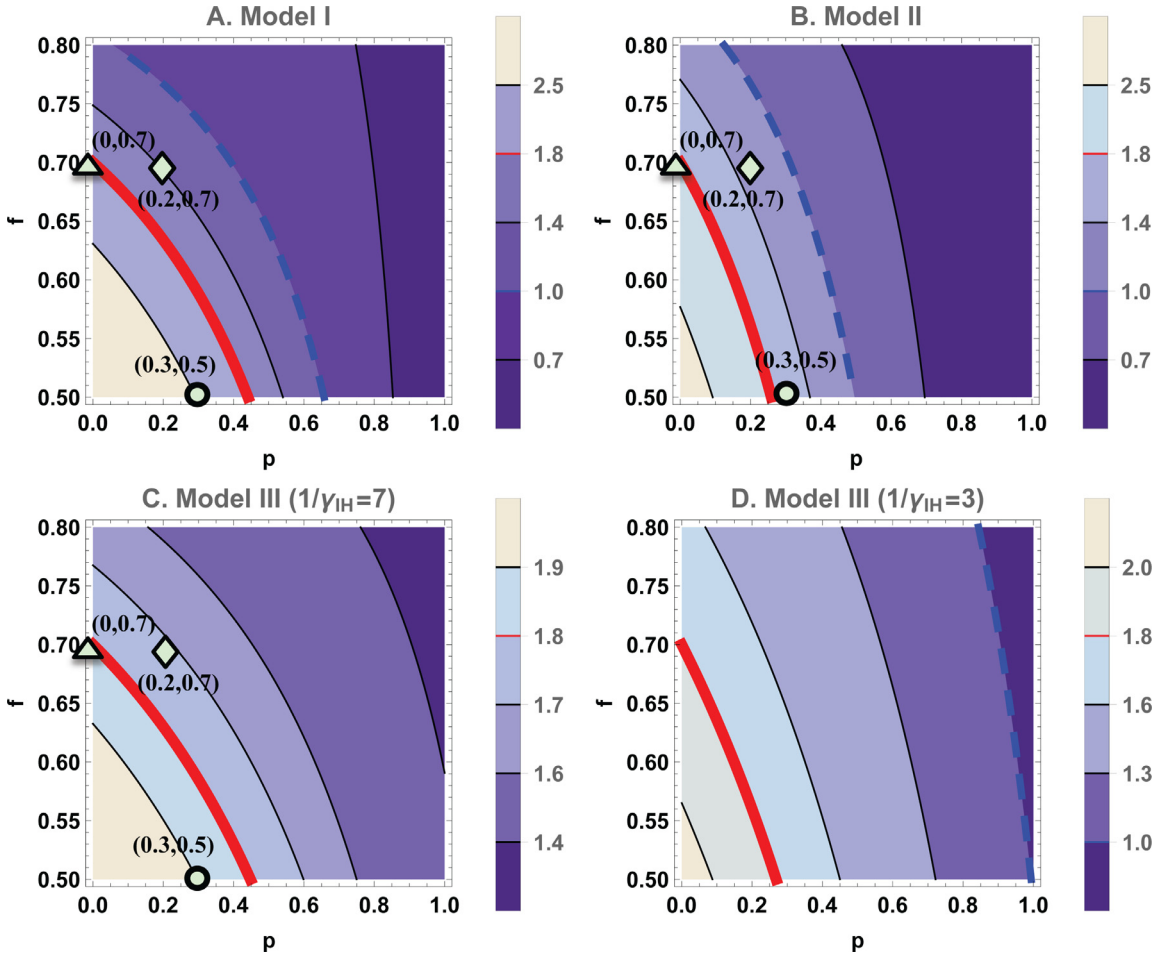


Fig. 6. Contour plots of $\mathcal{R}_C$ for Models I, II and III in the (p, f) plane.

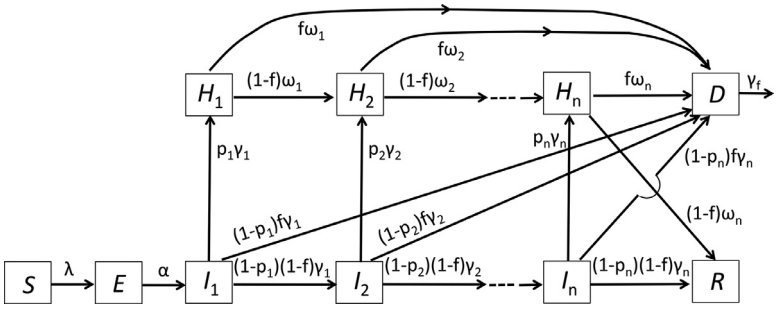


Fig. 7. A transition diagram for an alternative Legrand model with a Gamma distributed infectious stage or n exponential sub-stages. Hospitalization can occur during the stay in each I_i sub-stage, $1 \le i \le n$. Individuals leaves the I_i stage at the exiting rate γ_i with probability p_i being hospitalized and with probability f of dying.

Another significant contribution of this study is a detailed proof that systems of integro-differential equations under arbitrarily-distributed stage durations can be reduced to systems of ODEs under Gamma distributions. Although such reductions have been used in the literature (the so called "linear chain trick"), there has not heretofore been a rigorous proof, although similar arguments were presented by Smith [13].

The formulation of integral equations for Models I, II and III makes it possible to obtain simpler ODE models that represent the biological processes more accurately. It is known that, for diseases with relatively long infectious periods (which is the case of Ebola), the use of exponentially distributed stage durations can be inappropriate and may produce misleading outcomes and that Gamma distributions are more appropriate. Several authors, for example, have shown that impact assessments based on models with exponentially-distributed sojourns may be incorrect [4,7,9,14]). This is mainly due to the memory-less property of exponential distributions. Although Legrand *et al.* tried to correct this by using the constraint that the mean time from I to R is equal to the sum of the mean times from I to H and from H to R (all with exponentially distributed durations), such constraints may be difficult to satisfy if a Gamma distribution is considered for the duration from I to R. For example, Fig. 7 depicts a transition diagram for an alternative Legrand model with Gamma distributed infectious stages (or n exponential sub-stages). Infectious people can be hospitalized during their stays in each of sub-stages I_i with the probability p_i and may die with probability f in I_i and H_i. Notice that there are many possible paths from I to R because infectious

individuals may be hospitalized at at any of the I_i sub-stages (and move from I_i to H_i) for $1 \le i \le n$. It is very challenging to maintain consistency if we need to impose balance equations so that the average times spent from I_i to R, and from I_i to D are the same for all possible paths. However, the formulation of Model I and its ODE reductions would not require these constraints because the time spent in each of the stages is carefully tracked by the distribution functions, which is made possible by using integral equations with arbitrarily distributed stage durations. In fact, the exiting rate from I_i to I_{i+1} and from H_i to H_{i+1} are the same for all $1 \le i \le n-1$ (equal to $n\gamma_1$), and the recovery rate from I_n to R is the same as that from H_n to R (see Fig. 1(b)).

In this paper, we focused only on identifying assumptions in the Legrand model. We have started to explore possible differences in the outcomes of Models I, II and III as well as their ODE reductions, both under Gamma- and exponentially-distributed stage durations, particularly which model would better capture the observed epidemics. Results will be published elsewhere.

Acknowledgements

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention or other institutions with which they are affiliated. We thank the reviewers for comments and suggestions, which helped improve the presentation of the manuscript.

Appendix

In this appendix, we provide a detailed proof showing that the simpler formulation of model (2) is equivalent to the Legrand model (A.1). We also provide the detailed derivation showing that the general integro-differential equations model (17) can be reduced to the ODE model (20) under gamma distribution for $P_1 = G^n_{n\gamma_1}$ and exponential distributions for $L_1 = G^1_{\chi_1}$ and $M_1 = G^1_{\mu}$, as given in (19).

Appendix A. Equivalence of model (2) to the Legrand model

The Legrand model we consider in this paper reads

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D),\\
\frac{dE}{dt} &= \frac{1}{N}S(\beta_I I + \beta_H H + \beta_D D) - \alpha E,\\
\frac{dI}{dt} &= \alpha E - (\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1)I,\\
\frac{dH}{dt} &= \gamma_h\theta_1 I - (\gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2))H,\\
\frac{dD}{dt} &= \gamma_d(1-\theta_1)\delta_1 I + \gamma_{dh}\delta_2 H - \gamma_f D,\\
\frac{dR}{dt} &= \gamma_i(1-\theta_1)(1-\delta_1)I + \gamma_{ih}(1-\delta_2)H + \gamma_f D.
\end{aligned} \tag{A.1}$$

The parameters β_I, β_H and β_D are the transmission rates as in model (2); $1/\alpha$, $1/\gamma_f$ and the biological meanings of other γ's are listed in Table 1. The three key parameters that are in the Legrand model (A.1) but not in model (2) are θ_1, δ_1 and δ_2, which are computed based on the probabilities of hospitalization, and of disease-induced mortality with or without hospitalization. For example, the fraction of infectious people hospitalized is

$$p = \frac{\gamma_h\theta_1}{\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1}, \tag{A.2}$$

and the probabilities of death with (f_h) and without hospitalization (f_i) are given by

$$f_h = \frac{\gamma_{dh}\delta_2}{\gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2)} \quad \text{and} \quad f_i = \frac{\gamma_d\delta_1}{\gamma_i(1-\delta_1) + \gamma_d\delta_1}. \tag{A.3}$$

If we assume that $f_i = f_h = f$, then θ_1, δ_1 and δ_2 can be determined in terms of p and f using (A.2) and (A.3). For ease of comparison, the connections between the parameters of Legrand model (A.1) and model (2) are listed in Table 2.

Moreover, the Legrand model imposes the following constraints

$$\begin{aligned}
&\frac{1}{\gamma_i} = \frac{1}{\gamma_h} + \frac{1}{\gamma_{ih}} \quad (\text{or equivalently} \quad \frac{1}{\gamma_{IR}} = \frac{1}{\gamma_{IH}} + \frac{1}{\omega_{HR}}),\\
&\frac{1}{\gamma_d} = \frac{1}{\gamma_h} + \frac{1}{\gamma_{dh}} \quad (\text{or equivalently} \quad \frac{1}{\gamma_{ID}} = \frac{1}{\gamma_{IH}} + \frac{1}{\omega_{HD}}).
\end{aligned} \tag{A.4}$$

and assumes that hospitalization does not affect the time from onset to recovery or from onset to death.

Some assumptions made by Legrand et al. are associated with exponential waiting times. They assume that, after entering the infectious class I, individuals can leave due either to hospitalization (entering H) or recovery without being hospitalized (entering R from I) or death without being hospitalized (entering D from I) with average waiting times $1/\gamma_h$, $1/\gamma_i$, $1/\gamma_d$, respectively. Or equivalently, after onset, individuals enter the H, R and D classes at constant rates γ_h, γ_i and γ_d, respectively. Their model assumes that the overall rate of leaving the I class, denoted by Δ, is a weighted average of the three rates γ_h, γ_i and γ_d as

$$\Delta = \theta_1\gamma_h + (1-\theta_1)\delta_1\gamma_d + (1-\theta_1)(1-\delta_1)\gamma_i, \tag{A.5}$$

where θ_1 is the proportion of cases hospitalized, and δ_1 is a coefficient that is determined such that

$$\frac{\delta_1\gamma_d}{\delta_1\gamma_d + (1-\delta_1)\gamma_i}$$

is equal to case-fatality (i.e., the proportion of cases that die). It is not clear from condition (A.5) what underlying assumptions have been made regarding the relationship between the waiting times for the three individual transitions IR, IH, ID, and the overall waiting time in I.

Next, we show that model (2) is equivalent to the Legrand model (A.1) by showing that the coefficients in corresponding terms in the two models are equal. As mentioned before, the only minor difference between the two models is where to move the buried (whether or not to R). Note that model (2) involves fewer parameters than the Legrand model (A.1). In addition to the two common parameters, p and f, model (2) involves also γ and ω. Using the expressions for $1/\gamma$ and $1/\omega$ given in Table 2, and the connections between parameters of the two models as listed in Table 2, we have

$$\begin{aligned}
\frac{1}{\gamma} &= p\frac{1}{\gamma_h} + (1-p)f_i\frac{1}{\gamma_d} + (1-p)(1-f_i)\frac{1}{\gamma_i},\\
\frac{1}{\omega} &= f_h\frac{1}{\gamma_{dh}} + (1-f_h)\frac{1}{\gamma_{ih}},
\end{aligned} \tag{A.6}$$

which simplifies to (4) when $f_i = f_h = f$. Notice that

$$\begin{aligned}
&\delta_1 = \frac{\gamma_i f_i}{\gamma_i f_i + \gamma_d(1-f_i)}, \quad \delta_2 = \frac{\gamma_{ih} f_h}{\gamma_{ih} f_h + \gamma_{dh}(1-f_h)},\\
&\theta_1 = \frac{p(\gamma_d\delta_1 + \gamma_i(1-\delta_1))}{p[\gamma_d\delta_1 + \gamma_i(1-\delta_1)] + (1-p)\gamma_h}
\end{aligned} \tag{A.7}$$

Using $p = \theta_1$ and $f_i = f_h = \delta$, we have that

$$\begin{aligned}
&f_i = \frac{1}{\gamma_d\delta_1 + \gamma_i(1-\delta_1)}, \quad f_h = \frac{1}{\gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2)},\\
&p = \frac{1}{\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1}.
\end{aligned} \tag{A.8}$$

Substituting (A.8) into (A.6), we obtain

$$\gamma = \gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1, \tag{A.9}$$

$$\omega = \gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2). \tag{A.10}$$

Next, we match other coefficients in the H, D, and R equations of model (2) to the corresponding ones in model (A.1). This includes (note that $f_i = f_h = f$) $p\gamma$ in the H equations:

$$\begin{aligned} p\gamma &= \frac{\gamma_h\theta_1}{\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1} \\ &\quad\cdot(\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1) \\ &= \gamma_h\theta_1, \end{aligned}$$

$(1-p)f_i\gamma$ and $f_h\omega$ in the D equation (with $f_i = f_h = f$):

$$\begin{aligned} (1-p)f_i\gamma &= \frac{\gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1}{\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1} \\ &\quad\cdot\frac{\gamma_d(1-\theta_1)\delta_1}{\gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1} \\ &\quad\cdot(\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1) \\ &= \gamma_d(1-\theta_1)\delta_1, \end{aligned}$$

and

$$f_h\omega = \frac{\gamma_{dh}\delta_2}{\gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2)}\cdot(\gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2)) = \gamma_{dh}\delta_2,$$

$(1-p)(1-f_i)\gamma$ and $(1-f_h)w$ in the R equation (with $f_i = f_h = f$):

$$\begin{aligned} (1-p)(1-f_i)\gamma &= \frac{\gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1}{\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1} \\ &\quad\cdot\frac{\gamma_i(1-\theta_1)(1-\delta_1)}{\gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1} \\ &\quad\cdot(\gamma_h\theta_1 + \gamma_i(1-\theta_1)(1-\delta_1) + \gamma_d(1-\theta_1)\delta_1) \\ &= \gamma_i(1-\theta_1)(1-\delta_1), \end{aligned}$$

and

$$\begin{aligned} (1-f_h)\omega &= \frac{\gamma_{ih}(1-\delta_2)}{\gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2)}\cdot(\gamma_{dh}\delta_2 + \gamma_{ih}(1-\delta_2)) \\ &= \gamma_{ih}(1-\delta_2). \end{aligned}$$

It follows that all corresponding coefficients in the two models, (A.1) and (2), are the same. Thus, these two models are equivalent.

Appendix B. Derivation of the ODE formulation for Model I

In this appendix, we show that the ODE system (20) can be derived from the general Model I (17) under Gamma and exponential distributions. For ease of notation, we omit the subscripts in P, L, M, γ and χ.

Consider the I equation in (19). From the I equation in (17), we have

$$\begin{aligned} I(t) &= \int_0^t \alpha E(s)G_\mu^1(t-s)G_\chi^1(t-s)G_{n\gamma}^n(t-s)ds \\ &\quad + I(0)G_\mu^1(t)G_\chi^1(t)G_{n\gamma}^n(t), \\ &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\sum_{j=1}^n \frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}ds \\ &\quad + I(0)e^{-\mu t}e^{-\chi t}\sum_{j=1}^n \frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}, \\ &= \sum_{j=1}^n\left(\int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}ds\right. \\ &\quad \left. + I(0)e^{-\mu t}e^{-\chi t}\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}\right), \\ &:= \sum_{j=1}^n I_n(t), \end{aligned}$$

where

$$\begin{aligned} I_1(t) &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}e^{-n\gamma(t-s)}ds + I(0)e^{-\mu t}e^{-\chi t}e^{-n\gamma t}, \\ I_j(t) &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}ds \\ &\quad + I(0)e^{-\mu t}e^{-\chi t}\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}, \text{ for } j = 1,\ldots,n. \end{aligned}$$

Differentiation of this $I_1(t)$ equation yields

$$\begin{aligned} I_1'(t) &= \alpha E(t) - (n\gamma+\chi+\mu)\left(\int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}e^{-n\gamma(t-s)}ds\right. \\ &\quad \left. + I(0)e^{-\mu t}e^{-\chi t}e^{-n\gamma t}\right), \\ &= \alpha E(t) - (n\gamma+\chi+\mu)I_1(t), \end{aligned}$$

which is the I_1' equation in (20).

Differentiation of the $I_j(t)$ equation for $j > 1$ leads to

$$\begin{aligned} I_j'(t) &= \alpha E(t)e^{-\mu\cdot 0}e^{-\chi\cdot 0}\frac{(n\gamma\cdot 0)^{j-1}e^{-n\gamma\cdot 0}}{(j-1)!} \\ &\quad + \int_0^t \alpha E(s)\frac{d}{dt}\left(e^{-\mu(t-s)}e^{-\chi(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}\right)ds \\ &\quad + I(0)\frac{d}{dt}\left(e^{-\mu t}e^{-\chi t}\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}\right), \\ &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\left(n\gamma\frac{(n\gamma(t-s))^{j-2}e^{-n\gamma(t-s)}}{(j-2)!}\right. \\ &\quad \left. - n\gamma\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}\right)ds \\ &\quad - (\mu+\chi)\int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}ds \\ &\quad + I(0)e^{-\mu t}e^{-\chi t}\left(n\gamma\frac{(n\gamma t)^{j-2}e^{-n\gamma t}}{(j-2)!} - n\gamma\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}\right) \\ &\quad - (\mu+\chi)I(0)e^{-\mu t}e^{-\chi t}\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}, \\ &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\left(n\gamma\frac{(n\gamma(t-s))^{j-2}e^{-n\gamma(t-s)}}{(j-2)!}\right)ds \\ &\quad + I(0)e^{-\mu t}e^{-\chi t}\left(n\gamma\frac{(n\gamma t)^{j-2}e^{-n\gamma t}}{(j-2)!}\right) \\ &\quad + \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\left(-n\gamma\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}\right)ds \\ &\quad + I(0)e^{-\mu t}e^{-\chi t}\left(-n\gamma\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}\right) \\ &\quad - (\mu+\chi)\int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-\chi(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}ds \\ &\quad - (\mu+\chi)I(0)e^{-\mu t}e^{-\chi t}\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}, \\ &= n\gamma I_{j-1}(t) - (n\gamma+\chi+\mu)I_j(t), \end{aligned}$$

which is the same as the I_j' equation in (20).

From the H equation in (17),

$$\begin{aligned}H(t) &= \int_0^t \alpha E(s)P(t-s)M(t-s)(1-L(t-s))ds\\ &\quad +I(0)P(t)M(t)(1-L(t)),\\ &= \int_0^t \alpha E(s)e^{-\mu(t-s)}\sum_{j=1}^{n}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}(1-e^{-\chi(t-s)})ds\\ &\quad +I(0)e^{-\mu t}\sum_{j=1}^{n}\frac{(n\gamma t)e^{-n\gamma t}}{(j-1)!}(1-e^{-\chi t}),\\ &= \sum_{j=1}^{n}\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}(1-e^{-\chi(t-s)})ds\right.\\ &\quad \left.+I(0)e^{-\mu t}\frac{(n\gamma t)e^{-n\gamma t}}{(j-1)!}(1-e^{-\chi t})\right],\\ &\doteq \sum_{j=1}^{n}H_j(t).\end{aligned}$$

Thus, for $j=1$

$$\begin{aligned}H_1(t) &= \int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-n\gamma(t-s)}(1-e^{-\chi(t-s)})ds\\ &\quad +I(0)e^{-\mu t}e^{-n\gamma t}(1-e^{-\chi t}).\end{aligned}$$

Differentiating this H_1 equation we have

$$\begin{aligned}H_1'(t) &= \chi\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-n\gamma(t-s)}e^{-\chi(t-s)}ds+I(0)e^{-\mu t}e^{-n\gamma t}e^{-\chi t}\right]\\ &\quad -(n\gamma+\mu)\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}e^{-n\gamma(t-s)}\chi e^{-\chi(t-s)}ds\right.\\ &\quad \left.+I(0)e^{-\mu t}e^{-n\gamma t}\chi e^{-\chi t}\right],\\ &= \chi I_1(t)-(n\gamma+\mu)H_1(t),\end{aligned}$$

which is the H_1' equation in (20).

For $j>1$,

$$\begin{aligned}H_j(t) &= \int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}(1-e^{-\chi(t-s)})ds\\ &\quad +I(0)e^{-\mu t}\frac{(n\gamma t)e^{-n\gamma t}}{(j-1)!}(1-e^{-\chi t}).\end{aligned}$$

Thus,

$$\begin{aligned}H_j'(t) &= \chi\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}e^{-\chi(t-s)}ds\right.\\ &\quad \left.+I(0)e^{-\mu t}\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}e^{-\chi t}\right]\\ &\quad +\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{d}{dt}\left(\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}\right)e^{-\chi(t-s)}ds\right.\\ &\quad \left.+I(0)e^{-\mu t}\frac{d}{dt}\left(\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}\right)e^{-\chi t}\right]\\ &\quad -\mu\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}\chi e^{-\chi(t-s)}ds\right.\\ &\quad \left.+I(0)e^{-\mu t}\frac{(n\gamma t)^{j-1}e^{-n\gamma t}}{(j-1)!}\chi e^{-\chi t}\right],\\ &= \chi I_j(t)+n\gamma H_{j-1}(t)-n\gamma H_j(t)-\mu H_j(t),\end{aligned}$$

which is the H_j' $(j>1)$ equation in (20).

For the D equation

$$\begin{aligned}D(t) &= \int_0^t\left[\int_0^\tau \alpha E(s)P(\tau-s)g_M(\tau-s)ds\right.\\ &\quad \left.+I(0)P(\tau)g_M(\tau)\right]e^{-\gamma_f(t-\tau)}d\tau,\\ &= \int_0^t\left[\int_0^\tau \alpha E(s)\sum_{j=1}^{n}\frac{(n\gamma(\tau-s))^{j-1}e^{-n\gamma(\tau-s)}}{(j-1)!}\mu e^{-\mu(\tau-s)}ds\right.\\ &\quad \left.+I(0)\sum_{j=1}^{n}\frac{(n\gamma\tau)^{j-1}e^{-n\gamma\tau}}{(j-1)!}\mu e^{-\mu\tau}\right]e^{-\gamma_f(t-\tau)}d\tau,\\ &= \sum_{j=1}^{n}\int_0^t\left[\int_0^\tau \alpha E(s)\frac{(n\gamma(\tau-s))^{j-1}e^{-n\gamma(\tau-s)}}{(j-1)!}\mu e^{-\mu(\tau-s)}ds\right.\\ &\quad \left.+I(0)\frac{(n\gamma\tau)^{j-1}e^{-n\gamma\tau}}{(j-1)!}\mu e^{-\mu\tau}\right]e^{-\gamma_f(t-\tau)}d\tau,\end{aligned}$$

and thus,

$$\begin{aligned}D'(t) &= \mu\sum_{j=1}^{n}\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}e^{-\chi(t-s)}ds\right.\\ &\quad \left.+I(0)e^{-\mu t}\frac{(n\gamma t)e^{-n\gamma t}}{(j-1)!}e^{-\chi t}\right]\\ &\quad +\mu\sum_{j=1}^{n}\left[\int_0^t \alpha E(s)e^{-\mu(t-s)}\frac{(n\gamma(t-s))^{j-1}e^{-n\gamma(t-s)}}{(j-1)!}\right.\\ &\quad \left.\times(1-e^{-\chi(t-s)})ds+I(0)e^{-\mu t}\frac{(n\gamma t)e^{-n\gamma t}}{(j-1)!}(1-e^{-\chi t})\right]\\ &\quad -\gamma_f\sum_{j=1}^{n}\int_0^t\left[\int_0^\tau \alpha E(s)\frac{(n\gamma(\tau-s))^{j-1}e^{-n\gamma(\tau-s)}}{(j-1)!}\mu e^{-\mu(\tau-s)}ds\right.\\ &\quad \left.+I(0)\frac{(n\gamma\tau)^{j-1}e^{-n\gamma\tau}}{(j-1)!}\mu e^{-\mu\tau}\right]e^{-\gamma_f(t-\tau)}d\tau,\\ &= \sum_{j=1}^{n}\mu I_j(t)+\sum_{j=1}^{n}\mu H_j(t)-\gamma_f D(t),\end{aligned}$$

which is the D' equation in (20).

Similarly, from the integral equation for R, we can derive the R' equation in (20):

$$R'(t)=n\gamma I_n(t)+n\gamma H_n(t).$$

This completes the proof.

Appendix C. The probability of hospitalization p_{H1} for Model I

Consider the model (20), which is Model I in the case when $P_1(t)=G^n_{n\gamma_1}$, $L_1(t)=G^1_{\chi 1}$ and $M_1(t)=G^1_\mu$. The proportion of infected individuals that are hospitalized (see (44)) is given by

$$\begin{aligned}p_{H1} &= \int_0^\infty\int_0^t\int_0^u \chi e^{-\chi s}ds\ \mu e^{-\mu u}du\ \frac{(n\gamma)^n t^{n-1}e^{-n\gamma t}}{n!}dt\\ &\quad +\int_0^\infty\int_0^u\int_0^t \chi e^{-\chi s}ds\ \frac{(n\gamma)^n t^{n-1}e^{-n\gamma t}}{n!}dt\ \mu e^{-\mu u}du,\\ &= \int_0^\infty\int_0^t \left(1-e^{-\chi u}\right)\mu e^{-\mu u}du\ \frac{(n\gamma)^n t^{n-1}e^{-n\gamma t}}{n!}dt\\ &\quad +\int_0^\infty\int_0^u \left(1-e^{-\chi t}\right)\frac{(n\gamma)^n t^{n-1}e^{-n\gamma t}}{n!}dt\ \mu e^{-\mu u}du,\\ &= \int_0^\infty\int_0^t \left(1-e^{-\chi u}\right)\mu e^{-\mu u}du\ \frac{(n\gamma)^n t^{n-1}e^{-n\gamma t}}{n!}dt\end{aligned}$$

$$
\begin{aligned}
&+\int_0^\infty \int_t^\infty \mu e^{-\mu u} du \left(1-e^{-\chi t}\right) \frac{(n\gamma)^n t^{n-1} e^{-n\gamma t}}{n!} dt,\\
&=\int_0^\infty \left[1-e^{-\mu t}-\frac{\mu}{\chi+\mu}\left(1-e^{-(\chi+\mu)t}\right)\right] \frac{(n\gamma)^n t^{n-1} e^{-n\gamma t}}{n!} dt\\
&+\int_0^\infty e^{-\mu t}\left(1-e^{-\chi t}\right) \frac{(n\gamma)^n t^{n-1} e^{-n\gamma t}}{n!} dt,\\
&=\left[1-\frac{(n\gamma)^n}{(n\gamma+\mu)^n}-\frac{\mu}{\chi+\mu}\left(1-\frac{(n\gamma)^n}{(n\gamma+\chi+\mu)^n}\right)\right]\\
&+\left[\frac{(n\gamma)^n}{(n\gamma+\mu)^n}-\frac{(n\gamma)^n}{(n\gamma+\chi+\mu)^n}\right],\\
&=\left(1-\frac{\mu}{\chi+\mu}\right)\left(1-\frac{(n\gamma)^n}{(n\gamma+\chi+\mu)^n}\right)\\
&=\frac{\chi}{\chi+\mu}\left[1-\left(\frac{n\gamma}{\chi+n\gamma+\mu}\right)^n\right].
\end{aligned}
$$

References

[1] C.J. Browne, H. Gulbudak, G. Webb, Modeling contact tracing in outbreaks with application to ebola, J. Theor. Biol. 384 (2015) 33–49.

[2] D. Butler, Models overestimate ebola cases, Nature 515 (6) (2014) 18, doi:10.1038/515018a.

[3] Z. Feng, H.R. Thieme, Endemic models with arbitrarily distributed periods of infection I: fundamental properties of the model, SIAM J. Appl. Math. 61 (3) (2000) 803–833.

[4] Z. Feng, D. Xu, H. Zhao, Epidemiological models with non-exponentially distributed disease stages and applications to disease control, Bull. Math. Biol. 69 (5) (2007) 1511–1536.

[5] N. Hernandez-Ceron, Z. Feng, C. Castillo-Chavez, Discrete epidemic models with arbitrary stage distributions and applications to disease control, Bull. Math. Biol. 75 (10) (2013) 1716–1746.

[6] N. Hernandez-Ceron, Z. Feng, P. van den Driessche, Reproduction numbers for discrete-time epidemic models with arbitrary stage distributions, J. Differ. Equat. Appl. 19 (2013) 1671–1693.

[7] H. Hethcote, D. Tudor, Integral equation models for endemic infectious diseases, J. Math. Biol. 9 (1980) 37–47.

[8] J. Legrand, et al., Understanding the dynamics of Ebola epidemics, Epidemiol. Infect. 135 (2007) 610–621.

[9] A. Lloyd, Realistic distributions of infectious periods in epidemic models, Theor. Popul. Biol. 60 (2001) 59–71.

[10] N. MacDonald, Time Lags in Biological Models, Springer-Verlag, New York, 1978.

[11] C.M. Rivers, et al., Modeling the impact of interventions on an epidemic of Ebola in SierraLeone and Liberia, in: PLoS Current Outbreaks, 2014, Oct 16. Edition 1. doi:10.1371/currents.outbreaks.fd38dd85078565450b0be3fcd78f5ccf.

[12] S.M. Ross, A First Course in Probability, Pearson Education India, 2002.

[13] H. Smith, An Introduction to Delay Differential Equations with Applications to the Life Sciences, Springer Science & Business Media, 2010, p. 57.

[14] H. Wearing, P. Rohani, M. Keeling, Appropriate models for the management of infectious diseases, PLoS Med. 2 (7) (2005) 0621–0627. http://dx.doi.org/10.1371/journal.pmed.0020174