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Stochastic monotonicity and continuity properties of functions defined on Crump–Mode–Jagers branching processes, with application to vaccination in epidemic modelling

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This paper is concerned with Crump–Mode–Jagers branching processes, describing spread of an epidemic depending on the proportion of the population that is vaccinated. Births in the branching process are aborted independently with a time-dependent probability given by the fraction of the population vaccinated. Stochastic monotonicity and continuity results for a wide class of functions (e.g., extinction time and total number of births over all time) defined on such a branching process are proved using coupling arguments, leading to optimal vaccination schemes to control corresponding functions (e.g., duration and final size) of epidemic outbreaks. The theory is illustrated by applications to the control of the duration of mumps outbreaks in Bulgaria.

Keywords: coupling; general branching process; Monte-Carlo method; mumps in Bulgaria; SIR epidemic model; time to extinction; vaccination policies

1. Introduction

Branching processes have been applied widely to model epidemic spread (see, e.g., the monographs by Andersson and Britton [2], Daley and Gani [9] and Mode and Sleeman [23], and the review by Pakes [24]). The process describing the number of infectious individuals in an epidemic model may be well approximated by a branching process if the population is homogeneously mixing and the number of infectious individuals is small in relation to the total size of the susceptible population, since under these circumstances the probability that an infectious contact is with a previously infected individual is negligible (see, e.g., Isham [16]). Such an approximation dates back to the pioneering works of Bartlett [8] and Kendall [18], and can be made mathematically precise by showing convergence of the epidemic process to a limiting branching

process as the number of susceptibles tends to infinity (see Ball [5], Ball and Donnelly [7] and Metz [22]). The approximation may also be extended to epidemics in populations that are not homogeneously mixing, for example, those containing small mixing units such as households and workplaces (see Pellis *et al.* [25]).

Before proceeding we give outline descriptions of some common branching process models (see, e.g., Jagers [17] for further details), which describe the evolution of a single-type population. In all of these models, individuals have independent and identically distributed reproduction processes. In a Bienaymé–Galton–Watson branching process, each individual lives for one unit of time and then has a random number of children, distributed according to a random variable, ζ say. In a Bellman–Harris branching process (BHBP), each individual lives until a random age, distributed according to a random variable I say, and then has a random number of children, distributed according to ζ, where I and ζ are independent. The Sevast'yanov branching process (SBP) is defined similarly, except I and ζ may be dependent, so the number of children an individual has is correlated with that individual's lifetime. Finally, in a general branching process, also called a Crump–Mode–Jagers (CMJ) branching process, each individual lives until a random age, distributed according to I, and reproduces at ages according to a point process ξ. More precisely, if an individual, i say having reproduction variables (I_i, ξ_i), is born at time b_i and $0 \le \tau_{i1} \le \tau_{i2} \le \cdots \le I_i$ denote the points of ξ_i, then individual i has one child at each of times $b_i + \tau_{i1}, b_i + \tau_{i2}, \ldots$.

This paper is primarily concerned with models for epidemics of diseases, such as measles, mumps and avian influenza, which follow the so-called SIR (Susceptible $\to$ Infective $\to$ Removed) scheme in a closed, homogeneously mixing population or some of its extensions. A key epidemiological parameter for such an epidemic model is the basic reproduction number R_0 (see Heesterbeek and Dietz [15]), which in the present setting is given by the mean of the offspring distribution of the approximating branching process. In particular a major outbreak (i.e., one whose size is of the same order as the population size) occurs with nonzero probability if and only if $R_0 > 1$. Suppose that $R_0 > 1$ and a fraction c of the population is vaccinated with a perfect vaccine in advance of an epidemic. Then R_0 is reduced to $(1 - c)R_0$, since a proportion c of infectious contacts is with vaccinated individuals. It follows that a major outbreak is almost surely prevented if and only if $c \ge 1 - R_0^{-1}$. This well-known result, which gives the critical vaccination coverage to prevent a major outbreak and goes back at least to 1964 (e.g., Smith [26]), is widely used to inform public health authorities.

As a consequence of the above result, many analyses of vaccination strategies in the epidemic modelling literature have focussed on reducing R_0 to its critical value of one. However, if the population is large, both the total size and the duration of an outbreak may still be appreciable. Indeed, in the limit as the population size tends to infinity, when $R_0 = 1$, both of these quantities have infinite expectation under any plausible modelling assumptions. In practice, there may be a cost associated with an individual contracting the disease being modelled, in which case it is of interest to determine vaccination strategies which reduce the expected value of the total cost of an outbreak to an acceptable level. Alternatively, it may be desired to control the duration of an outbreak, for example, if the presence of an outbreak means that restrictions are placed on the population within which it is spreading. Clearly, for large populations, both of these aims necessitate that R_0 is reduced to somewhat less than one. The above remarks pertain to the common situation of controlling an epidemic that is in its increasing phase. A different situation

arises with diseases, such as measles and mumps, which are controlled by mass vaccination but small outbreaks still occur among unvaccinated individuals. Supplementary vaccination may be used to reduce the size or duration of such outbreaks (as in the illustrative example of mumps in Bulgaria in Section 4 of this paper). A similar phenomenon occurs with pathogens, such as monkeypox virus, which primarily affect animals but spill over into human populations giving stuttering chains of human-to-human transmission (Lloyd-Smith *et al.* [20]). In at least some of the above scenarios, it may be the case that a specific vaccination level cannot be achieved immediately but rather the fraction of the population that is vaccinated will be time-dependent. The aim of this paper is to develop a methodology based on branching processes for addressing the above issues in a unified fashion.

González *et al.* [13,14] studied properties of the time to extinction of an epidemic given that a fraction c of individuals is vaccinated, when the number of infectious individuals in the population is modelled by a continuous-time BHBP and a (more general) continuous-time SBP, respectively. In an earlier work, De Serres *et al.* [10] used a discrete-time Bienaymé–Galton–Watson branching process to study the spread of an infectious disease under various control measures, specifically to estimate the effective (i.e., post-control) value of R_0 from observations on size and durations of small outbreaks. The main objective in González *et al.* [13,14] was to determine the optimal proportion of susceptible individuals which has to be vaccinated so that the mean (or given quantile of the) extinction time of the disease is less than some specified value. To that end, stochastic monotonicity and continuity properties of the distribution function and mean of the time that the infection survives, depending on the vaccination coverage rate were first determined.

In the present paper, we extend the results in González *et al.* [13,14] in several directions that are both practically and theoretically important. First, we assume that the spread of infection is modelled as a CMJ branching process. The CMJ branching process is appropriate for modelling the early stages of a very wide variety of SIR epidemics, and includes both BHBP and SBP as special cases. Second, we consider more general vaccination processes. In González *et al.* [13, 14] it was assumed that the fraction of the population that is vaccinated remained constant with time. We now allow this fraction to be an arbitrary but specified function of time, thus capturing for example the setting in which people are vaccinated as the disease spreads. Third, we consider the control of more general functions of the epidemic process. González *et al.* [13,14] focused on controlling the duration of the epidemic. The methods developed in this paper are applicable to a wide class of functions of the epidemic process. In addition to the duration of an outbreak, this class includes, for example, the total number of people infected and the maximum number of infected people present during the epidemic.

The methodology of the paper is very different from that of González *et al.* [13,14]. The key stochastic monotonicity and continuity results in these papers were obtained by analysis of integral equations governing properties of the time to extinction of the branching process. In the present paper, a main tool is coupling and, in particular, a pruning method of constructing a realisation of a vaccinated process from that of the corresponding unvaccinated process. As indicated in Section 5, this methodology is very powerful and applicable to a broad range of processes.

The remainder of the paper is organised as follows. In Section 2, we describe a very general model for an SIR epidemic in a closed, homogeneously mixing community and explain why its

early spread may be approximated by a CMJ branching process. We introduce a very general vaccination process and give the basic coupling construction for obtaining a realisation of the vaccinated epidemic process from that of the unvaccinated process. The theoretical results of the paper are given in Section 3. In Section 3.1, we introduce functions of a realisation of a CMJ branching process that are monotonically decreasing with pruning. Examples of such functions include the extinction time, the maximum population size over all time and the total number of births over all time. Then we prove in general, that is, independently of the function, monotonicity and continuity properties of the mean (Section 3.2), distribution function (Section 3.3) and quantiles (Section 3.4) of such functions. In Section 3.5, we use the previous results to define optimal vaccination policies based on mean and quantiles. The theory is then specialised in Section 3.6 to the extinction time of an outbreak. The methodology is illustrated in Section 4 with applications to mumps in Bulgaria, where vaccination is targeted at reducing the duration of an outbreak. The paper ends with some concluding comments in Section 5.

2. Model and coupling construction

Consider first the following model for the spread of an epidemic in a closed, homogeneously mixing population. Initially there are a infectives and N susceptibles. Infectious individuals have independent and identically distributed life histories $\mathcal{H} = (I, \xi)$, where I is the time elapsing between an individual's infection and his/her eventual removal or death and ξ is a point process of times, relative to an individual's infection, at which infectious contacts are made. Each contact is with an individual chosen independently and uniformly from the population. If a contact is with an individual who is susceptible, then that individual becomes infected and itself makes contacts according to its life history. If a contact is with an individual who is not susceptible, then nothing happens. The epidemic ceases as soon as there is no infective present in the population. Note that, for simplicity, we assume that every infectious contact with a susceptible necessarily leads to that susceptible becoming infected. The model is easily extended to the situation when each contact with a susceptible is successful (i.e., leads to infection) independently with probability p by letting $\mathcal{H} = (I, \xi')$, where ξ' is a suitable thinning of ξ.

The above model is essentially that introduced by Ball and Donnelly [7], who noted that it included as special cases a range of specific models that had hitherto received considerable attention in the literature. For example, SIR and SEIR (Susceptible $\to$ Exposed (i.e., latent) $\to$ Infective $\to$ Removed) models come under the above framework. The only difference between the above model and that in Ball and Donnelly [7] is that, in the latter, each contact is with an individual chosen independently and uniformly from the N initial susceptibles (rather than from the entire population of $N + a$ individuals). In Ball and Donnelly [7], a coupling argument (which also holds for the present model) is used to prove strong convergence, as the number of initial susceptibles $N \to \infty$ (with the number of initial infectives a held fixed), of the process of infectives in the epidemic model to a CMJ branching process (see Jagers [17]), in which a typical individual lives until age I and reproduces at ages according to ξ. Thus for large N, the epidemic may be approximated by the CMJ branching process. The approximation assumes that every contact is with a susceptible individual. The proof in Ball and Donnelly [7] may be extended to epidemics other than SIR, for example, SIS (Susceptible $\to$ Infective $\to$ Susceptible)

and SIRS (Susceptible → Infective → Removed → Susceptible), by suitably generalizing the life history $\mathcal{H}$ to allow for removed individuals to become susceptible again (see, e.g., Ball [6] in the context of epidemics among a population partitioned into households). Indeed, for a very broad class of homogeneously mixing epidemic models, that covers all of the common stochastic formulations of infectious disease spread, the early stages of an epidemic in a large population with few initial infectives may be approximated by a CMJ branching process.

This paper is concerned with the use of vaccination schemes to control an epidemic, for example, in terms of its duration or of the total number of individuals infected. We are thus interested in the short-term behaviour of the epidemic, so we model the epidemic as a CMJ branching process, $Z = \{Z(t) : t \geq 0\}$, where $Z(t)$ denotes the number of infected individuals at time t. Thus $Z(0)$, which we assume to be fixed, represents the number of infected individuals at the beginning of the outbreak.

We model the vaccination process by a function $\alpha : [0, \infty) \to [0, 1]$, such that $\alpha(t)$ is the proportion of the population that are immune at time t ($t \geq 0$). Thus, the probability that a contact at time t is with a susceptible (i.e., non-immune) individual is $1 - \alpha(t)$. If the vaccine is perfect, that is, it confers immunity immediately with probability one, then $\alpha(t)$ is given by the proportion of the population that has been vaccinated by time t. If the vaccine is imperfect then that is implicitly included in the function α. For example, if the vaccine is all-or-nothing (i.e., it renders the vaccinee completely immune with probability ε, otherwise it has no effect), then $\alpha(t) = \varepsilon\tilde{\alpha}(t)$, where $\tilde{\alpha}(t)$ is the proportion of the population that has been vaccinated by time t. Note that if the immunity conferred by vaccination does not wane then α is nondecreasing in t. We denote by $Z_\alpha = \{Z_\alpha(t) : t \geq 0\}$ the vaccination version of Z, in which each birth in Z is aborted independently, with probability $\alpha(t)$ if the birth time is at time t.

Let $\mathcal{A}$ be the space of all functions $\alpha : [0, \infty) \to [0, 1]$. We construct coupled realizations of Z and Z_α ($\alpha \in \mathcal{A}$) on a common probability space $(\Omega, \mathcal{F}, P)$ as follows. Let $(\Omega_1, \mathcal{F}_1, P_1)$ be a probability space on which are defined independent life histories $\mathcal{H}_1, \mathcal{H}_2, \ldots$, each distributed as $\mathcal{H}$, which are pieced together in the obvious fashion to construct a realization of Z. More specifically, the life histories $\mathcal{H}_1, \mathcal{H}_2, \ldots, \mathcal{H}_a$ are assigned to the a initial infectives and, for $i = 1, 2, \ldots$, the ith individual born in Z is assigned the life history $\mathcal{H}_{a+i}$. Note that with this construction Z may be viewed as a tree, which is augmented with birth and death times of branches. Let $(\Omega_2, \mathcal{F}_2, P_2)$ be a probability space on which is defined a sequence $U_1, U_2, \ldots$ of independent random variables, each uniformly distributed on $(0, 1)$. Let $(\Omega, \mathcal{F}, P) = (\Omega_1 \times \Omega_2, \mathcal{F}_1 \times \mathcal{F}_2, P_1 \times P_2)$. Then, for $\alpha \in \mathcal{A}$, a realization of Z_α is constructed on $(\Omega, \mathcal{F}, P)$ as follows. For $i = 1, 2, \ldots$, let b_i denote the time of the ith birth in Z, if such a birth occurs. Then this birth is deleted in Z_α if and only if $U_i \leq \alpha(b_i)$. If a birth is deleted in Z_α, then none of the descendants of that individual in Z occurs in Z_α. Thus, if the jth birth in Z is such a descendant then U_j is redundant in the construction of Z_α. With the tree setting in mind, the process of deleting an individual and all of its descendants is called *pruning*. For a previous use of pruning in a branching process framework see, for example, Aldous and Pitman [1].

Finally, we give some notation concerned with functions in $\mathcal{A}$, which will be used throughout the paper. For $\alpha, \alpha' \in \mathcal{A}$, write $\alpha \prec \alpha'$ if $\alpha(t) \leq \alpha'(t)$ for all $t \in [0, \infty)$. Also, for any $c \in [0, 1]$ and any $t_0 \geq 0$, define the function $\alpha_c^{t_0} \in \mathcal{A}$ by

$$\alpha_c^{t_0}(t) = \begin{cases} 0 & \text{if } t < t_0, \\ c & \text{if } t \geq t_0. \end{cases}$$

Thus, for example, α_c^0 denotes the constant function equal to c and α_0^0 denotes the constant function equal to 0.

3. Monotonicity and continuity properties depending on vaccination function α

3.1. Functions $f(Z_\alpha)$ monotone to pruning

Let $f(Z)$ be any nonnegative function of Z taking values in the extended real line $\mathbb{R} \cup \{\infty\}$ and, for $\alpha \in \mathcal{A}$, let $\mu_\alpha^f = \mathrm{E}[f(Z_\alpha)]$. Again with the tree setting in mind, we say that f is monotonically decreasing with pruning, and write $f \in \mathcal{P}$, if $f(Z^P) \le f(Z)$ almost surely whenever Z^P is obtained from Z by pruning. For an event, E say, let 1_E denote the indicator function of E. Examples of functions that are monotonically decreasing with pruning include:

(i) the extinction time $T = \inf\{t \ge 0 : Z(t) = 0\}$ and $1_{\{T>t\}}$, where $t \in [0, \infty)$ is fixed;
(ii) the maximum population size (number of infected individuals in the epidemic context) over all time, $M = \sup_{t\ge 0} Z(t)$ and $1_{\{M>x\}}$, where $x \in [0, \infty)$ is fixed;
(iii) $N(t)$, the total number of births (new infections in the epidemic context) in $(0, t]$, where $t \in [0, \infty)$ is fixed, and the total number of births over all time (outbreak total size in the epidemic context) $N(\infty) = \lim_{t\to\infty} N(t)$, together with the corresponding indicator functions $1_{\{N(t)>x\}}$ and $1_{\{N(\infty)>x\}}$, where $x \in [0, \infty)$ is fixed.

Throughout the paper, we assume that Z is non-explosive, that is, that $\mathrm{P}(N(t) < \infty) = 1$ for any $t \in (0, \infty)$. Conditions which guarantee this property may be found in Jagers [17], Section 6.2.

3.2. Monotonicity and continuity of mean of $f(Z_\alpha)$

In this subsection, we derive monotonicity and continuity properties of $\mathrm{E}[f(Z_\alpha)]$, when viewed as a function of the vaccination process α, for functions f that are monotonically decreasing with pruning.

Theorem 3.1. *If $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$ and $f \in \mathcal{P}$, then $\mu_\alpha^f \ge \mu_{\alpha'}^f$.*

Proof. The result follows immediately from the above construction of Z and Z_α, $\alpha \in \mathcal{A}$, on $(\Omega, \mathcal{F}, P)$, since f is monotonically decreasing with pruning and $Z_{\alpha'}$ may be obtained from Z_α by successive prunings. □

We now give conditions under which μ_α^f is continuous in α. For $\alpha, \alpha' \in \mathcal{A}$, let $\|\alpha - \alpha'\| = \sup_{t\in[0,\infty)} |\alpha(t) - \alpha'(t)|$ and, for $t > 0$, let $\|\alpha - \alpha'\|_t = \sup_{s\in[0,t]} |\alpha(s) - \alpha'(s)|$. For $t > 0$, write $f \in \mathcal{P}_t$ if $f \in \mathcal{P}$ and $f(Z)$ depends on Z only through $\{Z(s) : 0 \le s \le t\}$. Let m be the offspring

mean for Z. For $c \in [0,1]$, let m_c denote the offspring mean of $Z_{\alpha_c^0}$, so $m_c = (1-c)m$. Further, let $c_{\inf} = \max(0, 1 - m^{-1})$ and note that $m_{c_{\inf}} \le 1$. For $t_0 \ge 0$ and $c \in [0,1]$, let

$$\mathcal{A}(c, t_0) = \big\{\alpha \in \mathcal{A} : \alpha(t) \ge c \text{ for all } t \ge t_0\big\}.$$

Theorem 3.2.

(a) *Fix $t > 0$, let $f \in \mathcal{P}_t$ and suppose that there exists a non-negative real-valued function $\hat{f}$, with $\mathrm{E}[\hat{f}(Z)] < \infty$, such that, for P-almost all $\omega \in \Omega$,*

$$f\big(Z_\alpha(\omega)\big) \le \hat{f}\big(Z(\omega)\big) \qquad \text{for all } \alpha \in \mathcal{A}. \tag{3.1}$$

Then, for each $\varepsilon > 0$, there exists $\eta = \eta(\varepsilon) > 0$ such that for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\|_t \le \eta$,

$$\big|\mu_\alpha^f - \mu_{\alpha'}^f\big| \le \varepsilon. \tag{3.2}$$

(b) *Suppose that $m < \infty$. Let $f \in \mathcal{P}$ and $t_0 \ge 0$, and suppose that there exists a non-negative real-valued function $\hat{f}(Z_{\alpha_{c_{\inf}}^{t_0}})$, with $\mathrm{E}[\hat{f}(Z_{\alpha_{c_{\inf}}^{t_0}})] < \infty$, such that, for P-almost all $\omega \in \Omega$,*

$$f\big(Z_\alpha(\omega)\big) \le \hat{f}\big(Z_{\alpha_{c_{\inf}}^{t_0}}(\omega)\big) \qquad \text{for all } \alpha \in \mathcal{A}(c_{\inf}, t_0). \tag{3.3}$$

Then, for each $\varepsilon > 0$, there exists $\eta = \eta(\varepsilon) > 0$ such that (3.2) holds for all $\alpha, \alpha' \in \mathcal{A}(c_{\inf}, t_0)$ satisfying $\|\alpha - \alpha'\| \le \eta$.

Proof. (a) For $n = 1, 2, \ldots$ and $\alpha, \alpha' \in \mathcal{A}$, let

$$B_n\big(\alpha, \alpha'\big) = \bigcap_{i=1}^{n} \big\{\omega \in \Omega : U_i(\omega) \notin \big(\min\big(\alpha(b_i), \alpha'(b_i)\big), \max\big(\alpha(b_i), \alpha'(b_i)\big)\big]\big\},$$

and let $B_0(\alpha, \alpha') = \Omega$. Now $\mathrm{P}(N(t) < \infty) = 1$, since Z is non-explosive. Observe that if $\omega \in B_{N(t)}(\alpha, \alpha')$ then, by construction, $Z_\alpha(s, \omega) = Z_{\alpha'}(s, \omega)$ for all $s \in [0, t]$, whence $f(Z_\alpha(\omega)) = f(Z_{\alpha'}(\omega))$ since $f \in \mathcal{P}_t$. Now, for any $\alpha \in \mathcal{A}$,

$$\mu_\alpha^f = \mathrm{E}\big[f(Z_\alpha) 1_{B_{N(t)}(\alpha,\alpha')}\big] + \mathrm{E}\big[f(Z_\alpha) 1_{B^c_{N(t)}(\alpha,\alpha')}\big],$$

where $B^c_{N(t)}(\alpha, \alpha') = \Omega \setminus B_{N(t)}(\alpha, \alpha')$. Thus, for any $\alpha, \alpha' \in \mathcal{A}$,

$$\mu_\alpha^f - \mu_{\alpha'}^f = \mathrm{E}\big[f(Z_\alpha) 1_{B^c_{N(t)}(\alpha,\alpha')}\big] - \mathrm{E}\big[f(Z_{\alpha'}) 1_{B^c_{N(t)}(\alpha,\alpha')}\big],$$

whence, since f is nonnegative,

$$\big|\mu_\alpha^f - \mu_{\alpha'}^f\big| \le \mathrm{E}\big[\hat{f}(Z) 1_{B^c_{N(t)}(\alpha,\alpha')}\big].$$

Now

$$\mathrm{E}\big[\hat{f}(Z) 1_{B^c_{N(t)}(\alpha,\alpha')}\big] = \mathrm{E}\big[\hat{f}(Z) \mathrm{E}[1_{B^c_{N(t)}(\alpha,\alpha')} | Z]\big].$$

Further, (i) Z determines $N(t)$ and (ii) $(U_1, U_2, \ldots)$ is independent of Z, so, P-almost surely,

$$\begin{aligned}\mathrm{E}[1_{B^c_{N(t)}(\alpha,\alpha')}|Z] &= 1 - \prod_{i=1}^{N(t)} \bigl(1 - \bigl|\alpha(b_i) - \alpha'(b_i)\bigr|\bigr) \\ &\le 1 - (1-\delta)^{N(t)},\end{aligned}$$

where $\delta = \|\alpha - \alpha'\|_t$. Hence, P-almost surely,

$$\mathrm{E}[1_{B^c_{N(t)}(\alpha,\alpha')}|Z] \le \mathrm{E}[1_{B^c_{N(t)}(\alpha^0_0,\alpha^0_\delta)}|Z],$$

whence, for $\alpha, \alpha' \in \mathcal{A}$,

$$\begin{aligned}\bigl|\mu^f_\alpha - \mu^f_{\alpha'}\bigr| &\le \mathrm{E}\bigl[\hat{f}(Z) 1_{B^c_{N(t)}(\alpha^0_0,\alpha^0_\delta)}\bigr] \\ &= \hat{\mu}_t(\delta) \qquad \text{say.}\end{aligned} \tag{3.4}$$

Now $\mathrm{P}(N(t) < \infty) = 1$, so P-almost surely,

$$\hat{f}(Z) 1_{B^c_{N(t)}(\alpha^0_0,\alpha^0_\delta)} \to 0 \qquad \text{as } \delta \downarrow 0$$

(in fact $\hat{f}(Z) 1_{B^c_{N(t)}(\alpha^0_0,\alpha^0_\delta)} = 0$ for all $\delta \in [0, \delta^*)$, where $\delta^* = \min(U_1, U_2, \ldots, U_{N(t)})$), so by the dominated convergence theorem $\hat{\mu}_t(\delta) \to 0$ as $\delta \downarrow 0$. Thus, given $\varepsilon > 0$, there exists η such that $\hat{\mu}_t(\delta) \le \varepsilon$ for all $\delta \in (0, \eta)$ and the theorem follows using (3.4).

(b) For $\alpha \in \mathcal{A}(c_{\inf}, t_0)$, the process Z_α can be viewed as a vaccinated version of the process $Z_{\alpha^{t_0}_{c_{\inf}}}$ with vaccination function $\tilde{\alpha}$ given by

$$\tilde{\alpha}(t) = \begin{cases} \alpha(t) & \text{if } t < t_0, \\ \dfrac{\alpha(t)}{1 - c_{\inf}} & \text{if } t \ge t_0. \end{cases}$$

Note that $Z_{\alpha^{t_0}_{c_{\inf}}}$ has offspring mean m until time t_0, and $m_{c_{\inf}} \le 1$ after time t_0. Thus, since Z is non-explosive (so $\mathrm{P}(Z(t_0) < \infty) = 1$), the total number of births over all time in $Z_{\alpha^{t_0}_{c_{\inf}}}$ (i.e., $N_{\alpha^{t_0}_{c_{\inf}}}(\infty)$) is finite almost surely. Also, $\|\tilde{\alpha} - \tilde{\alpha}'\| \le (1 - c_{\inf})^{-1} \|\alpha - \alpha'\|$. The proof then proceeds as in part (a), but with Z and $N(t)$ replaced by $Z_{\alpha^{t_0}_{c_{\inf}}}$ and $N_{\alpha^{t_0}_{c_{\inf}}}(\infty)$, respectively, and α, α' replaced by $\tilde{\alpha}, \tilde{\alpha}'$. □

Remark 3.1.

(a) Suppose that $m \le 1$. Then $c_{\inf} = 0$ and it follows that $Z_{\alpha^{t_0}_{c_{\inf}}} = Z$ and $\mathcal{A}(c_{\inf}, t_0) = \mathcal{A}$. Thus, for any $f \in \mathcal{P}$, Theorem 3.2(b) implies that, for any $\varepsilon > 0$, there exists $\eta = \eta(\varepsilon) > 0$ such that (3.2) holds for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\| \le \eta$.

(b) Suppose that $m > 1$ and $f \in \mathcal{P}$. Then the argument used to prove Theorem 3.2(b) breaks down since $\mathrm{P}(Z(\infty) < \infty) < 1$. Thus, with our argument we can prove continuity in α of μ_α^f for $f \in \mathcal{P}_t$, for any $t > 0$, but not for $f \in \mathcal{P}$. However, this is no restriction from a practical viewpoint since t in Theorem 3.2(a), or t_0 in Theorem 3.2(b), can be made arbitrarily large. For example, in any real life-setting there will be a maximum time frame over which it is of interest to evaluate the performance of a vaccination process and t or t_0 can be chosen accordingly.

3.3. Monotonicity and continuity of distribution function of $f(Z_\alpha)$

Using the previous results, we establish in this subsection monotonicity and continuity properties of the distribution function of $f(Z_\alpha)$. For $f \in \mathcal{P}$ and $\alpha \in \mathcal{A}$, let

$$v_\alpha^f(x) = \mathrm{P}\big(f(Z_\alpha) \le x\big) = 1 - \mathrm{E}[1_{\{f(Z_\alpha)>x\}}], \qquad x \ge 0,$$

be the distribution function of the random variable $f(Z_\alpha)$.

For $\alpha \in \mathcal{A}$ and $t \in [0, \infty]$, let $\phi_{N_\alpha(t)}(s) = \mathrm{E}[s^{N_\alpha(t)}]$ $(0 \le s \le 1)$ denote the probability generating function of $N_\alpha(t)$. Suppose that $P(N_\alpha(t) < \infty) = 1$. Then $\phi_{N_\alpha(t)}(1-) = 1$ and $\phi^{-1}_{N_\alpha(t)}(u)$ is well defined for all $u \in [u_{\alpha,t}, 1]$, where $u_{\alpha,t} = \mathrm{P}(N_\alpha(t) = 0)$. Extend the domain of $\phi^{-1}_{N_\alpha(t)}$ by defining $\phi^{-1}_{N_\alpha(t)}(u) = 0$ for $u \in [0, u_{\alpha,t})$. Define the function $\delta_{\alpha,t} : [0, 1] \to [0, 1]$ by

$$\delta_{\alpha,t}(\varepsilon) = 1 - \phi^{-1}_{N_\alpha(t)}(1 - \varepsilon), \qquad 0 \le \varepsilon \le 1. \tag{3.5}$$

Note that $\delta_{\alpha,t}(\varepsilon) > 0$ if $\varepsilon > 0$ and $\lim_{\varepsilon \downarrow 0} \delta_{\alpha,t}(\varepsilon) = 0$.

Theorem 3.3.

(a) *Suppose that $f \in \mathcal{P}$ and $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$. Then*

$$v_\alpha^f(x) \le v_{\alpha'}^f(x) \qquad \textit{for all } 0 \le x \le \infty. \tag{3.6}$$

(b) *Fix $t > 0$ and suppose that $f \in \mathcal{P}_t$. Then, for any $\varepsilon > 0$,*

$$\sup_{0 \le x < \infty} \big|v_\alpha^f(x) - v_{\alpha'}^f(x)\big| \le \varepsilon \tag{3.7}$$

for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\|_t \le \delta_{\alpha_0^0,t}(\varepsilon)$.

(c) *Suppose that $f \in \mathcal{P}$. Then, for any $\varepsilon > 0$, (3.7) holds for all $\alpha, \alpha' \in \mathcal{A}(c_{\inf}, t_0)$ satisfying $\|\alpha - \alpha'\| \le \delta_{\alpha_{c_{\inf}}^{t_0},\infty}(\varepsilon)$.*

Proof. (a) Fix $x \in [0, \infty)$ and let $\tilde{f}_x$ be the function of Z given by $\tilde{f}_x(Z) = 1_{\{f(Z)>x\}}$. Then $\tilde{f}_x \in \mathcal{P}$ and (3.6) follows from Theorem 3.1, since $v_\alpha^f(x) = 1 - \mathrm{E}[\tilde{f}_x(Z_\alpha)]$.

(b) For each $x \in [0, \infty)$,

$$\bigl|v_\alpha^f(x) - v_{\alpha'}^f(x)\bigr| = \bigl|\mathrm{E}\bigl[\tilde{f}_x(Z_\alpha)\bigr] - \mathrm{E}\bigl[\tilde{f}_x(Z_{\alpha'})\bigr]\bigr|$$

and $\tilde{f}_x(Z_\alpha(\omega)) \le 1$ for all $\alpha \in \mathcal{A}$ and all $\omega \in \Omega$. Fix $t > 0$ and note that $\tilde{f}_x \in \mathcal{P}_t$, since $f \in \mathcal{P}_t$. It then follows from (3.4), taking $\hat{f}(Z) = 1$, that, for $x \in [0, \infty)$ and $\alpha, \alpha' \in \mathcal{A}$,

$$\bigl|v_\alpha^f(x) - v_{\alpha'}^f(x)\bigr| \le \hat{\mu}_t\bigl(\bigl\|\alpha - \alpha'\bigr\|_t\bigr), \tag{3.8}$$

where, for $\delta \in [0, 1]$,

$$\hat{\mu}_t(\delta) = \mathrm{P}\bigl(B^c_{N(t)}\bigl(\alpha_0^0, \alpha_\delta^0\bigr)\bigr) = 1 - \mathrm{E}\bigl[(1-\delta)^{N(t)}\bigr] = 1 - \phi_{N(t)}(1-\delta).$$

Recall that $N(t) = N_{\alpha_0^0}(t)$ and note that $P(N_{\alpha_0^0}(t) < \infty) = 1$ since Z is non-explosive. Thus, $\phi^{-1}_{N_{\alpha_0^0}(t)}(u)$ is well defined for all $u \in [0, 1]$ and, since $1 - \phi_{N_{\alpha_0^0}(t)}(1 - \delta_{\alpha_0^0,t}(\varepsilon)) \le \varepsilon$, the theorem follows.

(c) The proof is similar to part (b) but with $N_{\alpha_0^0}(t)$ replaced by $N_{\alpha^{t_0}_{c_{\inf}}}(\infty)$. □

Remark 3.2.

(a) Observe that the function $\delta_{\alpha_0^0,t}$, defined using (3.5), is independent of both f and x, so the uniform continuity of $v_\alpha^f(x)$, with respect to α, holds uniformly over all $f \in \mathcal{P}$ and all $x \in [0, \infty)$.

(b) Similar to Remark 3.1(a), Theorem 3.3(c) shows that if $m \le 1$ (so $P(N(\infty) < \infty) = 1$) and $f \in \mathcal{P}$ then, for any $\varepsilon > 0$, (3.7) holds for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\| \le \delta_{\alpha_0^0,\infty}(\varepsilon)$.

3.4. Monotonicity and continuity of quantiles of $f(Z_\alpha)$

In applications, we wish to control the quantiles of $f(Z_\alpha)$, so we now derive related monotonicity and continuity properties. Fix $f \in \mathcal{P}$ and $\alpha \in \mathcal{A}$, and define, for $0 < p < 1$,

$$x_{\alpha,p}^f = \inf\bigl\{x : v_\alpha^f(x) \ge p\bigr\},$$

with the convention that $x_{\alpha,p}^f = \infty$ if $v_\alpha^f(x) < p$ for all $x \in [0, \infty)$. Thus, $x_{\alpha,p}^f$ is the quantile of order p of the random variable $f(Z_\alpha)$. For $\alpha \in \mathcal{A}$, let $\mathcal{A}^+(\alpha) = \{\alpha' \in \mathcal{A} : \alpha \prec \alpha'\}$. For a sequence $\{\alpha_n\}$ and α in $\mathcal{A}$, we define $\lim_{n\to\infty} \alpha_n = \alpha$ to mean $\lim_{n\to\infty} \|\alpha_n - \alpha\| = 0$.

Theorem 3.4. *Suppose that $f \in \mathcal{P}$ and $p \in (0, 1)$.*

(a) *If $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$, then $x_{\alpha',p}^f \le x_{\alpha,p}^f$.*

(b) *Suppose further that $f \in \mathcal{P}_t$ for some $t > 0$ and $\alpha \in \mathcal{A}$ is such that $x_{\alpha,p}^f < \infty$. Let $\{\alpha_n\}$ be any sequence in $\mathcal{A}$ satisfying $\lim_{n\to\infty} \alpha_n = \alpha$. Then $\lim_{n\to\infty} x_{\alpha_n,p}^f = x_{\alpha,p}^f$ in each of the following cases*:

(i) $\alpha_n \in \mathcal{A}^+(\alpha)$ *for all* n;
(ii) v_α^f *is continuous and strictly increasing at* $x_{\alpha,p}^f$.

Proof. (a) By Theorem 3.3(a), $\{x : v_\alpha^f(x) \geq p\} \subseteq \{x : v_{\alpha'}^f(x) \geq p\}$, which implies $x_{\alpha',p}^f \leq x_{\alpha,p}^f$.

(b) Choose $t > 0$ such that $f \in \mathcal{P}_t$. Suppose that (i) holds. Let $x_{\sup} = \limsup_{n\to\infty} x_{\alpha_n,p}^f$ and $x_{\inf} = \liminf_{n\to\infty} x_{\alpha_n,p}^f$. Then by part (a), $x_{\sup} \leq x_{\alpha,p}^f$. Fix $\varepsilon > 0$. Then, since $\lim_{n\to\infty} \alpha_n = \alpha$ and $\|\alpha_n - \alpha\|_t \leq \|\alpha_n - \alpha\|$, there exists n_0 such that $\|\alpha_n - \alpha\|_t \leq \delta_{\alpha_0^0,t}(\varepsilon)$ for all $n \geq n_0$, where $\delta_{\alpha_0^0,t}(\varepsilon)$ is defined at (3.5) – recall that $N(t) = N_{\alpha_0^0}(t)$. Now, $\alpha \prec \alpha_n$, hence, by Theorem 3.3(a) and (b), $v_{\alpha_n}^f(x) - v_\alpha^f(x) \leq \varepsilon$, for all $x \geq 0$ and for all $n \geq n_0$. In particular, setting $x = x_{\alpha_n,p}^f$ and noting that $v_{\alpha_n}^f(x_{\alpha_n,p}^f) \geq p$ since $v_{\alpha_n}^f$ is right-continuous, yields that $v_\alpha^f(x_{\alpha_n,p}^f) \geq p - \varepsilon$ for all $n \geq n_0$. Hence, $v_\alpha^f(x_{\inf}) \geq p - \varepsilon$, since v_α^f is increasing and right-continuous. This holds for all $\varepsilon > 0$, so $v_\alpha^f(x_{\inf}) \geq p$, whence $x_{\inf} \geq x_{\alpha,p}^f$. Thus, $x_{\inf} = x_{\sup} = x_{\alpha,p}^f$, so $\lim_{n\to\infty} x_{\alpha_n,p}^f = x_{\alpha,p}^f$, as required.

Suppose that (ii) holds. First, we assume that $\alpha_n \prec \alpha$ for all n. Then, by part (a), $x_{\inf} \geq x_{\alpha,p}^f$. Note that $v_\alpha^f(x_{\alpha,p}^f) = p$, since v_α^f is continuous at $x_{\alpha,p}^f$, and $v_\alpha^f(x) > p$ for all $x > x_{\alpha,p}^f$, since v_α^f is strictly increasing at $x_{\alpha,p}^f$. Fix $x > x_{\alpha,p}^f$ and let $\varepsilon = v_\alpha^f(x) - p$, so $\varepsilon > 0$. As before, there exists n_0 such that $\|\alpha_n - \alpha\|_t \leq \delta_{\alpha_0^0,t}(\varepsilon)$ for all $n \geq n_0$. It then follows from Theorem 3.3 that

$$v_\alpha^f(x) - v_{\alpha_n}^f(x) \leq \varepsilon = v_\alpha^f(x) - p \qquad \text{for all } n \geq n_0.$$

Thus $v_{\alpha_n}^f(x) \geq p$ for all $n \geq n_0$, whence $x_{\alpha_n,p}^f \leq x$ for all $n \geq n_0$, which implies that $x_{\sup} \leq x$. Since this holds for any $x > x_{\alpha,p}^f$, it follows that $x_{\sup} \leq x_{\alpha,p}^f$, which combined with $x_{\inf} \geq x_{\alpha,p}^f$ yields the required result.

Now, we consider an arbitrary sequence $\{\alpha_n\}$ that converges to α. For $q = 1, 2, \ldots$, define functions α_q^+ and α_q^- by $\alpha_q^+(s) = \min\{\alpha(s) + \frac{1}{q}, 1\}$ and $\alpha_q^-(s) = \max\{\alpha(s) - \frac{1}{q}, 0\}$ $(s \geq 0)$. Then $\lim_{q\to\infty} \alpha_q^+ = \lim_{q\to\infty} \alpha_q^- = \alpha$. Further, $\alpha_q^- \prec \alpha \prec \alpha_q^+$ for each $q = 1, 2, \ldots$. Hence, by part (i) and the above, $\lim_{q\to\infty} x_{\alpha_q^+,p}^f = \lim_{q\to\infty} x_{\alpha_q^-,p}^f = x_{\alpha,p}^f$. For any fixed $q \in \mathbb{N}$, $\alpha_n \prec \alpha_q^+$ for all sufficiently large n, so Theorem 3.4(a) implies that $\liminf_{n\to\infty} x_{\alpha_n,p}^f \geq x_{\alpha_q^+,p}^f$. Letting $q \to \infty$ then yields that $x_{\inf} \geq x_{\alpha,p}^f$. A similar argument using the sequence $\{\alpha_q^-\}$ shows that $x_{\sup} \leq x_{\alpha,p}^f$, whence $\lim_{n\to\infty} x_{\alpha_n,p}^f = x_{\alpha,p}^f$, as required. □

Remark 3.3.

(a) It is straightforward to extend Theorem 3.4(b) to a family of vaccination processes with a continuous index set, for example, $\{\alpha_s : s \in \mathcal{I}\}$, where $\mathcal{I}$ is a connected subset of $\mathbb{R}^d$ for some $d \in \mathbb{N}$. Theorem 3.4(b) implies that, under appropriate conditions, $\lim_{s\to s^*} x_{\alpha_s,p}^f = x_{\alpha_{s^*},p}^f$. We use this extension when studying optimal vaccination policies in the next subsection.
(b) Invoking Remark 3.2(b) shows that if $m \leq 1$ then Theorem 3.4(b) holds with $\mathcal{P}_t$ replaced by $\mathcal{P}$.

3.5. Optimal vaccination policies based on mean and quantiles

From the above monotonicity and continuity properties of mean and quantiles, we propose next how to choose optimal αs, that is, optimal vaccination policies in a sense that is made clear below, from a subset $\mathcal{A}^*$ of $\mathcal{A}$. Fix $f \in \mathcal{P}$, $b > 0$ and $0 < p < 1$, and let $\mathcal{A}_b^f = \{\alpha \in \mathcal{A}^* : \mu_\alpha^f \le b\}$ and $\mathcal{A}_{p,b}^f = \{\alpha \in \mathcal{A}^* : x_{\alpha,p}^f \le b\}$. Notice that if, for example, f is the time to extinction, then $\mathcal{A}_b^f$ and $\mathcal{A}_{p,b}^f$ comprise those vaccination policies in $\mathcal{A}^*$ for which the mean and the quantile of order p, respectively, of the time to extinction is less than or equal to some bound b. Then it is of interest to search for optimal vaccination policies which satisfy these properties.

Then, if they exist, optimal vaccination policies based on the mean are

$$\operatorname*{argmax}_{\alpha \in \mathcal{A}_b^f} \mu_\alpha^f$$

and optimal vaccination policies based on the quantiles are

$$\operatorname*{argmax}_{\alpha \in \mathcal{A}_{p,b}^f} x_{\alpha,p}^f.$$

We notice that the sets $\mathcal{A}_b^f$ and $\mathcal{A}_{p,b}^f$ can be empty. If they are not empty, optimal vaccination policies may not be unique when a total order is not defined on the sets $\mathcal{A}_b^f$ and $\mathcal{A}_{p,b}^f$. Otherwise, provided the conditions of Theorems 3.1, 3.2 and 3.4 are satisfied, the monotonicity and continuity properties of mean and quantiles of $f(Z_\alpha)$ proved in those theorems imply that there exist unique $\alpha_{\mathrm{opt},b}^f \in \mathcal{A}_b^f$ and $\alpha_{\mathrm{opt},p,b}^f \in \mathcal{A}_{p,b}^f$ such that

$$\mu_{\alpha_{\mathrm{opt},b}^f}^f = \max_{\alpha \in \mathcal{A}_b^f} \mu_\alpha^f \quad \text{and} \quad x_{\alpha_{\mathrm{opt},p,b}^f,p}^f = \max_{\alpha \in \mathcal{A}_{p,b}^f} x_{\alpha,p}^f.$$

Intuitively, $\alpha_{\mathrm{opt},b}^f$ and $\alpha_{\mathrm{opt},p,b}^f$ are the smallest vaccination policies in $\mathcal{A}^*$ such that the mean and the pth quantile, respectively, of $f(Z_{\alpha_{\mathrm{opt},b}^f})$ and $f(Z_{\alpha_{\mathrm{opt},p,b}^f})$ are less than or equal to b. Before giving some simple examples of $\mathcal{A}^*$, we discuss briefly conditions that ensure the existence and uniqueness of optimal policies.

For fixed $f \in \mathcal{P}$, define the binary relation $\prec_f$ on $\mathcal{A}$ by $\alpha \prec_f \alpha'$ if and only if $\mu_\alpha^f \le \mu_{\alpha'}^f$. Observe that, if $\alpha \prec \alpha'$ then, by Theorem 3.1, $\alpha' \prec_f \alpha$ for any $f \in \mathcal{P}$. The relation $\prec_f$ is not an ordering, because $\alpha \prec_f \alpha'$ and $\alpha' \prec_f \alpha$ imply only that $\mu_\alpha^f = \mu_{\alpha'}^f$ (and not that $\alpha = \alpha'$). However, we can consider the equivalence relation $\sim_f$ on $\mathcal{A}$ defined by $\alpha \sim_f \alpha'$ if and only if $\mu_\alpha^f = \mu_{\alpha'}^f$. Then $\prec_f$ is a total ordering on the quotient set $\mathcal{A}/\sim_f$, that is, the set of all possible equivalence classes, using the obvious definition of $\prec_f$ on $\mathcal{A}/\sim_f$.

Given a subset $\mathcal{A}^*$ of $\mathcal{A}$, a simple condition that ensures the existence of $\operatorname{argmax}_{\alpha \in \mathcal{A}_b^f} \mu_\alpha^f$ for any fixed $b > 0$ is that the set of real numbers $\{\mu_\alpha^f : \alpha \in \mathcal{A}^*\}$ is closed. More precisely, this ensures the existence of an equivalence class on which the maximum is attained. To obtain a

unique maximum requires that $\prec_f$ is a total ordering on $\mathcal{A}^*$ (or at least on $\mathcal{A}_b^f$ for fixed b). Note that even if $\prec$ is a total ordering on $\mathcal{A}^*$, Theorem 3.1 does not ensure that $\prec_f$ is a total ordering on $\mathcal{A}^*$. For the latter, we require that $\mu_\alpha^f > \mu_{\alpha'}^f$ for all $\alpha, \alpha' \in \mathcal{A}^*$ satisfying $\alpha \prec \alpha'$ and $\alpha \neq \alpha'$. The coupling argument in Section 2 can be used to show that this holds for any practically useful f and it is assumed implicitly in the sequel. Similar arguments to the above pertain for optimal vaccination policies based on quantiles.

A simple example of $\mathcal{A}^*$ is the set of constant functions, that is, $\mathcal{A}^* = \{\alpha_c^0 : 0 \le c \le 1\}$. On this set, the total order is defined by the order of the real numbers. Another example is the set $\mathcal{A}^* = \{\alpha_{M,t_v,p_0} : M \ge 0, 0 \le p_0 \le 1, 0 \le t_v \le p_0^{-1}\}$, where, for $s \ge 0$,

$$\alpha_{M,t_v,p_0}(s) = \begin{cases} 0 & \text{if } s \le M, \\ p_0(s-M) & \text{if } M < s \le M + t_v, \\ t_v p_0 & \text{if } M + t_v < s. \end{cases} \tag{3.9}$$

For fixed M, t_v and p_0, the function α_{M,t_v,p_0} describes the proportion of immune individuals in the population when the vaccination process starts at time M, takes t_v time units and the proportion of individuals vaccinated per unit time is p_0. We notice that a total order on $\mathcal{A}^*$ is not possible. However, in practice, M and p_0 are usually known before vaccination begins, and therefore, the functions can be parameterized through t_v alone. For fixed M and p_0, denote $\alpha_{t_v} = \alpha_{M,t_v,p_0}$ and $\mathcal{A}^* = \{\alpha_{t_v} : c_{\inf} p_0^{-1} \le t_v \le p_0^{-1}\}$. Then $\prec_f$ is a total ordering on $\mathcal{A}^*$ and Theorem 3.2(b) ensures that $\{\mu_\alpha^f : \alpha \in \mathcal{A}^*\}$ is closed, so, provided $\mathcal{A}_b^f$ is non-empty, the optimal vaccination policy exists and is unique. Moreover, it and the corresponding optimal policies based on the mean and quantiles are given by $\alpha_{t_{\mathrm{opt},\mu}^f}$ and $\alpha_{t_{\mathrm{opt},p}^f}$, with

$$t_{\mathrm{opt},\mu}^f = \inf\{t_v : \mu_{\alpha_{t_v}}^f \le b\} \quad \text{and} \quad t_{\mathrm{opt},p}^f = \inf\{t_v : x_{\alpha_{t_v},p}^f \le b\},$$

respectively.

Finally, we notice that, usually, μ_α^f and $x_{\alpha,p}^f$ cannot be derived in a closed form. Therefore, in order to obtain optimal vaccination policies, we need to approximate them. The coupling construction can be used to give a Monte-Carlo based estimation. Suppose, for simplicity of argument, that $m \le 1$. Fix $n \ge 1$, for $i = 1, \ldots, n$, one can simulate a realization $Z^{(i)}$ of Z and $U_j^{(i)}$ of U_j, for $j = 1, 2, \ldots, N^{(i)}(\infty)$, where $N^{(i)}(\infty)$ is the total number of births in $Z^{(i)}$. For each $\alpha \in \mathcal{A}^*$, we obtain a realization $f(Z_\alpha^{(i)})$ of $f(Z_\alpha)$, for $i = 1, \ldots, n$. From these realizations, we estimate μ_α^f and $x_{\alpha,p}^f$.

3.6. Time to extinction

We specialise the preceding results to the case when evaluation of a vaccination strategy α is based on the associated distribution of the time to extinction of the virus in an outbreak. To this end, for $z \in \mathbb{N}$, we denote by $T_{\alpha,z}$ the time to extinction of the process Z_α when $Z(0) = z$, that is,

$$T_{\alpha,z} = \inf\{t \ge 0 : Z_\alpha(t) = 0\}.$$

Thus, $T_{\alpha,z}$ is the maximal time that the infection survives in the population in an outbreak when the time-dependent proportion of immune individuals is given by α and the number of infected individuals at the beginning of the outbreak is z. Now individuals infect independently of each other, so we have that

$$T_{\alpha,z} = \max\bigl\{T_{\alpha,1}^{(1)}, T_{\alpha,1}^{(2)}, \ldots, T_{\alpha,1}^{(z)}\bigr\},$$

where $T_{\alpha,1}^{(i)}$ are independent random variables with the same distribution as $T_{\alpha,1}$. Hence

$$\mathrm{P}(T_{\alpha,z} \le t) = \bigl(v_\alpha(t)\bigr)^z,$$

where $v_\alpha(t) = \mathrm{P}(T_{\alpha,1} \le t)$. Therefore, to analyze the behaviour of $T_{\alpha,z}$, for any z, it is sufficient to study $T_{\alpha,1}$ through v_α. From now on, we denote $T_{\alpha,1}$ by T_α.

We first use the results of Sections 3 to derive some continuity and monotonicity properties of the distribution function v_α. When every individual is immune, that is, $\alpha(t) = 1$ for all $t > 0$, the infectious disease does not spread to any susceptible individual and then the extinction time is given by the survival time of the initial infected individual. It stands to reason that if there are non-immune individuals in the population, then it is probable that the infectious disease takes more time to become extinct. In the following result, which is an immediate application of Theorem 3.3(a) with $f = T$, we show this fact investigating the behaviour of v_α depending on the function α.

Corollary 3.1. *Suppose that $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$. Then $v_\alpha(t) \le v_{\alpha'}(t)$, for all $t \ge 0$.*

Intuitively, it is clear that the greater the proportion of immune individuals, the more likely it is that the infectious disease disappears quickly. Consequently, for any $\alpha \in \mathcal{A}$, the distribution function v_α is bounded above by $v_{\alpha_1^0}$, the distribution function of the survival time of the initial infected individual, and bounded below by $v_{\alpha_0^0}$, which is not necessarily a proper distribution function. Moreover, we obtain that minor changes in the proportion of the immune individuals generate minor changes in the distribution of outbreak duration. The following result is an immediate application of Theorem 3.3(b), (c) with $f = T$.

Corollary 3.2.

(a) *Fix $t > 0$. Then, for each $\varepsilon > 0$,*

$$\sup_{0 \le u \le t} \bigl|v_\alpha(u) - v_{\alpha'}(u)\bigr| \le \varepsilon,$$

for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\|_t \le \delta_{\alpha_0^0,t}(\varepsilon)$.

(b) *Fix $t_0 \ge 0$. Then, for each $\varepsilon > 0$,*

$$\sup_{0 \le t < \infty} \bigl|v_\alpha(t) - v_{\alpha'}(t)\bigr| \le \varepsilon,$$

for all $\alpha, \alpha' \in \mathcal{A}(c_{\inf}, t_0)$ satisfying $\|\alpha - \alpha'\| \le \delta_{\alpha_{c_{\inf}}^{t_0},\infty}(\varepsilon)$.

Finally, we consider the quantiles of T_α. For $\alpha \in \mathcal{A}$ and $0 < p < 1$, let $t_{\alpha,p} = \inf\{t : v_\alpha(t) \geq p\}$ be the quantile of order p of T_α.

Corollary 3.3.

(a) *If* $\alpha, \alpha' \in \mathcal{A}$ *satisfy* $\alpha \prec \alpha'$, *then* $t_{\alpha',p} \leq t_{\alpha,p}$ *for every* $0 < p < 1$.
(b) *Suppose that* $\alpha \in \mathcal{A}$ *and* $0 < p < 1$ *are such that* $t_{\alpha,p} < \infty$ *and* v_α *is continuous and strictly increasing at* $t_{\alpha,p}$. *Then* $\lim_{n\to\infty} t_{\alpha_n,p} = t_{\alpha,p}$, *for any sequence* $\{\alpha_n\}$ *in* $\mathcal{A}$ *satisfying* $\lim_{n\to\infty} \alpha_n = \alpha$.

Proof.

(a) The result follows directly from Theorem 3.4(a), on setting $f = T$.
(b) Let $t = t_{\alpha,p} + 1$ and $f = \min\{T, t\}$, so $f \in \mathcal{P}_t$. The conditions on $t_{\alpha,p}$ and v_α ensure that $t_{\alpha,p} = x^f_{\alpha,p}$ for all $\alpha \in \mathcal{A}$. The result then follows immediately from Theorem 3.4(b). □

Corollary 3.3 can be extended to a family of vaccination processes with a continuous index set; cf. Remark 3.3(b). In order to apply Corollary 3.3, we need to determine conditions which guarantee that v_α is both continuous and strictly increasing.

Theorem 3.5. *Suppose that the lifetime random variable* I *is continuous. Then, for any* $\alpha \in \mathcal{A}$, v_α *is a continuous distribution function.*

Proof. Let $B_0 = 0$ and, for $n = 1, 2, \ldots$, let B_n denote the time of the nth birth in Z, with the convention that $B_n = \infty$ if $N(\infty) < n$. For $n = 0, 1, \ldots, N(\infty)$, let I_n and $D_n = B_n + I_n$ denote respectively, the lifetime and time of death of the nth individual born in Z. Let $\mathcal{D} = \{D_0, D_1, \ldots, D_{N(\infty)}\}$ denote the random set of all death-times in Z. Observe that, for any $t > 0$ and any $\alpha \in \mathcal{A}$, $T_\alpha = t$ only if $t \in \mathcal{D}$. Thus, it is sufficient to show that $\mathrm{P}(t \in \mathcal{D}) = 0$ for any $t > 0$.

Fix $t > 0$ and define $D_n = \infty$ for $n > N(\infty)$. Then, since $\mathrm{P}(N(t) < \infty) = 1$,

$$\mathrm{P}(t \in \mathcal{D}) = \mathrm{P}\left(\bigcup_{n=0}^{\infty} \{D_n = t\}\right) \leq \sum_{n=0}^{\infty} \mathrm{P}(D_n = t). \tag{3.10}$$

Further, for $n = 0, 1, \ldots,$

$$\begin{aligned}
\mathrm{P}(D_n = t) &= \mathrm{P}\big(N(t) \geq n\big)\mathrm{P}\big(D_n = t | N(t) \geq n\big) \\
&= \mathrm{P}\big(N(t) \geq n\big)\mathrm{E}_{B_n | N(t)\geq n}\big[\mathrm{P}\big(D_n = t | B_n, N(t) \geq n\big)\big] \\
&= \mathrm{P}\big(N(t) \geq n\big)\mathrm{E}_{B_n | N(t)\geq n}\big[\mathrm{P}\big(I_n = t - B_n | B_n, N(t) \geq n\big)\big] \\
&= \mathrm{P}\big(N(t) \geq n\big)\mathrm{E}_{B_n | N(t)\geq n}\big[\mathrm{P}(I_n = t - B_n)\big] \\
&= 0,
\end{aligned}$$

since I_n is independent of both B_n and $\{N(t) \geq n\}$, and I is continuous. It then follows from (3.10) that $\mathrm{P}(t \in \mathcal{D}) = 0$, which completes the proof. □

We notice that under weak conditions, the function v_α is strictly increasing. Indeed, let R be the number of points of ξ in $[0, I]$, so R is a random variable giving the number of offspring of a typical individual in the CMJ branching process Z. Suppose that $\mathrm{P}(R = 0) > 0$ and that $I|R = 0$ is an absolutely continuous random variable, having density $f_{I|R=0}$ satisfying $f_{I|R=0}(t) > 0$ for all $t \in (0, \infty)$. Then it is easily seen that, for any $\alpha \in \mathcal{A}$, v_α is strictly increasing on $(0, \infty)$, since, for any open interval (a, b) in $(0, \infty)$, the probability that the initial individual has no offspring and dies in (a, b) is strictly positive. It is straightforward to give conditions under which v_α is strictly increasing on $(0, \infty)$ when I has bounded support. For example, suppose that $\mathrm{P}(R = 0)$ and $\mathrm{P}(R = 1)$ are both strictly positive, and $I|R = 0$ and $B|R = 1$ are both absolutely continuous with densities that are strictly positive on $(0, t_I)$, for some $t_I > 0$. Here, B is the age that a typical individual has his/her first child. Then, given any interval $(a, b) \subset (0, \infty)$, there exists $n_0 \in \mathbb{N}$ such that with strictly positive probability (i) each of the first n_0 individuals in Z has precisely one child, (ii) the $(n_0 + 1)$th individual in Z has no children and (iii) $T \in (a, b)$. It then follows that $\mathrm{P}(T_\alpha \in (a, b)) > 0$, provided $\alpha(t) < 1$ for all $t > 0$.

4. Illustrative example: Analyzing the control measures for mumps in Bulgaria

As an illustration of how to apply our theoretical results and to show their usefulness, we analyze a mumps data set from Bulgaria. In Bulgaria, an increasing number of new cases of individuals infected with mumps has been observed in recent years (see Figure 1). This may be a result of a poor immunization of birth cohorts 1982–1992 (see Kojouharova *et al.* [19]). In such a situation, it is necessary to provide supplementary doses of mumps, measles and rubella (MMR) vaccine targeted at those cohorts in order to shorten the duration of the outbreaks. Thus our objective is to determine, using the observed data, optimal vaccination levels based on the time to extinction that guarantee, with a high probability, that the outbreak durations will be less than some suitable

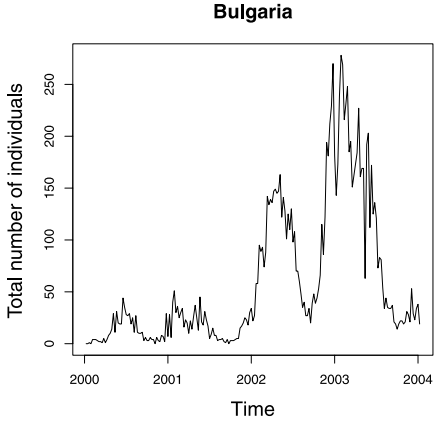

Figure 1. Numbers of new infected individuals weekly reported.

bound. As an example, we determine the percentage of the target cohort that must be vaccinated to guarantee that only primary and first-generation cases will be observed in at least 90% of outbreaks.

In order to apply our results, we model the spread of mumps by a CMJ branching process. This is reasonable since mumps is an infectious disease which follows the SEIR scheme, and in general, the early stages of outbreaks following this scheme can be approximated by a CMJ branching process. Although this is the general situation, a deeper discussion is needed in the case of mumps. This disease concerns predominantly young people in schools and universities, which means small separate populations and population-dependent propagation. Hence, the approximation of mumps outbreaks in these populations by CMJ processes is valid only when outbreaks are very short, which is the case for the outbreaks we study as we show later.

The data we analyze (reported by the Bulgarian Ministry of Health) are the total number of new cases of infected individuals with mumps observed weekly in each province of Bulgaria from 2005 to 2008, whose birth cohorts were poorly immunized. Notice that we do not observe outbreak durations, so, first, we describe the procedure to derive the outbreak durations from these data. Then, taking into account the main features of mumps transmission, we select an appropriate general branching process to describe the evolution of infected individuals in an outbreak and estimate its main parameters from the data set. Finally, once the model is fitted, we propose optimal vaccination levels based on the quantiles of the outbreak duration.

4.1. Deriving the outbreak duration

Our first task is to determine the behaviour of mumps outbreak durations in Bulgaria from 2005 to 2008, since our optimal vaccination level is based on outbreak duration. However, outbreak durations have not been registered; only the total number of new cases of infected individuals with mumps in each province has been observed (see Figure 2). Thus, instead, we derive the outbreak durations from this data set, taking into account the main features of mumps transmission. Mumps is a viral infectious disease of humans and spreads from person to person through the air. The period between someone being transmitted mumps and that person first showing

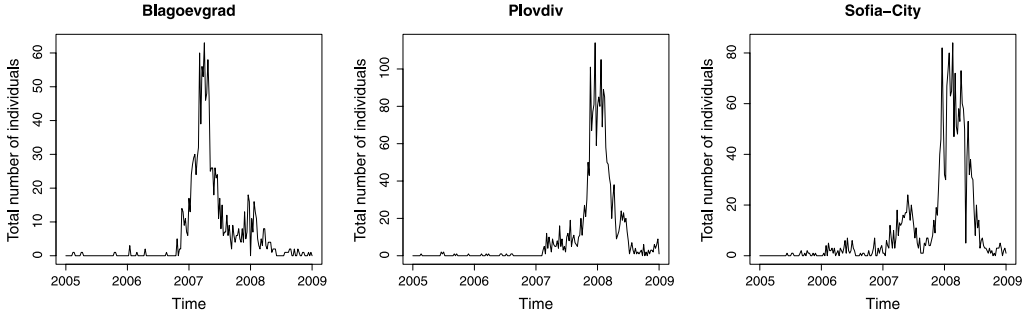

Figure 2. Numbers of new infected individuals per week for the provinces of Bulgaria with the highest incidence of mumps.

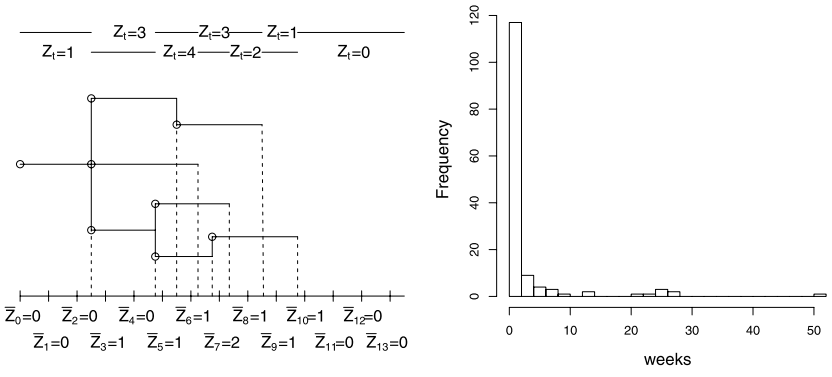

Figure 3. Left: Schematic representation of an outbreak. Z_t denotes the underlying branching process and $\bar{Z}_n$ the number of new cases in the nth week. Right: Durations for outbreaks started with one infected individual.

symptoms of mumps is called the incubation period for mumps. This incubation period can be 12 to 25 days and the average is 16 to 18 days. The infectious period (i.e., when an individual is able to transmit the mumps virus to others) starts about 2 days before the onset of symptoms and usually, an individual with mumps symptoms is immediately isolated from the population (see http://kidshealth.org). In view of the range of the incubation period, we consider that an outbreak is formed by the cases that appear in a province in a sequence of weeks with no more than three consecutive weeks without cases. That is, when we observe more than three weeks without cases we consider that the outbreak has become extinct, with the next outbreak starting in the first subsequent week in which there is at least one new case. Applying this procedure for each province, we have obtained 262 outbreaks. The left plot in Figure 3 could represent one such outbreak initiated by one infected individual. In this schematic representation, we have considered that the infectious period is *negligible* due to the fact that infected individuals are immediately isolated when they show symptoms. The variable Z_t denotes the underlying branching process, which is not observed. The segments over/under Z_t indicates the lengths of time for which Z_t takes the corresponding values. The tick marks on the axis represent weeks, and $\bar{Z}_n$ the number of new cases observed during the nth week. Indeed, $\bar{Z}_n$, $n \geq 0$, are the variables that are observed. In this context, by outbreak duration we mean the time elapsing between the appearance of the first case until isolation of the last one, that is the time to extinction of the branching process minus the incubation period of the first individual. Thus, a more accurate way to approximate outbreak duration from the observed data is by the total number of weeks until extinction of the virus (giving an error, due to discretization, of at most one week), yielding seven weeks in the outbreak of Figure 3 (left).

For each of the 262 outbreaks, we calculated the total number of weeks until extinction of the virus (and, also, the outbreak size, i.e., total number of infected individuals). We noticed that the behaviour of these outbreak durations depends on the initial number of infected individuals. Hence, we have considered only those outbreaks which started with one infected individual, a total of 144. We checked that both outbreak duration and outbreak size were homogeneous between provinces (Kruskal–Wallis test: p-values 0.4763 and 0.4782, resp.) and consequently

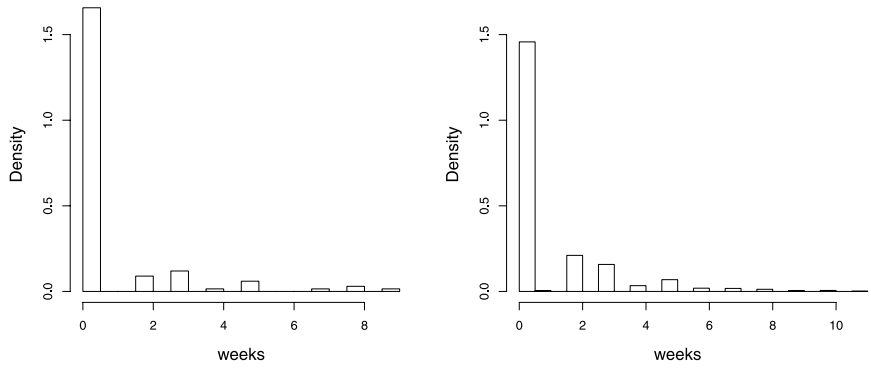

Figure 4. Left: Durations for outbreaks started with one infected individual without overlapping. Right: Simulated durations from a BHBP for outbreaks started with one infected individual.

assumed that disease propagation in the different provinces are independent replications of the same process. Thus, the right plot in Figure 3 shows the histogram of outbreak durations for all 144 outbreaks started with one infected individual. We observe two different groups, outbreaks for which their duration is less than 10 weeks (comprising 134 outbreaks) and another group where the outbreak duration is greater than 10 weeks (comprising the remaining ten outbreaks). Possibly, this happens because some cases observed in a week could not come from cases of previous weeks, and then new outbreaks could have appeared overlapping in time. Hence, we consider that the outbreaks corresponding to durations of this last group may have been initiated no more than 10 weeks before. Thus, outbreak durations greater than 10 weeks have been removed from our study, and only durations less than 10 weeks have been considered in order not to overestimate the duration of the outbreaks. Nevertheless, an outbreak with apparent duration less than 10 weeks could actually be the superposition of two or more separate outbreaks, but we cannot determine this.

The left plot of Figure 4 shows the durations of the 134 outbreaks considered. We notice that 83% of these outbreaks have only one infected individual, so their outbreak durations are 0. The remaining 17% of outbreaks seem to have a cyclical behaviour with period given by the mean of the incubation period (approximately 2.5 weeks).

4.2. Modelling mumps transmission

As noted above, mumps is a contagious disease of humans that is spread from person to person through the air. The most common method of transmission is through coughing or sneezing, which can spread droplets of saliva and mucus infected with the mumps virus. Hence, when an infected person coughs or sneezes, the droplets atomize and can enter the eyes, nose, or mouth of another person. Following mumps transmission, a person does not immediately become sick. Once the virus enters the body, it travels to the back of the throat, nose and lymph glands in the neck, where it begins to multiply. As indicated previously, this period between mumps transmission and the beginning of mumps symptoms is the incubation period for mumps. People who

have mumps are most contagious from 2 days before symptoms begin to 6 days after they end and transmission may occur at anytime in that period. Since an individual with mumps symptoms is immediately isolated from the population, the infectious period is very short in comparison with the incubation period, so, as indicated previously, we assume that transmission occurs only at the end point of an individual's incubation period. This assumption simplifies the mathematical model and does not influence strongly outbreak duration. As the end of the incubation period means that an individual's viral load has reached a given threshold to produce clinical signs, we assume that the mean number of individuals infected by an infected individual is constant and does not depend on the length of his/her incubation period.

An earlier analysis of these mumps data using Bienaymé–Galton–Watson branching processes is given in Angelov and Slavtchova–Bojkova [3]. However, the above observations imply that the Bellman–Harris branching process (BHBP) (see Athreya and Ney [4]) is a more appropriate model for mumps transmission and indeed it provides an improved fit to these data. Recall that a BHBP is a CMJ branching process, in which an individual reproduces only at the end of his/her life-time, according to an offspring law which is the same for all the individuals. In the epidemiological context, age is the incubation period and the reproduction law is the contagion distribution.

Next, we describe the incubation period and contagion distributions used to model mumps transmission in each outbreak in Bulgaria by means of the same BHBP (recall that we did not find any difference in the behaviour of the outbreaks in different provinces). We assume that the incubation period I follows a gamma distribution, with shape parameter $r > 0$ and rate $\gamma > 0$, so I has mean $r\gamma^{-1}$ and probability density function

$$f_I(u) = \frac{\gamma^r u^{r-1} \exp(-\gamma u)}{\Gamma(r)}, \qquad u > 0,$$

where Γ is the gamma function, and that the contagion distribution follows a Poisson distribution with mean m. These distributions are appropriate for the incubation period and the number of infections, respectively (see, e.g., Daley and Gani [9], Farrington and Grant [11], Farrington *et al.* [12] or Mode and Sleeman [23]). Intuitively, m, the mean number of individuals infected by an infected individual, represents the power of the virus. Taking into account that the incubation period is estimated between 12 and 25 days and the average is 16 to 18 days, we consider the gamma distribution with mean 17 and $r = 50$, which implies that the incubation period in 98.7% of individuals is between 12 and 25 days. To estimate m, we consider the maximum likelihood estimator (MLE) based on the total number of births in independent extinct realisations of a BHBP. The total number of births in a BHBP has the same distribution as that in a Bienaymé–Galton–Watson branching process with the same offspring distribution. In our application, the offspring distribution is Poisson and it follows that the total number of births $N(\infty)$ (excluding the initial a individuals) follows a Borel–Tanner distribution with probability mass function

$$\mathrm{P}\big(N(\infty) = k\big) = \frac{am^k(a+k)^{k-1}\mathrm{e}^{-(a+k)m}}{k!}, \qquad k = 0, 1, \ldots.$$

(Note that, for $l = 1, 2, \ldots$, the mean number of births in the lth generation is am^l, so the expectation of this Borel–Tanner distribution is $E[N(\infty)] = a(m + m^2 + \ldots) = am(1 - m)^{-1}$,

when $m < 1$.) It follows that the MLE of the offspring mean m, based on L independent realisations, is given by $\hat{m} = (\sum_{i=1}^{L} n^{(i)})(\sum_{i=1}^{L} a^{(i)} + n^{(i)})^{-1}$, where, for $i = 1, 2, \ldots, L$, $a^{(i)}$ and $n^{(i)}$ are respectively the initial number of individuals and the total number of births in the ith realisation (for details see Farrington *et al.* [12]). In our case $L = 134$, $\sum_{i=1}^{L} a^{(i)} = 134$ and $\sum_{i=1}^{L} n^{(i)} = 62$, whence $\hat{m} = 0.3163$. Note that inference based on duration of outbreaks is less sensitive to underreporting than that based on the total number of births. However, estimating the offspring law based on the time to extinction of each outbreak turns into a difficult problem in branching processes theory, even for the simplest model (see, e.g., Farrington *et al.* [12]).

Applying the general theory of branching processes, since the estimated value of m is less than 1, we deduce that mumps transmission can still occur in Bulgaria, but such spread cannot lead to a large-scale epidemic. This fact is consistent with the Figures 1 and 2. Although the epidemic becomes extinct, it can have different levels of severity. One measure of severity is the mean size of an outbreak, excluding the initial case, viz. $m(1-m)^{-1}$, which in our case is estimated by 0.463. However, we are concerned with the problem of how to shorten outbreak durations by vaccination. To this end, we analyze the random variable $T_{\alpha^0_{c_{\text{inf}}}}$, the time to extinction of a BHBP with incubation period and contagion distributions as described above. Note that $c_{\text{inf}} = 0$, as $m \leq 1$, so here $T_{\alpha^0_{c_{\text{inf}}}}$ is the extinction time when there is no supplementary vaccination. The variable $T_{\alpha^0_{c_{\text{inf}}}}$ includes the incubation period of the initial individual, which is not observed in practice. Thus, from now on, we use the random variable $\widetilde{T}_{\alpha^0_{c_{\text{inf}}}}$, the difference between $T_{\alpha^0_{c_{\text{inf}}}}$ and the incubation period of the initial individual (i.e., the definition of outbreak duration given in the previous subsection) to model mumps outbreak duration in Bulgaria. The right plot in Figure 4 shows a histogram of 10 000 simulated durations of outbreaks (rounded up to the nearest integer), each initiated by one infected individual and modelled by a BHBP with the above parameters. We notice that in 72.9% of these simulated outbreaks the initial infected individual does not infect any new individual (recall 83% for real data). Moreover, the simulated outbreak durations show the same cyclical behaviour as seen in the real data.

Comparing real and simulated durations, we deduce that mumps outbreak durations in Bulgaria can be modelled by the variable $\widetilde{T}_{\alpha^0_{c_{\text{inf}}}}$ (Pearson's chi-squared test: p-value 0.2951, grouping the tail for values greater than 8).

4.3. Determining the optimal vaccination levels

Once we have fitted the model, in order to apply our theoretical results we have assumed that the proportion of immune individuals is constant with time, since, generally, vaccination is applied when an individual is a child and the disease spreads when he/she is a teenager. In the particular case of supplementary vaccination for Bulgarian mumps, for simplicity we assume that this vaccination process occurs simultaneously across the country (e.g., in secondary schools at the same specific time). To determine the optimal vaccination levels, we denote by $\widetilde{T}_{\alpha^0_c}$ the difference between $T_{\alpha^0_c}$ and the incubation period of the initial individual, when the proportion of immune individuals in the population is c, with $0 \leq c \leq 1$. In the same way as was proved for $T_{\alpha^0_c}$ (see Corollary 3.3), we deduce that $\widetilde{T}_{\alpha^0_c}$ has the same quantile properties depending on c as $T_{\alpha^0_c}$ (notice

that $\widetilde{T}_{\alpha_c^0}$ is monotonically decreasing with pruning). Therefore, next we propose vaccination policies based on the quantiles of $\widetilde{T}_{\alpha_c^0}$, with $0 \le c \le 1$. Specifically, for fixed p and t, with $0 < p < 1$ and $t > 0$, we seek vaccination policies which guarantee that the mumps virus becomes extinct in each outbreak, with probability greater than or equal to p, not later than time t after the outbreak has been detected with z initial infected individuals, that is

$$c_{\mathrm{opt}} = c_{\mathrm{opt}}(z, p, t) = \inf\bigl\{c : 0 \le c \le 1, x^{\widetilde{T}}_{\alpha_c^0, p^{1/z}} \le t\bigr\},$$

where $x^{\widetilde{T}}_{\alpha_c^0, p^{1/z}}$ denotes the quantile of order $p^{1/z}$ of the variable $\widetilde{T}_{\alpha_c^0}$.

As an illustration, we take $z = 5$, $p = 0.9$ and $t = 3$, being the time measured in weeks. First we justify these values. Consider the value of z. Since the number of infected individuals at the beginning of an outbreak is unknown, we bound it by the greatest number of individuals infected by one infected individual. Taking into account that the contagion distribution is Poisson and the estimate of m, we obtain the upper bound to be 5, and therefore we take $z = 5$. Moreover, we select $t = 3$, which, taking into account the features of the incubation period, guarantees that only primary and first-generation cases will be observed. Since in our situation the estimated value of m is less than 1, to approximate c_{opt}, we need to obtain the empirical distribution of $\widetilde{T}_{\alpha_c^0}$, for $0 \le c \le 1$, using the Monte-Carlo method described in Section 3.5. To this end, for each $c = 0.01k$, with $k = 0, \ldots, 100$, 100 000 processes have been simulated and their duration calculated. The left plot in Figure 5 shows the behaviour of the empirical distribution function of $\widetilde{T}_{\alpha_c^0}$ for several values of c. Notice that as c increases, the outbreak duration decreases in a continuous way, in accordance with Corollaries 3.1 and 3.2. The right plot in Figure 5 shows the behaviour of $x^{\widetilde{T}}_{\alpha_c^0, 0.9^{1/5}}$ depending on c, which is in accordance with Corollary 3.3. Since $x^{\widetilde{T}}_{\alpha^0_{c_{\mathrm{inf}}}, 0.9^{1/5}} = 6.97$, our model estimates that the duration of 90% of outbreaks in Bulgaria is less than 6.97 weeks, if vaccination is not applied (in our real data 97% of outbreaks have durations less than 6 weeks). In order to shorten the outbreak duration, from our study, we deduce that $c_{\mathrm{opt}}(5, 0.9, 3) = 0.6$ (see right plot in Figure 5). Therefore, vaccinating a proportion of 60% of

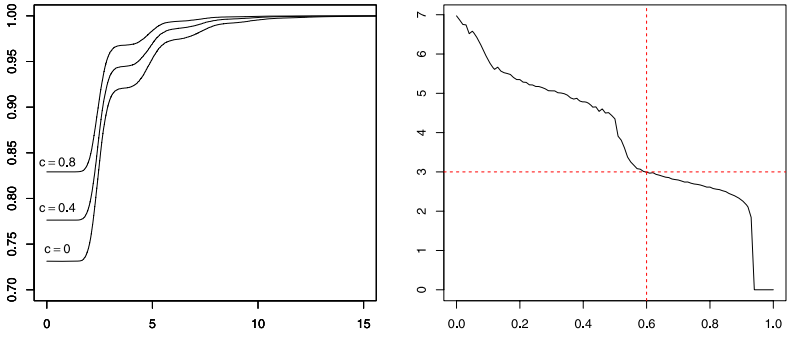

Figure 5. Left: Behaviour of the distribution function of $\widetilde{T}_{\alpha_c^0}$ for $c = 0, 0.4, 0.8$. Right: Behaviour of $x^{\widetilde{T}}_{\alpha_c^0, 0.9^{1/5}}$ depending on c, with $0 \le c \le 1$.

Table 1. Sensitivity analysis on the mean and shape parameter of the gamma incubation distribution

Mean		Shape parameter r				
		30	40	50	60	70
16	% Coverage	92.2	95.3	97.1	98.8	98.8
	$c_{\text{opt}}(5, 0.9, 3)$	0.60	0.57	0.56	0.54	0.54
16.5	% Coverage	93.0	96.6	98.1	98.9	99.4
	$c_{\text{opt}}(5, 0.9, 3)$	0.63	0.60	0.58	0.56	0.55
17	% Coverage	94.9	95.5	98.7	99.3	99.6
	$c_{\text{opt}}(5, 0.9, 3)$	0.66	0.64	0.60	0.58	0.57
17.5	% Coverage	95.4	97.9	99.0	99.5	99.8
	$c_{\text{opt}}(5, 0.9, 3)$	0.70	0.67	0.65	0.62	0.61
18	% Coverage	95.3	97.8	99.0	99.5	99.8
	$c_{\text{opt}}(5, 0.9, 3)$	0.73	0.71	0.68	0.65	0.64

susceptible individuals in the target cohort, guarantees that in at least 90% of outbreaks of mumps in Bulgaria only primary and first-generation cases will be observed after the vaccination. Finally, we notice that $c_{\text{opt}}(5, 0.9, 0) = 0.94$, that is, to guarantee that at least the 90% of outbreaks do not spread after vaccination, the vaccination level should be 94% of susceptible individuals in the target cohort.

The parameters of the gamma distribution used to model the incubation period have been derived from knowledge of mumps transmission rather than estimated from data. Thus we have performed a sensitivity analysis of their influence on the optimal vaccination level. We have considered gamma distributions with mean and shape parameter r taking values in a grid (giving different probabilities for the incubation period belonging to range 12–25, which we denote as percentages of coverage), yielding the results shown in Table 1. One can observe that increasing the mean (holding r fixed) clearly increases the duration of the epidemic leading to higher values of c_{opt}. Moreover, increasing the shape parameter r (holding the mean fixed) decreases the variance of lifetimes and hence also the chance of long outbreak duration, leading to lower values of c_{opt}. The optimal vaccination level $c_{\text{opt}}(5, 0.9, 3)$ is fairly stable in the vicinity of the chosen values of 17 and 50 for the mean and shape parameter r, respectively.

Remark 4.1. From a computational point of view it is interesting to note that to find optimal vaccination policies, the simulation method based on *pruning*, described at the end of Section 3.5, has proved to be at least 17% faster than those in González *et al.* [13,14], which are also simulation-based methods but work directly with the distribution of the extinction time. For the BHBP there exist other methods to approximate the distribution function of the time to extinction based on solving numerically an associated integral equation (see Martínez and Slavtchova-Bojkova [21], which includes comparison with simulation-based methods). Unlike the latter approach, the Monte-Carlo method proposed in Section 3.5 is easily extended to time-dependent vaccination processes. All the computations and simulations have been made with the statistical computing and graphics language and environment **R** ("GNU S", see [27]).

5. Concluding comments

The coupled pruning technique for proving monotonicity and continuity properties of functions defined on CMJ branching processes depending on the vaccination function α is both simple and powerful. It is clear that the proofs generalise easily to more general branching processes, such as multitype CMJ branching processes, time-inhomogeneous branching processes and branching processes in a random environment. The function α does not have to represent vaccination. It could represent any control of disease propagation that has the effect of reducing either the number of susceptibles or the probability that a contacted susceptible becomes infected. However, for the coupled pruning technique to work it is necessary that, in the branching process setting, the control affects only the probability that a birth is aborted and not the intrinsic reproduction law of the branching process. Thus, for example, the method cannot be applied to density-dependent processes, such as population size dependent branching processes, if the density dependence relates to the size of the unvaccinated population rather than the total population size.

Given that the results in the Bulgarian mumps illustration are based on simulation alone, it may seem more appropriate to use an epidemic model rather than a branching process that approximates such a model. However, there are several advantages in using the simpler branching process formulation. First, branching process models can be fitted directly to the data more easily; in particular they do not require knowledge of the size of the population in which the outbreaks are occurring. Second, the coupled pruning technique enables the monotonicity and continuity properties pertaining to vaccination functions to be proved easily. Third, the coupled pruning technique yields an associated Monte-Carlo method for determining optimal vaccination processes.

The framework for optimal vaccination policies studied in Section 3.5 can be extended to include alternative formulations of optimal policies. For example, one may define a cost $c(\alpha)$ associated with each vaccination process $\alpha \in \mathcal{A}$ and then seek vaccination processes from a subset $\mathcal{A}^*$ of $\mathcal{A}$ which either (i) minimise $c(\alpha)$ subject to $\mu_\alpha^f \leq b$ or (ii) minimise μ_α^f subject to $c(\alpha) \leq c_0$, where c_0 is specified. Provided the cost function, $c(\alpha)$ is suitably monotonic and continuous in α and $\mathcal{A}^*$ is totally ordered, Theorems 3.1 and 3.2 imply the existence of unique such optimal vaccination processes and it should be possible to extend the Monte-Carlo algorithm at the end of Section 3.5 to estimate the optimal vaccination processes. Optimal vaccination policies that permit vaccination costs to be taken into account are especially relevant in animal vaccination.

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