MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **5**, Number **3**, July **2008**

http://www.mbejournal.org/

pp. **429–435**

# THE EFFECT OF PATTERNS OF INFECTIOUSNESS ON EPIDEMIC SIZE

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(Communicated by Susanne Ditlevsen)

Abstract. In the course of an infectious disease in a population, each infected individual presents a different pattern of progress through the disease, producing a corresponding pattern of infectiousness. We postulate a stochastic infectiousness process for each individual with an almost surely finite integral, or total infectiousness. Individuals also have different contact rates. We show that the distribution of the final epidemic size depends only on the contact rates and the integrated infectiousness. As a particular case, zero infectiousness on an initial time interval corresponds to a period of latency, which does not affect the final epidemic size in general stochastic and deterministic epidemic models, as is well known from the literature.

1. **Introduction.** After an infectious agent invades a susceptible individual through a contact with an infective individual, the newly infected individual presents infectiousness which varies through time. The time-course depends on a variety of factors, including the extent to which the immune system has been compromised, how it reacts to medical treatment, the time from infection until symptoms appear, and biological stages of the infectious agent.

The effects of the pattern of infectiousness on the final epidemic size in a stochastic model is our focus. We define a non-negative stochastic infectiousness process for each individual, on a time line beginning with the time of infectious contact. The infectiousness process can be quite arbitrary as long as its integral is almost surely finite. It is reasonable to assume that the infectiousness processes for different individuals are independent. The ideas of latency and recovery are captured by the example of an infectiousness process which has the value zero for an initial random interval, followed by a constant value on the random time interval of infectiousness of the model, followed by the value zero on the entire time line after recovery.

2000 *Mathematics Subject Classification.* Primary: 92D30, Secondary: 93A30.
*Key words and phrases.* random infectiousness, variable infectiousness, final epidemic size.

We will show that the infectiousness process influences the final epidemic size only through its integral. In particular, the distribution of the final epidemic size is not influenced by latency, the time interval from exposure of an individual until time he becomes infective to others. This fact has been known for quite a while for the particular process known as the susceptible-exposed-infected-removed or SEIR model [4], and some of its extensions. The non-dependence of final size on latency has been shown in various contexts and has become "folklore" in the stochastic epidemic literature, e.g. [3, 2, 1]. In [3], for instance, Ball uses the Sellke construction, [16, 2], to derive a triangular linear system of equations for the probabilities of the number of susceptibles ultimately infected in the context of the SIR. From this derivation, he points out that periods of latency and time dependent contact rates may be allowed without modification of the main argument. One can infer that the distribution of the final epidemic size is independent of such additional structures. In [1], Addy et al. generalize the model presented in [3] in several directions. For instance, they take into account outbreaks within households in the presence of a community infection and allow susceptible individuals to be infected from outside the population. They show, as in [3], that the distribution of the final epidemic size does not change if, in the hypotheses, latency or variable contact rates are included in these specific contexts.

However, the formulations in the works mentioned are in the context of the SIR or SEIR models. We propose, instead, a formulation that is at the same time much more general and very simple, allowing a streamlined proof of the result that final size depends only on integrated infectiousness. The early work of Ludwig [11] in this direction inspires our method of proof. He regarded an epidemic as a sequence of generations of infective individuals, where each generation has an infective contact with some member of the previous one. In [14, 9, 10], Picard and Lefèvre also work with generations of infectives. They extend results of Ludwig [11] and Ball [3] to hold for the Reed-Frost and other models, but their populations remain homogeneous. Their arguments are sometimes intricate. Our setting is more general and allows a fresh and direct way to see that variable infectiousness does not affect final size.

In our setting, the contact rates between two individuals may vary with both individuals. Instead of infectiousness being assumed constant on an interval of time, as in the SIR, described through a non-random function of the time after infection, or taken as the mean infectiousness of an individual [5, 6, 13], here infectiousness is allowed to be a rather arbitrary random function of time. Its distribution may vary with the individual. It turns out that the distribution of the final epidemic size depends on the contact rates and the expected values of integrated infectiousness, but not on the particular patterns of infectiousness.

This result is particularly interesting in examples such as HIV-AIDS and tuberculosis. In the former, infectiousness is initially high and then declines gradually, remaining at a low level for a random time depending on the individual and surrounding circumstances. At some point, infectiousness may increase to a higher level again, [8]. In tuberculosis, and other infectious diseases with relapse, random periods of infectiousness may recur some time after the initial infectious period. A deterministic model of this type is studied in [18].

In [17], Thieme shows that the final epidemic size formula for the Kermack and McKendrick ODE [7] model holds for models that include variable infectiousness. Thieme notes that Kermack and McKendrick deal with a much more general model than the SIR ODE model, including, in particular, variable infectiousness, and show,

in the deterministic setting, that only the total expected infectiousness matters for the final size (see also [5], Section 2.1). Recently, Ma and Earn [12] have shown that the same final epidemic size formula holds under more general conditions, including latency, several infectious stages, transmission rates that are arbitrarily distributed, and for a class of spatial contact structures. These results for deterministic epidemic models are parallel to ours for stochastic ones.

2. **Transmission of disease.** We consider a fixed finite population of $N$ individuals, which we label with the values $1, ..., N$ simply for identification. The individuals may be thought of as distributed in space and related by a network of social or other connections. Or they may be thought of as moving in space and encountering one another with pair independent frequencies. The numbers $c_{ij} \geq 0$ will measure the rates of contact from individual $i$ to individual $j$ for all pairs $(i, j)$ with $1 \leq i, j \leq N$. Notice that $c_{ji} \neq c_{ij}$ in general.

At time zero, one or more individuals carrying an infectious disease have been introduced in a population of susceptible individuals. The event of infection passing from individual $i$ to individual $j$ is produced by the combination of two circumstances. One factor is contact from $i$ to $j$, and the second is that individual $i$ is infectious to some extent at the time of contact. Our model assumption is that the time $T_{ij}$ of first infectious contact from $i$ to $j$ happens in the time interval $[t, t+\Delta t)$ with hazard function (defined below)

$$P(T_{ij} \in [t, t + \Delta t) | T_{ij} > t, \mathcal{F}_i) = c_{ij} X_i(t) \Delta t + o(\Delta t). \tag{1}$$

Time in (1) runs according to a clock which starts at the first infectious contact made to individual $i$. The *infectiousness* process of individual $i$, $X_i(t)$, measures, at each time $t$, the probability that a contact made by $i$ at time $t$ is effective in transmitting the disease. In other words, $X_i(t)$ is the conditional probability of transmission of disease, given that the contact is made. The $\sigma$-algebra $\mathcal{F}_i$ represents the information generated by the entire history of the random infectiousness process $X_i$, not including its start time. Our definition could equally well condition on the information generated by $X_i$ only up to time $t$, as is more conventional in such expressions. However, in the sequel we wish to condition on the entire sample path, and the meaning of (1) is the same either way. The infectiousness clock of individual $i$ may start at time 0, but it may be that $X_i(0) = 0$, so that $i$ is not actually infectious at time 0. Nevertheless, we refer to such individuals as *initial infectives.* The product in (1) should be read as the probability of contact from $i$ to $j$ in the time interval $[t, t+\Delta t)$, $c_{ij}\Delta t + o(\Delta t)$, times the conditional probability of transmission of disease, given that contact is made, $X_i(t)$. The random function $c_{ij}X_i(t)$ is a random hazard function.

In general, the hazard function $h$ of a non-negative random variable $T$ with distribution $F_T$ and density $f_T$,

$$h_T(t) = \frac{f_T(t)}{1 - F_T(t)},$$

can be understood as the conditional density of $T$ at $t$ given that $T > t$. If the hazard function $h_T(t)$, $t \geq 0$, is given, the corresponding distribution satisfies, e.g. [15],

$$P(T > t) = e^{-\int_0^t h_T(s) ds}. \tag{2}$$

For clarity, we state the corresponding fact for our random hazard function, $c_{ij}X_i(t)$, as a lemma.

**Lemma 2.1.** *For every $t \geq 0$,*

$$P(T_{ij} > t|\mathcal{F}_i) = e^{-\int_0^t c_{ij}X_i(s)ds}. \tag{3}$$

Notice that conditioning on $\mathcal{F}_i$ allows us to choose a specific sample path, $X_i(s)$. With this path, the relation (2) holds.

**Corollary 1.** *Let*

$$D_i = \int_0^\infty X_i(s)ds < \infty. \tag{4}$$

*Then, the probability that an individual $j$ has no infectious contact from individual $i$, given the process $X_i$, is*

$$P(\text{no infection from } i \text{ to } j \ |\mathcal{F}_i) = e^{-c_{ij}D_i}.$$

*Proof.* Let $t \to \infty$ in (3). Then, on the right-hand side we have the probability that $T_{ij} = \infty$, or equivalently, the probability that a first infectious contact to individual $j$ from individual $i$ never happens. □

**Example 1.** Suppose

$$X_i(t) = \begin{cases} p & \text{for } t < \tau_i,\ 0 \leq p \leq 1, \\ 0 & \text{otherwise,} \end{cases} \tag{5}$$

for every $i$, where $\tau_i$ is exponentially distributed with parameter $\alpha$, $E\tau_i = 1/\alpha$, and the $\tau_i$'s are independent. A natural way to define the basic reproductive number for individual $i$, $R_{0,i}$, is as the expected number of secondary cases produced by individual $i$ when all the other individuals are susceptible, [2]. We have

$$\begin{aligned} R_{0,i} &= E\,[\text{number of infections produced by } i \text{ in a pool of susceptibles}] \\ &= E\left[\sum_{j\neq i} c_{ij}\int_0^\infty X_i(t)dt\right] \\ &= E\left[\sum_{j\neq i} c_{ij}p\tau_i\right] = \frac{\sum_{j\neq i} c_{ij}p}{\alpha}. \end{aligned}$$

If $c = \beta/(N-1)$ is the common, or average, contact rate of each individual with each other individual, then the expected number of secondary cases produced by the "typical" infective is

$$R_0 = \beta p/\alpha. \tag{6}$$

Given that individual $i$ has had infectious contact, at which the time of $X_i(t)$ starts, from Lemma 1,

$$\begin{aligned} P(T_{ij} > t|\mathcal{F}_i) &= e^{-cp(t\wedge\tau_i)}, \\ P(T_{ij} = \infty|\mathcal{F}_i) &= e^{-cp\tau_i}, \\ P(\text{no infectious contact from } i \text{ to } j) = E(e^{-cp\tau_i}) &= \int_0^\infty e^{-cpy}\alpha e^{-\alpha y}dy \\ &= \frac{\alpha}{cp+\alpha}. \end{aligned}$$

**Example 2.** Suppose that $c_{ij} = c$ for every $i$ and $j$, and

$$X_i(t) = \begin{cases} 0 & \text{for } t < \eta_i,, \\ p & \text{for } \eta_i \le t < \tau_i + \eta_i,\ 0 \le p \le 1, \\ 0 & \text{otherwise,} \end{cases} \tag{7}$$

where the $\eta_i$ are i.i.d. random variables exponentially distributed with parameter $\gamma$, the $\tau_i$ are defined as in Example 1, and the $\eta_i$ and $\tau_i$ are independent. In this example, latency and removal are captured as conceived in a susceptible-exposed-infected-removed model (SEIR).

**Example 3.** Suppose that $c_{ij} = c$ for every $i$ and $j$. The probability that an individual $j$ has no infectious contact from individual $i$ is

$$\int_0^\infty e^{-cy} f_{D_i}(y)dy,$$

where $f_{D_i}$ is the probability density of $D_i$. This is because

$$\begin{aligned} P(\text{no infectious contact from } i \text{ to } j) &= E(P(\text{no infectious contact from } i \text{ to } j|\mathcal{F}_i)) \\ &= \int_0^\infty e^{-cy} f_{D_i}(y)dy. \end{aligned}$$

3. **Epidemic size depends only on integrated infectiousness.** Consider a population of $N$ individuals. To simplify language, we say that an individual $i$ is *nominally contacted* when an infectious contact to $i$ occurs. This may not be the first infectious contact. If an individual $i$ is infected through contact with an individual $k$ and is subsequently infectuously contacted by $j$, who belongs to a generation previous to that of $k$, then $i$ is nominally contacted by $j$, even though his infection came from $k$.

Let $\mathcal{F} = \bigcup_i \mathcal{F}_i$, the $\sigma$-algebra generated by the infectiousness processes, $X_i$, of all individuals in the population. $\mathcal{F}$ contains the information of the patterns of infectiousness of the entire population, which may include latency periods, for instance. We have constructed each infectiousness process $X_i$ so that it starts when individual $i$ first receives an infectious contact, or at time 0 if $i$ is regarded as infective at time 0. Recall that $\mathcal{F}_i$ does not include the information of the start time of $X_i$. It is reasonable to assume that the infectiousness processes are independent for different individuals. In particular the $D_i$'s are independent random variables.

Let $\mathcal{P}$ denote the set of all individuals in the population. Let also $\mathcal{X}_k$ and $\mathcal{Y}_k$, $k = 0, 1, 2, ...$ be defined by

$$\begin{aligned} &\mathcal{X}_0 = \{\text{initial infectives}\}, \\ &\mathcal{Y}_0 = \mathcal{P} - \mathcal{X}_0, \\ &\mathcal{X}_1 = \{j : j \in \mathcal{Y}_0, \exists i \in \mathcal{X}_0 \text{ such that } j \text{ is nominally contacted by } i\}, \\ &\mathcal{Y}_1 = \mathcal{Y}_0 - \mathcal{X}_1, \\ &\dots \end{aligned}$$

and so on. Notice that $\mathcal{Y}_0 \supset \mathcal{Y}_1 \supset \dots$ and that the set of all nominally contacted individuals, $\bigcup_{k=0}^\infty \mathcal{X}_k$, where $\mathcal{X}_i \cap \mathcal{X}_j = \emptyset$ if $i \neq j$, is equal to the set of all individuals who become infected. The size of this set is the total epidemic size.

**Theorem 3.1.** *The probability distribution of the final epidemic size given $\mathcal{F}$, the information in all the infectiousness processes, depends only on the total infectiousness $D_i$, $i = 1, 2, ..., N$.*

*Proof.* Let $\mathcal{X} \subset \mathcal{Y}_0$. The probability that the random set $\mathcal{X}_1$ is exactly $\mathcal{X}$, given $\mathcal{F}$, is

$$\begin{aligned} P(\mathcal{X}_1 = \mathcal{X}|\mathcal{F}) &= \prod_{j\in\mathcal{X}} P(j \in \mathcal{X}_1|\mathcal{F}) \cdot \prod_{j\in\mathcal{Y}_0-\mathcal{X}} P(j \in \mathcal{Y}_0 - \mathcal{X}_1|\mathcal{F}) \\ &= \prod_{j\in\mathcal{X}} (1 - P(j \text{ has no nominal contact } \forall i \in \mathcal{X}_0)) \cdot \\ &\quad \cdot \prod_{j\in\mathcal{Y}_0-\mathcal{X}} P(j \text{ has no nominal contact } \forall i \in \mathcal{X}_0) \\ &= \prod_{j\in\mathcal{X}} \left(1 - \prod_{i\in\mathcal{X}_0} e^{-D_i c_{ij}}\right) \cdot \prod_{j\in\mathcal{Y}_0-\mathcal{X}} \prod_{i\in\mathcal{X}_0} e^{-D_i c_{ij}}. \end{aligned}$$

The distributions of $\mathcal{X}_k$, given $\mathcal{X}_{k-1}$, $k = 2, 3, ...$ can be computed similarly. Finally, the probability distribution of the number of individuals that have nominal contacts is

$$P\left(|\cup_k \mathcal{X}_k| = n|\mathcal{F}\right) = \sum_{\substack{\mathcal{X}\subset\mathcal{P} \\ |\mathcal{X}|=n}} P\left(\cup_k \mathcal{X}_k = \mathcal{X}|\mathcal{F}\right). \tag{8}$$

The value in (8) depends only on the random variables $D_i$, $i = 1, ..., N$, and of course, the $c_{ij}$'s. □

By the above argument, we can in principle, calculate the probability of any particular sample path of the nominal infectious contact process, $\{X_i, i \geq 0\}$, conditional on the random variables $D_i$. Taking the expectation with respect to the distribution of the $D_i$'s gives the unconditional probability of a particular sample path.

The actual calculation is impractical because it involves iterated sums over all sequences of subsets which might be a sample path of the nominal contact process. There is a very large number of different sequences $\{\mathcal{X}_k\}$ leading to the same $\cup_k \mathcal{X}_k$. However, we see from this analysis that the distribution of $\cup_k \mathcal{X}_k$ depends only on the $c_{ij}$ and the random $D_i$, but not on the values of the random infectiousness processes $X_i(t)$.

4. **Discussion.** The model we have introduced has directed contact rates which depend on each pair of individuals. Each individual, beginning when he first receives an infective contact, has his own random infectiousness process. The stochastic law of the infectiousness process may depend on the individual. Possible interpretations of the model are very broad. For example, the contact rates may be high in certain subgroups, like classrooms or clubs, or persons sharing transportation. The character of the infectiousness process may depend on genetics, diet, lifestyle, or the pre-existing load on the immune system of the individual, although not on the time of infectious contact. We construct an algorithm which, in principle, recursively computes the distribution of the source of the epidemic in terms of generations of individuals. A generation is defined, recursively, as the set of individuals infectively contacted by the previous such generation. We conclude that the distribution of epidemic size depends on the shapes of infectiousness functions only through the distributions of their integrals.

This theoretical result has practical impact. For instance, if a medicine extends the period of infectiousness of HIV while lowering the risk level, we see that epidemic

size will depend on integrated infectiousness, the area under the curve. And this is true with no assumption about homogeneity of the population.

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Received January 5, 2007. Accepted on May 7, 2008

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