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# Generality of endemic prevalence formulae

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ABSTRACT

In simple infection models, the susceptible proportion $s^*$ in endemic equilibrium is related to the basic reproduction number $R_0$ by $s^* = 1/R_0$. We investigate the extent to which this relationship remains valid under more realistic modelling assumptions. In particular, we relax the biologically implausible assumptions that individuals' lifetimes and infectious periods follow exponential distributions; allow a general recruitment process; allow for multiple stages of infection; and consider extension to a multigroup model in which the groups may represent, for instance, spatial heterogeneity, or the existence of super-spreaders. For a homogeneous population, we find that: (i) the susceptible proportion is $s^* = 1/R_0^e$, where $R_0^e$ is a modified reproduction number, equal to $R_0$ only in certain circumstances; (ii) the proportions of the population in each stage of infection are proportional to the expected time spent by an infected individual in that stage before recovery or death. We demonstrate robustness of the formula $s^* = 1/R_0$ for many human infections by noting conditions under which $R_0^e$ is approximately equal to $R_0$, while pointing out other circumstances under which this approximation fails. For heterogeneous populations, the formula $s^* = 1/R_0$ does not hold in general, but we are able to exhibit symmetry conditions under which it is valid.



## 1. Introduction

A key question in infectious disease modelling is the extent to which results derived from highly simplified models remain valid under more realistic modelling assumptions. With this in mind, the authors in [23,24] recently investigated the well-known epidemic final size equation of Kermack and McKendrick [17], with a view to understanding the extent to which the original equation remains valid under a range of modelling assumptions. In fact, the original derivation of [17] is already rather general, in that the expected infectivity of an individual is allowed to be an arbitrary function of time since infection, and in particular an individual's infectious period may be drawn from a general distribution. An illuminating discussion of the work of [17] appears in [5]. Sections 9 and 10 of [23] extend the model to allow for population heterogeneity; the final size equation obtained is a special case of Eq. (7) of [27]. Ma and Earn [23] discuss conditions under which the form of the original Kermack–McKendrick [17] equation is retained, and note that in the presence of heterogeneities, appropriate modification of the equation is generally required. Further recent discussion of the form of the final size equation, with particular reference to network models, appears in [24].

In the current work, we focus rather upon the prevalence level of an infection in long-term endemic equilibrium. We shall be concerned throughout with deterministic models, which is to say that we study mean behaviour in a large, well-mixed population. Nevertheless, we find it useful to present individual-based stochastic formulations of our models, since this aids intuitive understanding and leads to more transparent derivation of results.

The simplest model for endemic infection is the susceptible–infective–susceptible (SIS) model of [32], the deterministic version of which is represented by the system of differential equations

$$\frac{ds}{dt} = -\beta si + \gamma i,$$
$$\frac{di}{dt} = \beta si - \gamma i,$$

where $s(t)$ and $i(t)$ represent the proportions of individuals who are susceptible or infective, respectively, at time $t$, with $s(t) + i(t) = 1$ for all $t \geq 0$. The constants $\beta > 0$ and $\gamma > 0$ are known as the infection rate parameter and recovery rate parameter, respectively. The basic reproduction number (the expected number of secondary cases caused by a typical primary case in an otherwise susceptible population) is here given by $R_0 = \beta/\gamma$. For $R_0 \leq 1$ the only feasible equilibrium point is the disease-free equilibrium $(s, i) = (1, 0)$, whilst for $R_0 > 1$ there is also an endemic equilibrium point $(s^*, i^*) = (1/R_0, 1 - (1/R_0))$.

Clearly the above SIS model is greatly over-simplified. In particular, for any model purporting to describe long-term behaviour, it seems hard to justify the neglect of demographic processes of birth, migration and death. A more plausible model is the susceptible–

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infective–removed (SIR) model with demography ([26] and references therein). Individuals are recruited (by birth or immigration) into the susceptible category at constant rate $\mu > 0$ and die at per-capita rate $\mu$, and following infection are assumed to become permanently immune. The deterministic version of the model is

$$\frac{ds}{dt} = \mu - \beta si - \mu s, \tag{1}$$

$$\frac{di}{dt} = \beta si - \gamma i - \mu i, \tag{2}$$

$$\frac{dr}{dt} = \gamma i - \mu r, \tag{3}$$

where $s(t)$, $i(t)$ and $r(t)$ represent scaled numbers of susceptible, infective and immune ('removed') individuals, respectively. That is, these variables give the numbers of individuals in each category divided by some overall constant scaling factor indicative of population size. Writing $p(t) = s(t) + i(t) + r(t)$, then summing Eqs. (1)–(3) gives $dp/dt = \mu(1 - p)$ so that $p(t) \to 1$ as $t \to \infty$. Since we are interested in populations in equilibrium we will take $p(0) = 1$, and then $p(t) = 1$ for all $t$ so that $s$, $i$, $r$ may be interpreted as proportions of the population. For this model, $R_0 = \beta/(\gamma + \mu)$, and we find that for $R_0 \leq 1$ the only feasible equilibrium point is the disease-free equilibrium $(s, i, r) = (1, 0, 0)$, whilst for $R_0 > 1$ there is also an endemic equilibrium point $(s^*, i^*, r^*) = (1/R_0, (1 - (1/R_0))\mu/(\gamma + \mu), (1 - (1/R_0))\gamma/(\gamma + \mu))$.

From these two very simple models, we immediately see some common features emerging. For $R_0 \leq 1$, the only equilibrium point is the disease-free equilibrium. For $R_0 > 1$, in addition to the disease-free equilibrium there exists a unique endemic equilibrium point with susceptible proportion $s^* = 1/R_0$. Our aim is to investigate the extent to which observations such as these remain valid for more sophisticated and realistic models. It is worth noting that we shall not be concerned with the dynamics of the infection process, but only with the existence, uniqueness, and form of the endemic equilibrium point. In particular we do not consider stability of equilibria, nor whether the infection process displays oscillatory behaviour. These are of course crucial properties, but the objective here is to study the simplest aspects in quite a general context. We discuss issues of stability briefly in Section 4.

There are many aspects of the two models presented thus far that are clearly gross simplifications of biological reality. Firstly, the ordinary differential equation formulations imply that individuals' lifetimes and infectious periods are exponentially distributed. These are in general not biologically plausible assumptions. In fact, the early work of Kermack and McKendrick on endemicity [18,19] already allowed an individual's expected infectivity to be a general function of time since infection, so that in particular, infectious periods need not be exponentially distributed. In terms of individuals' lifetimes, the treatment in [18,19] is somewhat less satisfactory. In [18] there is no death except due to infection, whereas in [19] natural deaths occur at constant per-capita rates, so that an individual who never becomes infected will live for an exponentially distributed time. More recent work that does not assume exponentially distributed lifetimes and infectious periods has generally fallen into two categories. Firstly, some authors follow the lead of [19] in allowing for a realistic infectious period distribution while assuming that lifetimes are exponentially distributed, for instance [10,12,16]. This assumption is clearly unrealistic, but can greatly simplify the analysis. Alternatively, so-called 'age-structured' models ([9,14,31] and Chapter 22 of [30]) allow for a realistic lifetime distribution, but often not a realistic infectious period distribution. In such models the rate at which individuals recover from infection is typically allowed to depend upon the individual's age, but not upon the time since infection. This makes the model somewhat difficult to interpret, since the distribution of an individual's infectious period is not straightforward to extract from this framework. For instance, for many infections a reasonable simplifying assumption is that the infectious period is a constant. This means that the rate of recovery depends in the most extreme way upon time since infection, and there is no way to even approximate this within such an age-structured model. Age-structured models in which the recovery rate is allowed to depend upon both age and time since infection are described and studied in [8,13,15,16]. Closer to the spirit of the current work is the recent paper [1], in which the authors study a model based upon that of [18,19], in that an individual's expected infectivity is allowed to be a general function of time since infection, but allowing a general lifetime distribution.

Rather than follow [1,18,19] in modelling infectivity as a continuously varying function, we prefer to treat the infection process as consisting of a sequence of distinct stages of infection. This formulation in terms of multiple stages may be regarded as a special form of time-varying infectivity function; however, we prefer the formulation of stages, which has become standard in modern infection modelling, for the following reasons. Many infections exhibit clinically meaningful stages, such as a latent period or post-infectious period of temporary immunity; and some infections (e.g. HIV) are commonly modelled as comprising multiple stages of infection. Further, in fitting to data it seems reasonable to estimate a small number of infectivity parameters, whereas to estimate an continuously varying infectivity function would present a much greater challenge.

Another simplifying assumption often made is that recruitment to the population occurs at constant rate $\mu$. This has the desirable effect that the population size stabilises at $p(t) = 1$, providing a simple way to study an infection spreading in a stable population. However, other recruitment rate functions may be more biologically plausible, such as a combination of immigration and linear birth giving rate $\mu + \alpha p(t)$ for some $\mu, \alpha > 0$ [18,19], or logistic recruitment at rate $\mu(1 - (p(t)/K))$ for some $\mu, K > 0$ [20]. We allow quite a general recruitment rate function.

Finally, a variety of heterogeneities may be present in the population; for instance, heterogeneous susceptibility, heterogeneous infectivity, or heterogeneity of mixing. We will allow for heterogeneity by stratifying the population into a finite number of groups. Related previous work includes [11], Chapter 23 of [30] and Sections 8.5 and 8.6 of [28]; in each of these references, exponentially distributed lifetimes were assumed.

In summary, we aim to study a model for infection which incorporates a general recruitment rate function; non-exponentially distributed lifetimes and infectious periods; multiple stages of infection; and heterogeneous population structure. In contrast to previous authors, we focus specifically upon the form of the endemic equilibrium point, and the extent to which this form is dependent upon common simplifying assumptions.

## 2. Endemic infection in a homogeneous population

Consider a population which at time $t$ consists of $P(t)$ individuals. Individuals are recruited into the susceptible population according to an inhomogeneous Poisson process of rate $\Lambda(P(t))$, where $\Lambda(\cdot)$ is some non-negative function. Each individual lives for a time distributed as a non-negative random variable $L$ before being removed from the population (e.g. by death), and we assume $E[L] < \infty$. We will assume no disease-related mortality (although see discussion in Section 4 below), and so total population size $P(t)$ can be analysed separately from the infection process. Denote by $P^*$ the expected equilibrium population level (or quasi-equilibrium level in the case $\Lambda(0) = 0$), and consider the large-population limit in which the process $p(t) = P(t)/P^*$ may be treated as deterministic. We have

$$\begin{aligned} p(t) &= \frac{1}{P^*}\int_{-\infty}^{t} \Lambda(p(u)P^*)\,\Pr(L > t - u)\,du \\ &= \frac{1}{P^*}\int_{0}^{\infty} \Lambda(p(t - v)P^*)\,\Pr(L > v)\,dv. \end{aligned}$$