Published in final edited form as:

Bull Math Biol. 2013 October ; 75(10): 1716–1746. doi:10.1007/s11538-013-9866-x.

Discrete epidemic models with arbitrary stage distributions and applications to disease control

Nancy Hernandez-Ceron¹, Zhilan Feng^{1,*}, and Carlos Castillo-Chavez²

¹Purdue University, West Lafayette, IN 47907

²Arizona State University, Tempe, AZ 85287

Abstract

W. O. Kermack and A. G. McKendrick introduced in their fundamental paper, A Contribution to the Mathematical Theory of Epidemics, published in 1927, a simple deterministic model that captured the qualitative dynamic behavior of single infectious disease outbreaks. A Kermack-McKendrick discrete-time general framework, motivated by the emergence of a multitude of models used to forecast the dynamics of SARS and influenza outbreaks, is introduced in this manuscript. Results that allow us to measure quantitatively the role of classical and general distributions on disease dynamics are presented. The case of the geometric distribution is used to evaluate the impact of waiting-time distributions on epidemiological processes or public health interventions. In short, the geometric distribution is used to set up the baseline or null epidemiological model used to test the relevance of realistic stage-period distribution on the dynamics of single epidemic outbreaks. A final size relationship involving the control reproduction number, a function of transmission parameters and the means of distributions used to model disease or intervention control measures, is computed. Model results and simulations highlight the inconsistencies in forecasting that emerge from the use of specific parametric distributions. Examples, using the geometric, Poisson and binomial distributions, are used to highlight the impact of the choices made in quantifying the risk posed by single outbreaks and the relative importance of various control measures.

1 Introduction

The birth of mathematical theory of epidemics can be traced to the work of *three* physicians Daniel Bernoulli in 1760 ([5]), Sir Ronald Ross ([14]), Anderson Gray McKendrick (see [10]), and the statistician William Ogilvy Kermack. Sir Ronald Ross, an English physician and Nobel Laureate, developed the first mathematical models for the study of the transmission dynamics of malaria ([14]). McKendrick and Kermack published a series of papers, introducing deterministic general epidemic model and their celebrated threshold theorem ([10, 11, 12]). As a result of the 2003 SARS outbreaks, efforts to connect models to data increased. Single-outbreak epidemic models are now routinely used to estimate $\mathcal{R}_0$ and to evaluate disease control strategies ([7, 8, 9]). The analytic formula for the final epidemic

*Corresponding author: zfheng@math.purdue.edu.

size derived, as a function of the control reproduction number $\mathcal{R}_c$, in [1, 2, 13, 15] is confirmed in our general setting.

In this paper, we expand on the discrete-time single-outbreak models introduced and analyzed in [2] through the inclusion of arbitrary exposed and infectious period distributions. A single epidemic outbreak model built on geometric period distributions, the baseline model in our analyses and discussion, is introduced and analyzed. geometric distribution model results will provide the reference frame (“null model”) used to evaluate the impact of alternative stage-duration period distributions (see [6] for a continuous-time model study along these lines).

The focus of this manuscript is on the formulation and analyses of a discrete-time model that allows for the inclusion of *arbitrarily distributed* waiting time distributions. The choice of specific distributions in a model is particularly important when the model is used to evaluate disease control strategies such as quarantine and isolation, which are considered in our model. In order to bring into the context of epidemiological applications, we proceed to derive the formulas for $\mathcal{R}_c$ for the geometric distribution model (acronym GDM) and the generalized arbitrary distribution model (acronym ADM). Our detailed derivations help reveal the explicit dependance of $\mathcal{R}_c$ on the mean values of the stage distributions, the mean sojourn times, and the quarantine-adjusted probability in the ADM case. Further, an analytic formula from where the final epidemic size can be determined, involving $\mathcal{R}_c$ and key epidemiological parameters, is also included. Epidemiological reasons support our decision to only pay attention to distributions with finite means. Throughout, we highlight the role of modeling assumptions (a priori selection of disease stage duration distributions) have on the quantitative assessment of disease control strategies. Examples that exhibit similar discrepancies (as discussed in [6]) are provided.

The organization of this paper is as follows. In Section 2, we develop a discrete analogue of the continuous-time model where the per-capita rates of exit for the latent and infectious stages are constant. Formulas for the control reproduction number $\mathcal{R}_c$ and the final epidemic size relation are derived. Section 3 is devoted to the derivation and analyses of a generalized version of the GDM. Specifically, we replace the use of the geometric distributions for the disease stages with *arbitrary* discrete time distributions. Formulas for $\mathcal{R}_c$ and the final epidemic size relation are also derived in the general case. Section 4 focuses on applications of the results collected in Sections 3. Particularly, we compare model outcomes when the disease durations follow classical distributions (geometric, Poisson, or binomial). A discussion of model results and final thoughts are included in Section 5.

2 A simple discrete-time model with quarantine and isolation

A discrete-time analogue of the continuous-time single epidemic outbreak model, with exponentially distributed stage durations in [6], is formulated following the approach in [2]. If we let n denote time (time step or generation time) then S_n represent the number of susceptible, E_n the number of exposed but not yet infectious, Q_n the number of quarantined, I_n the number of infectious, and H_n the number of isolated individuals at time (generation) n . It is also assumed that only individuals in the I and H classes are capable of transmitting the

disease; and that individuals leave the latent and infectious stages at per-capita constant rates. Furthermore, we let α denote the fraction of individuals remaining in stages E and Q after each time step ($0 < \alpha < 1$); $\beta > 0$ the fraction of infectious individuals remaining in the infectious stage after each time step ($0 < \beta < 1$); and $1-\gamma$ and $1-\sigma$ the fractions of newly quarantined and isolated individuals at each time step, respectively. Finally, we let λ denote the transmission coefficient and ρ the isolation efficiency. Here $\rho = 0$ represents the case of no isolation and $\rho = 1$ the case of perfect isolation. A summary of the definitions used are collected in Table 1.

Using the diagram in **Fig. 1**, we arrive at the following discrete-time single-outbreak model:

$$\begin{aligned} S_{n+1} &= S_n G_n \\ E_{n+1} &= (1 - G_n) S_n + \alpha \gamma E_n \\ Q_{n+1} &= \alpha (1 - \gamma) E_n + \alpha Q_n \\ I_{n+1} &= (1 - \alpha) E_n + \beta \sigma I_n \\ H_{n+1} &= (1 - \alpha) Q_n + \beta (1 - \sigma) I_n + \beta H_n, \quad n=1, 2, 3, \dots, \end{aligned} \quad (1)$$

where the force of infection at generation n is defined by

$$G_n = e^{-\frac{\lambda}{N} [I_n + (1-\rho)H_n]}. \quad (2)$$

The equation for the recovered class R is ignored since it does not affect any other equations in (1). The initial conditions are denoted by $S_0, E_0, Q_0, I_0, H_0, R_0$ with $S_0, E_0 > 0$ and $I_0 = Q_0 = H_0 = R_0 = 0$.

The control reproduction number for Model (1) is given by

$$\hat{\mathcal{R}}_C = \hat{\mathcal{R}}_I + \hat{\mathcal{R}}_{IH} + \hat{\mathcal{R}}_{QH}, \quad (3)$$

where the three quantities on the right-hand-side are explicitly given by

$$\begin{aligned} \hat{\mathcal{R}}_I &= \lambda \frac{1-\alpha}{1-\alpha\gamma} \cdot \frac{1}{1-\beta\sigma}, \\ \hat{\mathcal{R}}_{IH} &= \lambda (1-\rho) \frac{1-\alpha}{1-\alpha\gamma} \left(\frac{1}{1-\beta} - \frac{1}{1-\beta\sigma} \right), \\ \hat{\mathcal{R}}_{QH} &= \lambda (1-\rho) \frac{\alpha(1-\gamma)}{1-\alpha\gamma} \cdot \frac{1}{1-\beta}. \end{aligned} \quad (4)$$

Each term representing the contributions (to secondary infections) by individuals stationed on distinct epidemiological states (a biological interpretation will be provided later). $\hat{\mathcal{R}}_C$ gives the average number of secondary infections produced by a “typical” infectious individual during his/her entire period of infectiousness within a population of susceptibles restricted by the presence of control measures and/or public health interventions.

If we let

$$S_\infty = \lim_{n \rightarrow \infty} S_n,$$

then since Model (1) does not include vital dynamics, we immediately see that the final epidemic size (also called the final size) can be described in terms of $N - S_\infty$ or the fraction $1 - S_\infty/N$.

Result 1

Let $\hat{\mathcal{R}}_c$ be given by Expression (3) then the final epidemic size generated by the dynamics of Model (1) satisfies the following equation

$$\ln \frac{S_0}{S_\infty} = \left(1 - \frac{S_\infty}{N}\right) \hat{\mathcal{R}}_c. \quad (5)$$

Proof. From the S equation in (1) and Equation (2), we see that

$$\ln \left(\frac{S_0}{S_\infty} \right) = \frac{\lambda}{N} \sum_{n=0}^{\infty} [I_n + (1 - \rho) H_n] \quad (6)$$

We observe, making use of the E and S equations in (1), $S_{n+1} + E_{n+1} = S_n + \alpha \gamma E_n - S_n + E_n$, that the sequence $\{S_n + E_n\}$ is decreasing and bounded by zero, thus convergent. Therefore, as $n \rightarrow \infty$

$$S_{n+1} - S_n + E_{n+1} - E_n = (\alpha \gamma - 1) E_n \rightarrow 0.$$

Similar arguments lead to the conclusion that $Q_n, I_n, H_n \rightarrow 0$ as $n \rightarrow \infty$. Moreover, the relationship

$$\begin{aligned} \sum_{n=0}^{m+1} E_n &= E_0 + \sum_{n=1}^{m+1} [(1 - G_{n-1}) S_{n-1} + \alpha \gamma E_{n-1}] \\ &= E_0 + \sum_{n=1}^{m+1} (S_{n-1} - S_n) + \alpha \gamma \sum_{n=0}^m E_n, \end{aligned}$$

and the fact that $S_0 + E_0 = N$, lead to

$$(1 - \alpha \gamma) \sum_{n=0}^m E_n = N - S_{m+1} - E_{m+1}.$$

Letting $m \rightarrow \infty$ we see that

$$\sum_{n=0}^{\infty} E_n = \frac{N - S_\infty}{1 - \alpha \gamma}. \quad (7)$$

From the Q equation in (1), it follows that

$$\sum_{n=1}^{m+1} Q_n = \alpha (1 - \gamma) \sum_{n=1}^{m+1} E_{n-1} + \alpha \sum_{n=1}^{m+1} Q_{n-1}. \quad (8)$$

Making use of (7) and (8), we conclude that

$$\sum_{n=1}^{\infty} Q_n = \frac{\alpha (1 - \gamma)}{1 - \alpha} \cdot \frac{N - S_{\infty}}{1 - \alpha \gamma} = (N - S_{\infty}) \left(\frac{1}{1 - \alpha} - \frac{1}{1 - \alpha \gamma} \right). \quad (9)$$

Similarly, using the I equation in (1) and Equation (7), we arrive at

$$\sum_{n=1}^{\infty} I_n = (N - S_{\infty}) \frac{1 - \alpha}{1 - \alpha \gamma} \cdot \frac{1}{1 - \beta \sigma}, \quad (10)$$

from where we conclude that

$$\frac{\lambda}{N} \sum_{n=1}^{\infty} I_n = \left(1 - \frac{S_{\infty}}{N} \right) \mathcal{R}_I. \quad (11)$$

Finally, from the H equation in (1), we see that

$$\sum_{n=1}^{m+1} H_n = (1 - \alpha) \sum_{n=1}^{m+1} Q_{n-1} + \beta (1 - \sigma) \sum_{n=1}^{m+1} I_{n-1} + \beta \sum_{n=1}^{m+1} H_{n-1},$$

which together with equations (9) and (11), yield

$$\begin{aligned} \sum_{n=1}^{\infty} H_n &= (N - S_{\infty}) \left(\frac{1}{1 - \beta} \cdot \frac{\alpha(1 - \gamma)}{1 - \alpha \gamma} + \frac{1}{1 - \beta} \cdot \beta (1 - \sigma) \cdot \frac{1 - \alpha}{1 - \alpha \gamma} \cdot \frac{1}{1 - \beta \sigma} \right) \\ &= (N - S_{\infty}) \left(\frac{1}{1 - \beta} - \frac{1 - \alpha}{1 - \alpha \gamma} \cdot \frac{1}{1 - \beta \sigma} \right) \\ &= (N - S_{\infty}) \left[\frac{1 - \alpha}{1 - \alpha \gamma} \left(\frac{1}{1 - \beta} - \frac{1}{1 - \beta \sigma} \right) + \frac{\alpha(1 - \gamma)}{1 - \alpha \gamma} \cdot \frac{1}{1 - \beta} \right]. \end{aligned} \quad (12)$$

Thus,

$$\frac{\lambda}{N} \sum_{n=1}^{\infty} (1 - \lambda) H_n = \left(1 - \frac{S_{\infty}}{N} \right) (\mathcal{R}_{IH} + \mathcal{R}_{QH}). \quad (13)$$

Since our initial conditions include $Q_0 = I_0 = H_0 = 0$ then the use of (3), (11), and (13) lead to Equation (5).

This last computation concludes the proof of Result 1.

The final size relation in (5) can be rewritten using the proportional size of the final epidemic $y = 1 - S_{\infty}/N$ as follows:

$$\ln S_0 / (N (1 - y)) = y \mathcal{R}_C. \quad (14)$$

Although this last equation cannot be solved analytically, the relation between $\mathcal{R}_c$ and the final size y can, from the above expression, be numerically determined using Equation (14). A contour plot of the equation $\ln S_0 / (N(1-y)) - y\mathcal{R}_c = 0$, **Fig. 3**, supports the view that the final size y is an increasing function of $\mathcal{R}_c$.

3 The discrete model with arbitrarily distributed durations

A general single-outbreak discrete epidemic model involving arbitrarily distributed stage-duration distributions for the latent and the infectious stages is introduced in this section. Clarity is added to model derivation by making use of a probabilistic perspective. Hence, we let X represent the time an individual has spent being latent, Y the time an individual has spent being infectious, Z the time at which an exposed individual is quarantined (from E to Q), and W the time at which an infected individual is isolated (from I to H). X , Y , Z and W must take values on $\{1, 2, 3, \dots\}$ and their dynamics are assumed to be governed by underlying probabilistic processes. Making use of probabilistic language facilitates the interpretation and applicability of our deterministic model results. Hence, it is understood that the distribution of waiting time in each of the above classes can be described by probability distributions associated with the random variables X , Y , Z and W :

$$\begin{aligned} p_i &= \mathbb{P}(X > i), & \text{probability that an individual remains latent } i \text{ steps after infection;} \\ q_i &= \mathbb{P}(Y > i), & \text{probability that an individual remains infectious } i \text{ steps after becoming infectious;} \\ k_i &= \mathbb{P}(Z > i), & \text{probability of not being quarantined } i \text{ steps after infection;} \\ l_i &= \mathbb{P}(W > i), & \text{probability of not being isolated } i \text{ steps after becoming infectious.} \end{aligned} \quad (15)$$

Notice that $p_i - p_{i+1} = \mathbb{P}(X=i) = p_{i-1} - p_i$ and $\mathbb{E}(X) = \sum_{i=0}^{\infty} p_i$, where $\mathbb{E}(X)$ is the mean or expectation of X . Similar equalities hold for q_i , k_i and l_i . For ease of presentation, we introduce the following notation:

$$\begin{aligned} A_n & \quad \text{the input to } E \text{ at time } n \text{ (new infections),} \\ B_n & \quad \text{the input to } I \text{ at time } n, \\ C_n & \quad \text{the input to } Q \text{ at time } n, \\ D_n & \quad \text{the input to } H \text{ from } Q \text{ at time } n, \\ F_n & \quad (=B_n + D_n) \text{ the total input to infectious class at time } n. \end{aligned}$$

A transition diagram using the above notation is shown in **Fig. 2**.

In our general formulation, the equation associated with changes in the susceptible population is

$$S_{n+1} = S_n G_n, \quad n=1, 2, 3, \dots, \quad (16)$$

where $G_n = e^{-\frac{\lambda}{N}[I_n + (1-\rho)H_n]}$. Equations for A_n are given recursively by

$$A_0 = E_0, \quad A_{n+1} = S_n(1 - G_n) = S_n - S_{n+1}, \quad n \geq 0. \quad (17)$$

Equations for E_n are formulated in terms of A_n and p_n as follows:

$$E_{n+1} = A_{n+1} + A_n p_1 k_1 + \cdots + A_1 p_n k_n + A_0 p_{n+1} k_{n+1}. \quad (18)$$

The number of latent individuals at time n is given by $E_n + Q_n$. These individuals leave this stage according to the distribution p_i . Therefore,

$$E_{n+1} + Q_{n+1} = A_{n+1} + A_n p_1 + \cdots + A_1 p_n + A_0 p_{n+1}. \quad (19)$$

It follows from (18) and (19) that

$$Q_{n+1} = A_n p_1 (1 - k_1) + \cdots + A_1 p_n (1 - k_n) + A_0 p_{n+1} (1 - k_{n+1}). \quad (20)$$

The input to I at time n is given recursively by $B_0 = 0$ and

$$\begin{aligned} B_{n+1} &= A_n \mathbb{P}(X=1) + A_{n-1} k_1 \mathbb{P}(X=n) + \cdots + A_1 k_{n-1} \mathbb{P}(X=n) + A_0 k_n \mathbb{P}(X=n+1) \\ &= A_n (1 - p_1) + A_{n-1} (p_1 - p_2) k_1 + \cdots + A_1 (p_{n-1} - p_n) k_{n-1} + A_0 (p_n - p_{n+1}) k_n. \end{aligned} \quad (21)$$

Thus,

$$I_{n+1} = B_{n+1} + B_n q_1 l_1 + \cdots + B_1 q_n l_n. \quad (22)$$

We observe also that latent individuals leaving the E class at time $n + 1$ will enter either I or Q , that is, $E_n - (E_{n+1} - A_{n+1}) = B_{n+1} + C_{n+1}$. Therefore, we have that

$$C_{n+1} = E_n - E_{n+1} + A_{n+1} - B_{n+1}, \quad (23)$$

with $C_0 = 0$. Similarly, the input into H from Q is computed using $D_0 = 0$ and the recursive relationship

$$D_{n+1} = Q_n - (Q_{n+1} - C_{n+1}). \quad (24)$$

The number of infectious individuals at time $n+1$, $I_{n+1} + H_{n+1}$, turns out to be the sum of all individuals infectious at time $j < n + 1$ still infectious at $n + 1$. Thus,

$$I_{n+1} + H_{n+1} = F_{n+1} + F_n q_1 + \cdots + F_1 q_n,$$

from where we obtain that

$$H_{n+1} = F_{n+1} + F_n q_1 + \cdots + F_1 q_n - I_{n+1}. \quad (25)$$

We are now ready to formulate a model with arbitrarily distributed stage durations using the above definitions and derivations:

$$\begin{aligned} S_{n+1} &= S_n G_n, \quad G_n = e^{-\frac{\lambda}{N} [I_n + (1-\rho) H_n]} \\ E_{n+1} &= A_{n+1} + A_n p_1 k_1 + \cdots + A_1 p_n k_n + A_0 p_{n+1} k_{n+1} \\ Q_{n+1} &= A_n p_1 (1 - k_1) + \cdots + A_1 p_n (1 - k_n) + A_0 p_{n+1} (1 - k_{n+1}) \\ I_{n+1} &= B_{n+1} + B_n q_1 l_1 + \cdots + B_1 q_n l_n. \\ H_{n+1} &= F_{n+1} + F_n q_1 + \cdots + F_1 q_n - I_{n+1}, \quad n=1, 2, 3, \dots, \end{aligned} \quad (26)$$

where A_n , B_n , C_n and D_n are given in (17), (21), (23) and (24). The initial conditions are the same as those in Model (1), that is, S_0 , $E_0 > 0$ and $I_0 = Q_0 = H_0 = R_0 = 0$.

Furthermore, the mean sojourn time and the “quarantine adjusted” mean sojourn time in the exposed stage are given by

$$\mathcal{D}_E = \mathbb{E}(X) \quad \text{and} \quad \mathcal{D}_{E_k} = \mathbb{E}(X \wedge Z), \quad (27)$$

respectively, where $X \wedge Z = \min\{X, Z\}$ and

$$\mathbb{E}(X \wedge Z) = \sum_{j=0}^{\infty} \mathbb{P}(X \wedge Z > j) = 1 + \sum_{j=1}^{\infty} p_j k_j.$$

Similarly, the mean sojourn and the “isolation adjusted” mean sojourn times in the infectious stage are given by

$$\mathcal{D}_I = \mathbb{E}(Y) \quad \text{and} \quad \mathcal{D}_{I_l} = \mathbb{E}(Y \wedge W). \quad (28)$$

respectively, where

$$\mathbb{E}(Y \wedge W) = \sum_{j=0}^{\infty} \mathbb{P}(Y \wedge W > j) = 1 + \sum_{j=1}^{\infty} q_j l_j.$$

Letting

$$\mathcal{T}_{E_k} = \sum_{j=1}^{\infty} (p_{j-1} - p_j) k_{j-1} \quad (29)$$

and making use of

$$\begin{aligned} \mathbb{P}(X \leq Z) &= \sum_{j=1}^{\infty} \mathbb{P}(X=j, j \leq Z) = \sum_{j=1}^{\infty} \mathbb{P}(X=j) \mathbb{P}(j-1 < Z) \\ &= \sum_{j=1}^{\infty} (p_{j-1} - p_j) k_{j-1}, \end{aligned}$$

and since $\mathcal{T}_{E_k}$ represents the probability that a latent individual becomes infectious without getting quarantined, we see that

$$\mathcal{R}_1 = \lambda \mathcal{T}_{E_k} \mathcal{D}_{I_l}, \quad (30)$$

which represents the number of secondary infections produced in a susceptible population by an individual in the I class during his/her infectious period. Similarly, rewriting the quantities $\mathcal{R}_{IH}$ and $\mathcal{R}_{QH}$ as follows

$$\begin{aligned}\mathcal{R}_{IH} &= \lambda(1-\rho) \mathcal{T}_{E_k} (\mathcal{D}_I - \mathcal{D}_{I_l}), \\ \mathcal{R}_{QH} &= \lambda(1-\rho) (1 - \mathcal{T}_{E_k}) \mathcal{D}_I,\end{aligned}\quad (31)$$

allow us to conclude that they represent the number of secondary infections produced by an individual who entered the H class from the I class or the Q class, respectively.

Result 2. The control reproduction number $\mathcal{R}_c$ for the general model (26) can be expressed in terms of the mean $\mathcal{D}_I$, the isolation-adjusted mean $\mathcal{D}_{I_l}$, and the quarantine-adjusted probability of disease progression $\mathcal{T}_{E_k}$. That is,

$$\mathcal{R}_c = \mathcal{R}_I + \mathcal{R}_{IH} + \mathcal{R}_{QH} \quad (32)$$

where $\mathcal{R}_I$, $\mathcal{R}_{IH}$ and $\mathcal{R}_{QH}$ are the stage-specific reproduction numbers defined in (30) and (31), with $\mathcal{D}_I$, $\mathcal{D}_{I_l}$ and $\mathcal{T}_{E_k}$ being given in (28) and (29).

Result 3. Let $\mathcal{R}_c$ be as given in (32). The final epidemic size generated by the dynamics of Model (26) satisfies the following final size relationship

$$\ln \frac{S_0}{S_\infty} = \left(1 - \frac{S_\infty}{N}\right) \mathcal{R}_c. \quad (33)$$

Proof. From (18) and (20) we obtain

$$\begin{aligned}\sum_{n=0}^{\infty} E_n &= \sum_{n=0}^{\infty} \left(A_n + \sum_{j=1}^n A_{n-j} p_j k_j \right) = A_0 + S_0 - S_\infty + \sum_{j=1}^{\infty} \sum_{n=j}^{\infty} A_{n-j} p_j k_j \\ &= N - S_\infty + \sum_{j=1}^{\infty} \left(p_j k_j \sum_{n=0}^{\infty} A_n \right) = (N - S_\infty) \left(1 + \sum_{j=1}^{\infty} p_j k_j \right) \\ &= (N - S_\infty) \mathbb{E}(X \wedge Z) = (N - S_\infty) \mathcal{D}_{E_k}\end{aligned}$$

and

$$\begin{aligned}\sum_{n=1}^{\infty} Q_n &= \sum_{n=1}^{\infty} \sum_{j=1}^n A_{n-j} p_j (1 - k_j) = \sum_{j=1}^{\infty} \sum_{n=j}^{\infty} A_{n-j} p_j (1 - k_j) \\ &= \sum_{j=1}^{\infty} \left((p_j - p_j k_j) \sum_{n=0}^{\infty} A_n \right) = (N - S_\infty) \left(\sum_{j=1}^{\infty} p_j - \sum_{j=1}^{\infty} p_j k_j \right) \\ &= (N - S_\infty) [\mathbb{E}(X) - \mathbb{E}(X \wedge Z)] = (N - S_\infty) [\mathbb{E}(X) - \mathcal{D}_{E_k}].\end{aligned}$$

By definition of B_n (see (21)) we get

$$\begin{aligned}\sum_{n=1}^{\infty} B_n &= \sum_{n=1}^{\infty} \sum_{j=1}^n A_{n-j} (p_{j-1} - p_j) k_{j-1} = \sum_{j=1}^{\infty} \left((p_{j-1} - p_j) k_{j-1} \sum_{n=j}^{\infty} A_{n-j} \right) \\ &= (N - S_\infty) \sum_{j=1}^{\infty} (p_{j-1} - p_j) k_{j-1} = (N - S_\infty) \mathcal{T}_{E_k}.\end{aligned}$$

Thus,

$$\begin{aligned}\sum_{n=1}^{\infty} I_n &= B_1 + \sum_{n=2}^{\infty} \left(B_n + \sum_{j=1}^{n-1} B_{n-j} q_j l_j \right) = \sum_{n=1}^{\infty} B_n + \sum_{j=1}^{\infty} \left(q_j l_j \sum_{n=j+1}^{\infty} B_{n-j} \right) \\ &= \left(\sum_{n=1}^{\infty} B_n \right) \left(1 + \sum_{j=1}^{\infty} q_j l_j \right) = (N - S_{\infty}) \mathcal{T}_{E_k} \mathbb{E}(Y \wedge W) \\ &= (N - S_{\infty}) \mathcal{T}_{E_k} \mathcal{D}_{I_l}.\end{aligned}\quad (34)$$

Notice from (23) and (24) that

$$\begin{aligned}\sum_{n=1}^{\infty} F_n &= \sum_{n=1}^{\infty} (B_n + D_n) = \sum_{n=1}^{\infty} B_n + \sum_{n=1}^{\infty} (Q_{n-1} - Q_n + C_n) \\ &= \sum_{n=1}^{\infty} B_n + Q_0 + \sum_{n=1}^{\infty} C_n = \sum_{n=1}^{\infty} B_n + \sum_{n=1}^{\infty} (E_{n-1} - E_n + A_n - B_n) \\ &= \sum_{n=1}^{\infty} B_n + E_0 + \sum_{n=1}^{\infty} A_n - \sum_{n=1}^{\infty} B_n \\ &= N - S_{\infty}.\end{aligned}\quad (35)$$

Using (25), (34) and (35) we have that

$$\begin{aligned}\sum_{n=1}^{\infty} H_n &= F_1 - I_1 + \sum_{n=2}^{\infty} \left(F_n + \sum_{j=1}^{n-1} F_{n-j} q_j - I_n \right) = \sum_{n=1}^{\infty} F_n + \sum_{j=1}^{\infty} \left(q_j \sum_{n=1}^{\infty} F_n \right) - \sum_{n=1}^{\infty} I_n \\ &= \left(\sum_{n=1}^{\infty} F_n \right) \left(1 + \sum_{j=1}^{\infty} q_j \right) - \sum_{n=1}^{\infty} I_n = \mathbb{E}(Y) \left(\sum_{n=1}^{\infty} F_n \right) - \sum_{n=1}^{\infty} I_n \\ &= (N - S_{\infty}) \left(\mathcal{D}_I - \mathcal{T}_{E_k} \mathcal{D}_{I_l} \right).\end{aligned}\quad (36)$$

From the S equation in (26), (34) and (36) we obtain a set of equation satisfied by the final epidemic size:

$$\begin{aligned}\ln \frac{S_0}{S_{\infty}} &= \frac{\lambda}{N} \left[\sum_{n=1}^{\infty} I_n + (1 - \rho) \sum_{n=1}^{\infty} H_n \right] \\ &= \left(1 - \frac{S_{\infty}}{N} \right) \left[\lambda \mathcal{T}_{E_k} \mathcal{D}_{I_l} + \lambda (1 - \rho) \left(\mathcal{D}_I - \mathcal{T}_{E_k} \mathcal{D}_{I_l} \right) \right] \\ &= \left(1 - \frac{S_{\infty}}{N} \right) \mathcal{R}_c.\end{aligned}$$

This completes the proof of Result 3.

Remark 1. The final size relation (33) is given by the expression (formally) generated under Model (5), that is, the expression derived when constant per-capita rates were assumed.

However, it is worth noticing that the details involved in each $\mathcal{R}_c$ are important since they are expressed in terms of quantities associated with specific probability distributions (e.g., expectations, etc.). In other words, changes in distributions lead to the same *formal* formulae but most often to quantitatively distinct results.

Remark 2. The usefulness of the $\mathcal{R}_c$ formula given in (32) emerges from the fact that it was derived for general stage distributions. The expression for $\mathcal{R}_c$ allows for the investigation of its dependence on the means and control-adjusted means (e.g., $\mathcal{D}_I$, $\mathcal{D}_{I_l}$ etc.) of the stage distributions. These expressions also allow us to explore the role of control measures

(quarantine and isolation) in reducing $\mathcal{R}_c$ as a function of pre-selected stage distributions (see Section 4).

The case of geometric distribution

The general model (26) allows for the use of any distribution; including the use of empirical probability distributions computed from data and three of the most common discrete distributions, the geometric, Poisson and binomial distributions (see Figs. 4, 5 and theoretical results). We show first that the $\mathcal{R}_c$ formula (3) obtained for Model (1) is but a special case of the formula (32); the expression that one gets when the distributions for the latent and infectious stages are given by geometric distributions.

The geometric distribution, a discrete probability distribution supported on $\{1, 2, 3, \dots\}$, represents the number of independent Bernoulli trials needed to get a single success (see [4]). When X follows a geometric distribution with parameter α ($X \sim \text{Geom}(\alpha)$, see Fig. 4),

$$\mathbb{P}(X=i) = \alpha^{i-1}(1-\alpha), \quad \mathbb{P}(X>i) = \alpha^i \quad \text{and} \quad \mathbb{E}(X) = \frac{1}{1-\alpha}.$$

Like its continuous analogue (the exponential distribution), the geometric distribution is memoryless, that is, for any $i, j \in \mathbb{N}$,

$$\mathbb{P}(X>i+j|X>i) = \mathbb{P}(X>j).$$

Consider the case where the distributions in (15) are geometric. Assumed that $X \sim \text{Geom}(\alpha)$, $Y \sim \text{Geom}(\beta)$, $Z \sim \text{Geom}(\gamma)$ and $W \sim \text{Geom}(\sigma)$, that is,

$$\begin{aligned} p_i &= \alpha^i, & q_i &= \beta^i, \\ k_i &= \gamma^i, & l_i &= \sigma^i. \end{aligned}$$

The mean of X can be easily computed

$$\mathbb{E}(X) = \sum_{i=0}^{\infty} \alpha^i = \frac{1}{1-\alpha}.$$

Similarly $\mathbb{E}(Y) = \frac{1}{1-\beta}$, $\mathbb{E}(Z) = \frac{1}{1-\gamma}$ and $\mathbb{E}(W) = \frac{1}{1-\sigma}$. Moreover, $\mathbb{P}(X \wedge Z > i) = \alpha^i \gamma^i$, so that $\mathbb{E}(X \wedge Z) = \frac{1}{1-\alpha\gamma}$. Therefore

$$\begin{aligned} \mathcal{D}_E &= \frac{1}{1-\alpha}, & \mathcal{D}_{E_k} &= \frac{1}{1-\alpha\gamma}, \\ \mathcal{D}_I &= \frac{1}{1-\beta}, & \mathcal{D}_{I_l} &= \frac{1}{1-\beta\sigma}, \end{aligned} \quad (37)$$

Similarly, we are also able to compute $\mathcal{D}_{E_k}$

$$\mathbb{P}(X \leq Z) = \sum_{j=1}^{\infty} (p_{j-1} - p_j) k_{j-1} = \sum_{j=1}^{\infty} \alpha^{j-1} (1 - \alpha) \gamma^{j-1} = \frac{1 - \alpha}{1 - \alpha\gamma}. \quad (38)$$

If we go back to (18) we see that, under the geometric distribution assumption,

$$\begin{aligned} A_n p_1 k_1 + \dots + A_1 p_n k_n + A_0 p_{n+1} k_{n+1} &= A_n \alpha \gamma + \dots + A_1 \alpha^n \gamma^n + A_0 \alpha^{n+1} \gamma^{n+1} \\ &= \alpha \gamma E_n, \end{aligned}$$

so that

$$E_{n+1} = (1 - G_n) S_{n+\alpha\gamma} E_n. \quad (39)$$

Similarly, from (21)

$$\begin{aligned} B_{n+1} &= A_n (1 - \alpha) + A_{n-1} \alpha (1 - \alpha) \gamma + \dots + A_1 \alpha^{n-1} (1 - \alpha) \gamma^{n-1} + A_n \alpha^n (1 - \alpha) \gamma^n \\ &= (1 - \alpha) E_n; \end{aligned}$$

and from (23) $C_{n+1} = \alpha(1 - \gamma)E_n$. Similar arguments show that

$$Q_{n+1} = \alpha(1 - \gamma) + \alpha Q_n \quad \text{and} \quad I_{n+1} = (1 - \alpha) E_n + \beta \sigma I_n. \quad (40)$$

Hence (24) becomes $D_{n+1} = (1 - \alpha)Q_n$ and Equation (25) is equivalent to

$$H_{n+1} = (1 - \alpha) Q_n + \beta (1 - \sigma) I_n + \beta H_n. \quad (41)$$

Notice that the equations in (39)–(41) for E , Q , I and H are the same as those in Model (1).

Finally, combining (37) and (38), we can rewrite the control reproduction number (31) in this case explicitly as follows:

$$\begin{aligned} \mathcal{R}_I &= \lambda \mathcal{T}_{E_k} \mathcal{D}_{I_l} = \lambda \frac{1 - \alpha}{1 - \alpha\gamma} \cdot \frac{1}{1 - \beta\sigma}, \\ \mathcal{R}_{IH} &= \lambda (1 - \rho) \mathcal{T}_{E_k} \left(\mathcal{D}_I - \mathcal{D}_{I_l} \right) = \lambda (1 - \rho) \frac{1 - \alpha}{1 - \alpha\gamma} \cdot \left(\frac{1}{1 - \beta} - \frac{1}{1 - \beta\sigma} \right), \\ \mathcal{R}_{QH} &= \lambda (1 - \rho) \left(1 - \mathcal{T}_{E_k} \right) \mathcal{D}_I = \lambda (1 - \rho) \frac{\alpha(1 - \gamma)}{1 - \alpha\gamma} \cdot \frac{1}{1 - \beta}. \end{aligned}$$

Formally, the same expression for $\hat{\mathcal{R}}_I$, $\hat{\mathcal{R}}_{IH}$, and $\hat{\mathcal{R}}_{QH}$ given in (4).

Thus, we have verified that Model (1) is a special case of the general model (26) when the stage distributions are geometric.

4 Applications of the general model (26)

The control reproduction number and final epidemic size are important measures, which are often to compare the effectiveness of control strategies like quarantine and/or isolation. In our framework, $\mathcal{R}_C$ can be used to examine the impact of the shape of the waiting time distributions as well (see [6] in the continuous-time models case). In this section, we

compare the role of three classical discrete distributions when they are used to model the latent and infectious stage durations (described by X and Y , respectively). The geometric distribution assumption (GDA) will be linked to the random variables X_g and Y_g ; the poisson distribution assumption (PDA) to X_p and Y_p ; and binomial distribution assumption (BDA) to X_b and Y_b . We refer to the models corresponding to these distributions as GDM (geometric distribution model), PDM (poisson distribution model), and BDM (binomial distribution model), respectively. As for the quarantine (described by Z) and isolation (described by W) period distributions it will be assumed here, for simplicity, that they follow geometric distributions with means

$$\mathbb{E}(Z) = \frac{1}{1-\gamma} \quad \text{and} \quad \mathbb{E}(W) = \frac{1}{1-\sigma}.$$

4.1 Specific stage distribution examples

The GDA with means

$$\mathbb{E}(X_g) = \mu_1 \quad \text{and} \quad \mathbb{E}(Y_g) = \mu_2.$$

is used as to model our baseline case. The GDA case is compared to the PDA case with parameters

$$X_p - 1 \sim \text{Poisson}(\mu_1 - 1) \quad \text{and} \quad Y_p - 1 \sim \text{Poisson}(\mu_2 - 1),$$

and the BDA case with parameters

$$X_b - 1 \sim \text{Binomial}(n_1, a) \quad \text{and} \quad Y_b - 1 \sim \text{Binomial}(n_2, b).$$

The support of a Poisson distributed random variable P with parameter λ is the set $\{0, 1, 2, \dots\}$, **Fig. 5**. In fact,

$$\mathbb{P}(P=i) = e^{-\lambda} \frac{\lambda^i}{i!} \quad \text{and} \quad \mathbb{E}(P) = \lambda; \quad (42)$$

and thus, X_p is a shifted Poisson random variable with support $\{1, 2, 3, \dots\}$ and mean μ_1 .

The support of a binomial distributed random variable B with integer size parameter $m > 0$ and probability parameter $p \in (0, 1)$ is the set $\{0, 1, 2, \dots, m\}$ (**Fig. 6**). Its density function and expectation are given by

$$\mathbb{P}(B=i) = \binom{m}{i} p^i (1-p)^{m-i} \quad \text{and} \quad \mathbb{E}(B) = mp. \quad (43)$$

Thus, the parameters n_1 and a of the shifted binomial r.v. X_b must satisfy $(n_1 - 1)a + 1 = \mu_1$. Here, n_1 is the maximum amount of time that an infected individual will remain latent (i.e., either in the E or the Q class). That is, X_b is bounded by n_1 .

4.2 Expected remaining sojourns

The analysis on the role of exponential and gamma distributed stage durations distributions in continuous-time models carried out using expected remaining sojourns in ([6]). In the case of exponential distributions, the mean sojourn and the expected remaining sojourn are identical (memoryless property) whereas in the case of the gamma distribution the expected remaining sojourn can be much shorter than the mean sojourn. Hence, it is not surprising to see that the use of distinct distributions leads to discrepancies as well when uses discrete-time models to make predictions. We follow the philosophy in [6] as we proceed to document stage-distribution generated model discrepancies here.

We start with a definition, if s units of time have elapsed at a given stage (latent or infectious) then the expected remaining sojourn at step s is

$$\mathcal{M}_U(s) = \begin{cases} \sum_{n=0}^{\infty} \mathbb{P}(U > n | U > s) = \sum_{n=0}^{\infty} \frac{\mathbb{P}(U > n+s)}{\mathbb{P}(U > s)} & \text{if } \mathbb{P}(U > s) > 0 \\ 0 & \text{if } \mathbb{P}(U > s) = 0 \end{cases}$$

where $U = X, Y$. In the first case,

$$\mathcal{M}_X(s) = \sum_{n=0}^{\infty} \frac{p_{n+s}}{p_s}, \quad \mathcal{M}_Y(s) = \sum_{n=0}^{\infty} \frac{q_{n+s}}{q_s}.$$

Clearly $\mathcal{M}_U(0) = \mathbb{E}(U)$ for $U = X, Y$. If U is bounded by M , say $\mathbb{P}(U > M) = 0$, then for all $m \geq M$ $\mathcal{M}_U(m) = 0$. Note that in the case of GDM, i.e., for X_g (GDA) with parameter α , we have $p_{i,g} = \alpha^i$ and

$$\mathcal{M}_{X_g}(s) = \sum_{n=0}^{\infty} \frac{\alpha^{n+s}}{\alpha^s} = \sum_{n=0}^{\infty} \alpha^n = \mathbb{E}(X_g) = \mathcal{M}_{X_g}(0),$$

which shows that the expected remaining sojourn after an individual already spent s units of time in the latent stage is independent of s . This may contribute in a significant way to the potentially biased model predictions on the effect of disease control strategies. The use of PDM and BDM may lead to more reliable assessments because of their ability to capture more accurately the description for the expected remaining sojourns. **Fig. 7** illustrates the difference among the three distribution assumptions (GDA, PDA, and BDA) by plotting the expected remaining sojourn as a function of s (the time elapsed after entering the latent stage). This figure shows that the function is constant under GDA, while the functions correspond to PDA and BDA decreases with s .

4.3 The control reproduction number $\mathcal{R}_C$ under specific distributions

Let $\mathcal{R}_{C,g}$, $\mathcal{R}_{C,p}$ and $\mathcal{R}_{C,b}$ denote the control reproduction numbers for the GDM, PDM and BDM, respectively. The formula for $\mathcal{R}_{C,p}$ has been discussed in Section 3.1. For $\mathcal{R}_{C,p}$, we can first specify $\mathcal{I}_{E_{k,p}}$ and $\mathcal{I}_{I_{l,g}}$ using (42) as follows:

$$\begin{aligned}
\mathcal{T}_{E_{k,p}} &= \sum_{i=1}^{\infty} \mathbb{P}(X_p=i) \mathbb{P}(Z>i-1) = e^{-(\mu_1-1)} \sum_{i=1}^{\infty} \frac{(\mu_1-1)^{i-1}}{(i-1)!} \cdot \gamma^{i-1} \\
&= e^{-(\mu_1-1)(1-\gamma)} \\
\mathcal{D}_{I_{l,p}} &= 1 + \sum_{i=1}^{\infty} q_{i,p} l_i = 1 + \sum_{i=1}^{\infty} \left(1 - e^{-(\mu_2-1)} \sum_{j=1}^{\infty} \frac{(\mu_2-1)^{j-1}}{(j-1)!} \right) \sigma^i \\
&= 1 + \frac{\sigma}{1-\sigma} - e^{-(\mu_2-1)} \sum_{i=1}^{\infty} \sum_{j=1}^{i-1} \frac{(\mu_2-1)^j}{j!} \sigma^i = \frac{1}{1-\sigma} - e^{-(\mu_2-1)} \sum_{j=0}^{\infty} \sum_{i=j+1}^{\infty} \frac{(\mu_2-1)^j}{j!} \sigma^i \\
&= \frac{1}{1-\sigma} - e^{-(\mu_2-1)} \sum_{j=0}^{\infty} \frac{(\mu_2-1)^j}{j!} \frac{\sigma^{j+1}}{1-\sigma} = \frac{1}{1-\sigma} - e^{-(\mu_2-1)} \frac{\sigma}{1-\sigma} \sum_{j=0}^{\infty} \frac{[(\mu_2-1)\sigma]^j}{j!} \\
&= \frac{1-\sigma e^{-(\mu_2-1)(1-\sigma)}}{1-\sigma}.
\end{aligned}$$

Notice that, $\mathcal{D}_{I_l} = \mathcal{D}_I$ for $\sigma = 1$. Then, from (31)

$$\mathcal{R}_{C,p} = \begin{cases} \lambda \left[(1-\rho) \mu_2 + \rho e^{-(\mu_1-1)(1-\gamma)} \cdot \frac{1-\sigma e^{-(\mu_2-1)(1-\sigma)}}{1-\sigma} \right] & \text{if } 0 \leq \sigma < 1, \\ \lambda \mu_2 \left[1 - \rho \left(1 - e^{-(\mu_1-1)(1-\gamma)} \right) \right] & \text{if } \sigma = 1. \end{cases}$$

The formula for $\mathcal{R}_{C,b}$ is much easier to obtain, as well as the expressions for $\mathcal{T}_{E_{k,b}}$ and $\mathcal{D}_{I_{l,b}}$, due to the fact that $p_{i,b} = q_{j,b} = 0$ for all $i \neq n_1, j \neq n_2$.

The derivatives of $\mathcal{R}_C$ with respect to the control parameters (e.g., γ and σ) can provide useful information about the effect of controls on the reduction of $\mathcal{R}_C$. Note that $0 < \alpha, \beta, \gamma, \sigma < 1$ and $\mu_i > 1$ for $i = 1, 2$. Then the partial derivatives under GDA and PDA have the following properties:

$$\begin{aligned}
\frac{\partial \mathcal{R}_{C,g}}{\partial \gamma} &= \lambda \rho \cdot \frac{1-\alpha}{1-\beta\sigma} \cdot \frac{\alpha}{(1-\alpha\gamma)^2} > 0, \\
\frac{\partial \mathcal{R}_{C,g}}{\partial \sigma} &= \lambda \rho \cdot \frac{1-\alpha}{1-\alpha\gamma} \cdot \frac{\beta}{(1-\beta\sigma)^2} > 0,
\end{aligned}$$

and

$$\begin{aligned}
\frac{\partial \mathcal{R}_{C,p}}{\partial \gamma} &= \lambda \rho (\mu_1 - 1) \cdot e^{-(\mu_1-1)(1-\gamma)} \cdot \frac{1-\sigma e^{-(\mu_2-1)(1-\sigma)}}{1-\sigma} > 0, \\
\frac{\partial \mathcal{R}_{C,p}}{\partial \sigma} &= \lambda \rho \cdot e^{-(\mu_1-1)(1-\gamma)} \cdot \frac{e^{-(\mu_2-1)(1-\sigma)} [(\mu_2-1)\sigma^2 - (\mu_2-1)\sigma - 1] + 1}{(1-\sigma)^2} > 0.
\end{aligned}$$

In the derivation of the last inequality we have used the several facts:

We noticed first that in order to prove $\frac{\partial \mathcal{R}_{C,p}}{\partial \sigma} > 0$ we just have to show $f(\sigma) > 0$, where

$$f(\sigma) = e^{-(\mu_2-1)(1-\sigma)} \left[(\mu_2 - 1) \sigma^2 - (\mu_2 - 1) \sigma - 1 \right] + 1.$$

Then from $f'(\sigma) = (\mu_2 - 1)e^{-(\mu_2 - 1)(1 - \sigma)}[(\mu_2 - 1)\sigma^2 - (\mu_2 - 1 - 2)\sigma - 2]$ we managed to compute the critical points of f : $\sigma = -\frac{2}{\mu_2 - 1}$ and $\sigma = 1$. Finally, using the fact that $f(0) > 0$ and $f(1) = 0$ we get the desired result.

The sensitivity of the reproduction number to the variations on control parameters can be evaluated using the normalized derivatives

$$\frac{\frac{\partial \mathcal{R}_{C,w}}{\partial \gamma}}{\frac{\mathcal{R}_{C,w}}{\gamma}} \quad \text{and} \quad \frac{\frac{\partial \mathcal{R}_{C,w}}{\partial \sigma}}{\frac{\mathcal{R}_{C,w}}{\sigma}} \quad \text{for } w=g, p. \quad (44)$$

We can examine how these functions change with γ and/or σ . Two examples are illustrated in **Fig. 8** in the geometric (left) and the Poisson distributions (right) cases. The solid and dashed curves show the changes in γ or σ , respectively, while the other control parameter is fixed at the value 0.5. We observe that in the case of geometric distribution, the sensitivities to γ and σ do not differ significantly. However, in the case of Poisson distribution, the sensitivity to γ (quarantine) is much higher than that to σ (isolation). Other parameter values used in the generation of this figure are $\lambda = 0.75$, $\rho = 0.95$, $\mu_1 = 8$, $\mu_2 = 6$.

Next, we examine the role of model assumptions (GDA, PDA and BDA) on the impact of quarantine and isolation in reducing $\mathcal{R}_C$ and, consequently, the final epidemic size for the models (GDM, PDM and BDM). For the purpose of comparison, we take X_g, X_p, X_b with mean μ_1 and Y_g, Y_p, Y_b with mean μ_2 . **Fig. 9** plots the control reproduction number $\mathcal{R}_C$ vs γ (quarantine) or σ (isolation). The left figure is for $\mathcal{R}_{C,g}$ (i.e., when X and Y are geometric distributions) and the right figure is for $\mathcal{R}_{C,p}$ (i.e., when X and Y are poisson distributions). **Fig. 9** shows reduction in $\mathcal{R}_C$ under two control strategies: Strategy I corresponds to $\gamma = 0.5$ and $\sigma = 0.8$ (represented by a circle on the curve) while Strategy II corresponds to $\gamma = 0.8$ and $\sigma = 0.5$ (represented by a diamond on the curve). We see that the two distributions (geometric and poisson) may generate contradictory assessments. For example, it is shown in the left figure that under the geometric distribution assumption, Strategy II is more effective than Strategy I, since it leads to larger reductions in $\mathcal{R}_{C,g}$. However, it is shown in the right figure that under the poisson distribution, Strategy I is more effective than Strategy II, since it leads to larger reductions in $\mathcal{R}_{C,p}$. The parameter values used are $\lambda = 0.75$, $\rho = 0.95$, $\mu_1 = 5$, $\mu_2 = 10$.

Similar discrepancies are also identified when the final epidemic sizes are compared (the final size can be represented by $N - S_\infty$ where N is constant). **Fig. 10** shows curves of final epidemic sizes generated by GDM and PDM as functions of γ (for fixed σ) or σ (for fixed γ). Again, we evaluate two strategies: Strategy I represented by $\gamma = 0.5$ and $\sigma = 0.8$ and Strategy II represented $\gamma = 0.8$ and $\sigma = 0.5$. It is shown in the left figure that under GDA, Strategy II is more effective than Strategy I since it leads to larger reductions in the final size $N - S_\infty$. However, the figure on the right shows that under PDA, Strategy I is more effective than Strategy II. Parameter values used in **Fig. 10** are $\lambda = 0.75$, $\rho = 0.95$, $\mu_1 = 5$, $\mu_2 = 10$.

Figs. 9 and 10 illustrate how $\mathcal{R}_C$ and the final size vary as a function of one of the control measures when the other remains fixed. In **Fig. 11**, the joint effect of quarantine (γ) and isolation (σ) on the reduction of $\mathcal{R}_C$ is illustrated. (A) shows the surface under GDA and (B) shows the same surface but under PDA. The plane corresponds to $\mathcal{R}_C=1$ and (C) collects the graphs of both surfaces. The parameter values used are the same as in the previous figure. We observe that for this set of parameter values, PDA provides a lower estimate of $\mathcal{R}_C$ for most values of γ and σ , except when either γ is large (less quarantine) or σ is large (less isolation). We also observe that within PDM is possible to decrease γ so that $R < 1$ for each fixed σ (including the case when $\sigma = 1$, i.e., no isolation), while this is not possible in the GDM case.

In addition to the reproduction number and final epidemic size, we can also examine some of the characteristics of epidemic curves generated by the three models (GDM, PDM, and BDM) and the influence on these characteristics of quarantine and isolation, as shown in **Fig. 12**. The values for the control parameters are $\gamma = .7$, $\sigma = .8$, the initial condition is $S = 980$, $E_0 = 20$, $I_0 = Q_0 = H_0 = R_0 = 0$, and $\lambda = .75$, $\rho = .95$. We observe that the GDM predicts a much higher peak for the initial epidemic than the other two models. However, it is not the case that the epidemic peak generated by the GDM is always higher. It is shown in **Fig. 13** that for different parameter values, the epidemic peak from the GDM may be lower than that generated by the other two models. The production of **Fig. 12** made use of modified the control parameters $\gamma = .9$ and $\sigma = .8$, the same initial conditions and $\lambda = .4$, $\rho = .95$.

5 Conclusions and Observations

This paper focuses primarily on the evaluation of the impact of epidemiological and control stage-duration distributions on the quantitative dynamics of discrete-time single-outbreak epidemiological models. The analyses allow the evaluation of the final epidemic size and the role of stage-duration distributions on the additive components in the control reproduction number. The models considered are discrete-time SEIR-type single-outbreak epidemic models with built in control strategies (quarantine and isolation). The model's analyses are carried out under unrestricted that is, general stage-duration distributions for the latent and the infectious stages. The results are discussed in particular within the context of three classical discrete parametric distributions, the geometric, Poisson and binomial. We observe, as expected, that geometric distribution corresponds to the constant transition rates between epidemic classes submodel (1); the simplest and most commonly used. General model results suggest for example, that the use of distinct parametric distributions can lead to contradictory predictions (see **Figs. 9 and 10**). We tried to tease out some of the consequences that arise from the use of selected distributions in the context of particular intervention efforts. A comprehensive evaluation requires the use of data sets and model validation approaches, topics beyond the scope of this manuscript. It would not be surprising to see that the priori selection of parametric distribution plays a critical important role in forecasting. Fortunately, the framework introduced in this manuscript allows for the incorporating of empirical stage-duration distributions. The use of data-generated stage-duration distributions directly provides an approach that some may consider satisfactory,

particularly when model results turned out to be highly sensitive to distribution shape parameters.

In addition, it seems natural to inquire whether or not the use of continuous-time distributions lead to different conclusions. We re-introduce the continuous-time model studied in ([6]) in order to discuss the relations between discrete and continuous-time models. The continuous time model in ([6]), the analogue of the geometric distribution model (GDM), is given by the following set of nonlinear equations:

$$\begin{aligned} S' &= -\lambda S \frac{I+(1-\rho)H}{N} \\ E' &= \lambda S \frac{I+(1-\rho)H}{N} - (\chi+\theta) E \\ Q' &= \chi E - \theta Q \\ I' &= \theta_1 E - (\phi+\kappa) I \\ H' &= \theta_2 Q + \phi I - \kappa H \\ R' &= \kappa_1 I + \kappa_2 H, \end{aligned} \quad (45)$$

where all derivatives are taken with respect to time. The state variables (i.e., S, E, Q, I, H, R, N) are defined essentially as in the discrete-time model given by System (1). The parameter θ denotes the rate at which latent individuals in E and Q become infectious; κ denotes the rates at which infectious individuals in I and H recover; χ and ϕ denote the rates at which individuals in E and I become quarantined or isolated, respectively; λ is the infection rate and ρ the isolation efficiency. The transition parameters in Model (45) (e.g., transition from E to I or to Q) are rates, with values in $(0, \infty)$ whereas the parameters describing the transitions are probabilities per generation, with values in $(0, 1)$, for the discrete-time model (1). It was shown ([6]) that the exponential distribution assumption supports contradictory assessment on the relative impact of disease control strategies within the context of Model (45). The results in this manuscript show that discrete-time models are just as capable of generating the same type of discrepancies that those under Model (45) ([6]).

The general formula for $\mathcal{R}_C$ allows further examination of the role of its additive components ($\mathcal{R}_I$, $\mathcal{R}_{IH}$ and $\mathcal{R}_{QH}$). Components that represent the contributions from individuals in the I and the Q classes who enter the H class. These effects are illustrated in the geometric distribution (left) and the Poisson distribution (right) cases, Fig. 14. Here, Fig. 14 plots $\mathcal{R}_{I,w}$, $\mathcal{R}_{IH,w}$ and $\mathcal{R}_{QH,w}$ ($\omega = g, p$) as a function of the infectious period. The thin solid curve corresponds to $\mathcal{R}_C$. The parameter values used for in Fig. 14 are $\lambda = 0.75$, $\rho = 0.7$, $\gamma = 0.6$, $\sigma = 0.9$. We observe that $\mathcal{R}_{I,w}$ and $\mathcal{R}_{IH,w}$ have a much bigger impact on $\mathcal{R}_C$ than on $\mathcal{R}_{IQ,w}$. Further, the contributions from $\mathcal{R}_{I,w}$ and $\mathcal{R}_{IH,w}$ are different for both distributions. These effects are observed in particular, in the case of the geometric distribution where $\mathcal{R}_{I,g} > \mathcal{R}_{IH,g}$ for small infectious periods and $\mathcal{R}_{I,g} < \mathcal{R}_{IH,g}$ for larger infectious periods. In the case of the Poisson distribution, $\mathcal{R}_{IH,p}$ turns out to be significantly larger than $\mathcal{R}_{I,p}$ for all values of the infectious period, in the range displayed. Hence, the use of the PDM is more likely to emphasize the importance of isolation.

In Section 3 it was shown that the use of geometric distributions means that the expected remaining time in each stage is independent of the time (s) that an individual has already

spent in that stage (i.e., $\mathcal{M}_{x_g}(s) = \mathcal{M}_{x_g}(0)$). In the same section, it was also shown that for the PDM, $\mathcal{M}_{x_p}(s)$ is a decreasing function of time s . From these last two observations we conclude that the PDM may be a more appropriate model if the goal is to evaluate disease control strategies. The applications of our framework is extremely flexible because the probabilities p_i , q_i , k_i , and l_i do not have to come from a particular parametric family of discrete distributions. Model (26) can in fact incorporate directly empirically estimated (from the raw data) probabilities. That is, no specific assumptions on the shape of the duration-stage distribution of latent and infectious stages or on the waiting-time distributions in quarantine and/or isolation classes are required within the framework of this manuscript.

In addition, the question of what stage distribution(s) is (are) more appropriate depends on what we actually know about the epidemiological process. The specifics of each disease provide the most critical information. Researchers involved in the study of the dynamics of infectious diseases seem to prefer to work with models that make use of geometric stage-duration distributions. Needless to say, the latent or infectious stage distributions may be fit better alternative distributions, for a great number of infectious diseases. Does the general use of geometric distributions matter? In the goal is to carry out a qualitative study within single-outbreak epidemic models then no but if the goal is to assess quantitatively the efficacy of control measures for specific diseases then the answer is, most likely yes.

Finally, starting with the general model (26) an analytic formula for the control reproduction number $\mathcal{R}_C$ (see (30)–(32)) is derived as well as a final epidemic size relation; completely specified by $\mathcal{R}_C$ (see (33)). The formula for $\mathcal{R}_C$ is expressed in terms of the means and control-adjusted means of the general stage distributions (see **Remark 2** in Section 3). This level of specificity makes it possible and convenient to connect both with specific distributions. The use of Model (26) facilitates the comparison of epidemic curves. Here, primarily for expository reasons we have focused on situations involving explicit distributions, the geometric, Poisson, and binomial. From the use of specific parametric families, we see, for example, that the GDM supports higher epidemic peaks than the PDM or BDM in some cases (see **Fig. 12**). These observations reinforces the need for caution when simple models (such as the GDM) are used in the study of infectious diseases or as the dynamic framework used to estimate parameters from data, or as the cornerstone of efforts to assess the relative effectiveness of distinct control or intervention strategies.

Acknowledgments

This research is supported in part by the NSF grant DMS-1022758 and by grant number 1R01GM100471-01 from the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health.

References

1. Brauer F. Age-of-infection and the final size relation. *Math. Biosc. Eng.* 2008; 5:681–690.
2. Brauer F, Feng Z, Castillo-Chavez C. Discrete Epidemic Models. *Math. Biosc. and Eng.* 2010; 7:1–15.
3. Brauer, F.; Castillo-Chavez, C. *Texts in Applied Mathematics*. 2nd Edition.. Springer-Verlag; 2012. Mathematical models in population biology and epidemiology..
4. Berger RL, Casella G. *Statistical Inference*. Duxbury Advance Series (2nd edition). 2001

5. Dietz K, Heesterbeek JAP. Daniel Bernoulli's epidemiological model revisited. *Math. Biosc.* 1992; 180:1–21.
6. Feng Z, Xu D, Zhao H. Epidemiological models with non exponentially distributed disease stages and applications to disease control. *Bulletin of Mathematical Biology.* 2007; 69:1511–1539. [PubMed: 17237913]
7. Chowell G, Fenimore PW, Castillo-Garsow MA, Castillo-Chavez C. SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism. *J. Theor. Biol.* 2003; 224:1–8. [PubMed: 12900200]
8. Chowell G, Castillo-Chavez C, Fenimore PW, Kribs-Zaleta C, Arriola L, Hyman JM. Model parameters and outbreak control for SARS. *Emerging Infectious Diseases.* 2004; 10:1258–1263. [PubMed: 15324546]
9. Gumel A, Ruan S, Day T, Watmough J, van den Driessche P, Brauer F, Gabrielson D, Bowman C, Alexander ME, Ardal S, Wu J, Sahai BM. Modeling strategies for controlling SARS outbreaks based on Toronto, Hong Kong, Singapore and Beijing experience. *Proc. Roy. Soc. London.* 2004; 271:2223–2232.
10. Kermack WO, McKendrick AG. A Contribution to the Mathematical Theory of Epidemics. *Proceedings of the Royal Society of London. Series A.* 1927; 115:700–721.
11. Kermack WO, McKendrick AG. Contributions to the mathematical theory of epidemics, part. II. *Proc. Roy. Soc. London.* 1932; 138:55–83.
12. Kermack WO, McKendrick AG. Contributions to the mathematical theory of epidemics, part. III. *Proc. Roy. Soc. London.* 1933; 141:94–112.
13. Ma J, Earn DJD. Generality of the final size formula for an epidemic of a newly invading infectious disease. *Bull. Math. Biol.* 2006; 68:679–702. [PubMed: 16794950]
14. Ross, R. *The Prevention of Malaria.* 2nd Edition. John Murray; London: 1911.
15. Yang CK, Brauer F. Calculation of R_0 for age-of-infection models. *Math. Biosc. Eng.* 2008; 5:585–599.

Figure 1.
Disease transmission diagram for the discrete model (1) with constant transition rates.

Figure 2.
Transmission diagram for the discrete model with arbitrarily distributed stage durations.

Figure 3.
A contour plot of the function for the final epidemic size given in (14)

Geometric density function

(a) $\mathbb{P}(G = i)$

Geometric survival function

(b) $\mathbb{P}(G > i)$ **Figure 4.**

Plots of the geometric distributions with parameter α . It shows several curves corresponding different values of α .

Figure 5.

Similar to Fig. 4 but it is for the Poisson distributions with parameter λ . The curves correspond to values of $\lambda = 3, 5, 7, 10$ are shown.

(a) $\mathbb{P}(B=i)$ (b) $\mathbb{P}(B>i)$ **Figure 6.**

Similar to Fig. 4 but it is for the binomial distributions with parameter p and $m = 15$. The curves correspond to values of $p = 0.1, 0.2, 0.6, 0.9$.

Figure 7.

Plots of the expected remaining sojourn time, $\mathcal{M}_X(s)$, in a disease stage (latent or infectious) when s units of time have elapsed after entering the stage. It illustrates the difference among the three distributions as specified in the legend. Since the binomial random variable X is bounded, $\mathcal{M}_X(s) = 0$ after its upper bound.

Figure 8.

Sensitivity of $\mathcal{R}_c$ to the variation in one of the control parameters (γ and σ) while the other is fixed. The two models considered are the GDM and PDM.

Figure 9.

Comparison of the GDM and PDM in terms of their evaluations on various control measures when the corresponding control reproduction numbers, $\mathcal{R}_{C,g}$ and $\mathcal{R}_{C,p}$ are used. The two control strategies considered are represented by $\gamma = 0.5$ and $\sigma = 0.8$ (see the solid circle) and by $\gamma = 0.8$ and $\sigma = 0.5$ (see the solid diamond). The GDM (the left figure) suggests that the diamond strategy is more effective (as it reduces $\mathcal{R}_C$ the most), whereas the PDM (the right figure) suggests the opposite that the circle strategy is more effective.

Figure 10.

Similar to Fig. 9 but the comparison is made by using the final epidemic size. It illustrates a similar discrepancy as seen in Fig. 9 where $\mathcal{R}_C$ is used for the comparison.

Figure 11.

Plots showing the joint effect of quarantine (γ) and isolation (σ) on the reduction of reproduction number. The two surfaces corresponding to the GDM and the PDM, and the plane corresponds to $\mathcal{R}_C=1$.

Figure 12.

Numerical simulations showing the epidemic curves generated by the three models: GDA, PDA, and BDA from time $n = 10$ to $n = 250$. The control parameters have values $\gamma = .7$ and $\sigma = .8$. It shows that for this set of control parameters, the GDM generates a much higher epidemic peak than the other two models.

Figure 13.

Similar to **Fig. 12** but it is for a larger value of $\gamma = .95$ (a lower probability for quarantine). All other parameters have the same values as in **Fig. 12**. It shows that for this set of parameter values, the GDM generates a much lower epidemic peak than the other two models.

Figure 14.

Plots of the components of $\mathcal{R}_c$ ($\mathcal{R}_I$, $\mathcal{R}_{IH}$, and $\mathcal{R}_{QH}$) as functions of the control parameters (γ and σ). The two models considered are the GDM and the PDM.

Table 1

Definition of symbols and parameters frequently used in the model analysis and simulations.

Symbol	Definition
S_n	Number of susceptible individuals at time n
E_n	Number of exposed (not infectious) at time n
I_n	Number of infected (infectious) at time n
Q_n	Number of quarantined (not infectious) at time n
H_n	Number of isolated (infectious)
λ	Transmission coefficient, $\lambda \in [0, 1]$
ρ	Isolation efficiency, $\rho \in [0, 1]$
α	Proportion of those who stay in latent stages for the next step (under GDA)
β	Proportion of those who stay in infectious stages for the next step (under GDA)
$1 - \gamma$	Quarantine rate (in GDM, PDM and BDM)
$1 - \sigma$	Isolation rate (in GDM, PDM and BDM)
X	Random variable for the latent stages (E, Q)
Y	Random variable for the infectious stages (I, H)
Z	Random variable for the quarantined class (E, Q)
W	Random variable for the isolated class (E, Q)
p_j	$P(X > i)$, survival probability of X : probability of remaining non infectious j or more units of time after entering the E class
q_j	$P(Y > i)$, survival probability of Y
k_j	$P(Z > i)$, survival probability of Z
l_j	$P(W > i)$, survival probability of W
D_E	Latent period ($= E(X)$)
D_I	Infectious period ($= E(Y)$)
D_{I_l}	Isolation adjusted infectious period ($= E(Y \wedge Z)$)
T_E	Quarantine adjusted probability, $P(X \leq Z)$
R_C	Control reproduction number
μ_1, μ_2	Fixed mean of X and Y , when comparing GDM, PDM and BDM
GDA, PDA, BDA	geometric, Poisson, binomial distribution assumption, respectively
GDM, PDM, BDM	geometric, Poisson, binomial distribution model, respectively