

AGE-OF-INFECTION AND THE FINAL SIZE RELATION

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ABSTRACT. We establish the final size equation for a general age-of-infection epidemic model in a new simpler form if there are no disease deaths (total population size remains constant). If there are disease deaths, the final size relation is an inequality but we obtain an estimate for the final epidemic size.

1. Introduction. The final size relation in an epidemic model is a transcendental equation relating the final size of the epidemic to the reproduction number. It was derived originally for a general age-of-infection model by Kermack and McKendrick [7], although it was not expressed in terms of the reproduction number. The age-of-infection model is a very general epidemic model, including models with multiple infective stages and treatment stages, and the final size relation is a very useful tool for analyzing the behavior of epidemic models [3, 8]. However, the derivation of the final size relation assumes mass action incidence. It is more realistic to assume density dependence in the contact rate and therefore if there are disease deaths the incidence is not mass action. In this case the final size relation is an inequality [1].

Our goal in this paper is to develop a final size relation for an age-of-infection epidemic model similar to the model of [2] with density dependence but in a form different from previous forms by avoiding the neglect of an initial term. We also show how to estimate the final size of an epidemic in which there are disease deaths in terms of the final size of an epidemic with no disease deaths but a larger reproduction number. If the disease death rate is small, the final size of the epidemic is very close to the final size of an epidemic with the same reproduction number and no disease deaths.

2. The age-of-infection epidemic model. The general epidemic model described by Kermack and McKendrick [7] included a dependence of infectivity on the time since becoming infected (age-of-infection). We let $S(t)$ denote the number of susceptibles at time t and let $\varphi(t)$ be the total infectivity at time t , defined as the sum of products of the number of infected members with each infection age and the mean infectivity for that infection age. We assume that on average members of the population make a constant number a of contacts in unit time. We let $B(\tau)$ be

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the fraction of infected members remaining infected at infection age τ and let $\pi(\tau)$ with $0 \leq \pi(\tau) \leq 1$ be the mean infectivity at infection age τ . Then we let

$$A(\tau) = \pi(\tau)B(\tau),$$

the mean infectivity of members of the population with infection age τ . For the moment, we assume that there are no disease deaths, so that the total population size is a constant N_0 .

The age-of-infection epidemic model is

$$\begin{aligned} S' &= -\frac{a}{N_0}S\varphi \\ \varphi(t) &= \varphi_0(t) + \int_0^t \frac{a}{N_0}S(t-\tau)\varphi(t-\tau)A(\tau)d\tau \\ &= \varphi_0(t) + \int_0^t [-S'(t-\tau)]A(\tau)d\tau. \end{aligned} \quad (1)$$

The basic reproduction number is

$$\mathcal{R}_0 = a \int_0^\infty A(\tau)d\tau.$$

We write

$$-\frac{S'(t)}{S(t)} = \frac{a}{N_0}\varphi_0(t) + \frac{a}{N_0} \int_0^t [-S'(t-\tau)]A(\tau)d\tau.$$

Integration with respect to t from 0 to ∞ gives

$$\begin{aligned} \ln \frac{S_0}{S_\infty} &= \frac{a}{N_0} \int_0^\infty \varphi_0(t)dt + \frac{a}{N_0} \int_0^\infty \int_0^t [-S'(t-\tau)]A(\tau)d\tau dt \\ &= \frac{a}{N_0} \int_0^\infty \varphi_0(t)dt + \frac{a}{N_0} \int_0^\infty A(\tau) \int_\tau^\infty [-S'(t-\tau)]dtd\tau \\ &= \frac{a}{N_0} \int_0^\infty \varphi_0(t)dt + a \left[\frac{S_0 - S_\infty}{N_0} \right] \int_0^\infty A(\tau)d\tau \\ &= \frac{a}{N_0} [N_0 - S_\infty] \int_0^\infty A(\tau)d\tau + \frac{a}{N_0} \int_0^\infty [\varphi_0(t) - (N_0 - S_0)A(t)]dt \\ &= \mathcal{R}_0 \left[1 - \frac{S_\infty}{N_0} \right] - \frac{a}{N_0} \int_0^\infty [(N_0 - S_0)A(t) - \varphi_0(t)]dt. \end{aligned} \quad (2)$$

Here, $\varphi_0(t)$ is the total infectivity of members of the population who were infected at $t = 0$ at time t . If all initial infectives have infection-age zero at $t = 0$, $\varphi_0(t) = [N_0 - S_0]A(t)$, and

$$\int_0^\infty [\varphi_0(t) - (N_0 - S_0)A(t)]dt = 0.$$

Then (2) takes the form

$$\ln \frac{S_0}{S_\infty} = \mathcal{R}_0 \left(1 - \frac{S_\infty}{N_0} \right), \quad (3)$$

and this is the general final size relation. Note that the final size of the epidemic, the number of members of the population who are infected over the course of the epidemic, is $N_0 - S_\infty$. This is often described in terms of the *attack ratio* $1 - S_{infy}/N_0$.

If there are initial infectives with infection age greater than zero, let $u_0(\tau)$ be the average infectivity of these individuals. Then, since $u_0(\tau) \leq B(\tau)$,

$$\begin{aligned}\varphi_0(t) &= (N_0 - S_0)u_0(\tau)\pi(t + \tau)\frac{B(t + \tau)}{B(\tau)} \\ &\leq (N_0 - S_0)A(t + \tau) \leq (N_0 - S_0)A(\tau).\end{aligned}$$

Thus, the initial term satisfies

$$\int_0^\infty [(N_0 - S_0)A(t) - \varphi_0(t)]dt \geq 0.$$

The final size relation is sometimes presented in the form

$$\ln \frac{S_0}{S_\infty} = \mathcal{R}_0 \left(1 - \frac{S_\infty}{S_0} \right), \quad (4)$$

with an initial term which is assumed small and omitted, see for example [1, 3, 6].

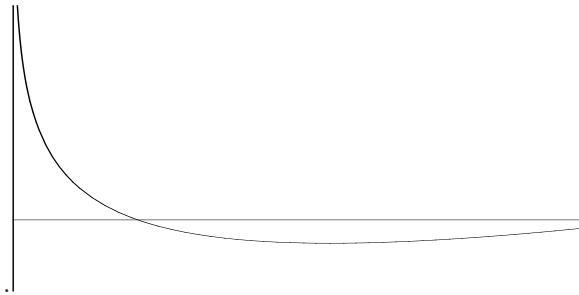


FIGURE 1. The function $g(x)$

It is not difficult to prove that there is a unique solution of the final size relation (3). To see this, we define the function

$$g(x) = \ln \frac{S_0}{x} - \mathcal{R}_0 \left[1 - \frac{x}{N_0} \right].$$

Then

$$g(0+) > 0, \quad g(N_0) < 0,$$

and $g'(x) < 0$ if and only if

$$0 < x < \frac{N_0}{\mathcal{R}_0}.$$

If $\mathcal{R}_0 \leq 1$, $g(x)$ is monotone decreasing from a positive value at $x = 0+$ to a negative value at $x = N_0$, and thus there is a unique zero S_∞ of $g(x)$ with $S_\infty < N_0$.

If $\mathcal{R}_0 > 1$, $g(x)$ is monotone decreasing from a positive value at $x = 0+$ to a minimum and then increases to a negative value at $x = N_0$. Thus there is a unique zero S_∞ of $g(x)$ with

$$S_\infty < \frac{N_0}{\mathcal{R}_0}.$$

In fact, since

$$g\left(\frac{S_0}{\mathcal{R}_0}\right) < 0,$$

we actually have

$$S_\infty < \frac{S_0}{\mathcal{R}_0}.$$

We can improve this estimate if $\mathcal{R}_0 > 1$. The function

$$\ln u - u$$

defined for $u > 0$ increases to a global maximum at $u = 1$ and then decreases. Thus if $\mathcal{R}_0 > 1$ there is a unique value $c(\mathcal{R}_0) < 1$ such that

$$\ln c(\mathcal{R}_0) - c(\mathcal{R}_0) = \ln \mathcal{R}_0 - \mathcal{R}_0.$$

Then

$$\begin{aligned} g\left(c(\mathcal{R}_0)\frac{S_0}{\mathcal{R}_0}\right) &= \ln \frac{\mathcal{R}_0}{c(\mathcal{R}_0)} - \mathcal{R}_0 + c(\mathcal{R}_0)\frac{S_0}{N_0} \\ &< \ln \frac{\mathcal{R}_0}{c(\mathcal{R}_0)} - \mathcal{R}_0 + c(\mathcal{R}_0) \\ &= \ln \mathcal{R}_0 - \mathcal{R}_0 - \ln c(\mathcal{R}_0) + c(\mathcal{R}_0) < 0, \end{aligned}$$

and thus

$$S_\infty < \frac{c(\mathcal{R}_0)}{\mathcal{R}_0} S_0. \quad (5)$$

If the final size relation is written in the form (4), it may be solved for S_∞ as a function of \mathcal{R}_0 , and its solution is

$$S_\infty = \frac{c(\mathcal{R}_0)}{\mathcal{R}_0} S_0.$$

The estimate (5) is no easier to find than the solution of (3) or (4), but it gives an explicit estimate for the final size of an epidemic in terms of the reproduction number.

TABLE 1. $N_0 = 1000$, $S_0 = 995$

\mathcal{R}_0	S_∞	c	$c\frac{S_0}{\mathcal{R}_0}$
1.0	903.2	1.0	995.0
1.2	668.2	0.82356	682.9
1.4	481.4	0.68458	486.5
1.6	353.9	0.57283	356.2
1.8	265.0	0.48163	266.2
2.0	201.5	0.40638	202.2
2.2	155.1	0.34378	155.5
2.4	120.5	0.29137	120.8

To show the accuracy of this estimate, we calculate S_∞ directly from (3) and from (5) for various values of \mathcal{R}_0 with $N_0 = 1000$, $S_0 = 995$. The results are shown in Table 1. We see that for values of \mathcal{R}_0 not too close to 1, (5) gives a very good approximation to S_∞ .

3. An example: The *SLIR* model. The age-of-infection model includes models with multiple infective and treatment stages. For example, consider the standard *SLIR* epidemic model but with individuals in L having infectivity reduced by a factor ϵ . We assume that the number a of contacts per individual in unit time is a nondecreasing function of total population size N and that a/N is a nonincreasing function of N . The disease survival rate is f , $0 \leq f \leq 1$. The model can be described by the system

$$\begin{aligned} S' &= -\frac{a}{N}S(I + \epsilon L) \\ L' &= \frac{a}{N}S(I + \epsilon L) - \kappa L \\ I' &= \kappa L - \alpha I \\ N' &= -(1 - f)I \end{aligned} \quad (6)$$

with initial conditions

$$S(0) = S_0, \quad L(0) = L_0, \quad I(0) = I_0, \quad N(0) = N_0 = S_0 + L_0 + I_0.$$

The initial condition assumption is that there are no removed members at the start of the epidemic. We assume that there are no disease deaths. In this case, the total population size $N(t)$ is a constant N_0 and the equation for N can be omitted from the model (6).

The method of [9] gives the basic reproduction number as

$$\mathcal{R}_0 = a \left(\frac{1}{\alpha} + \frac{\epsilon}{\kappa} \right).$$

We derive the final size relation directly from the model. For any non-negative function g defined on $0 \leq t < \infty$ we use the notations

$$g_\infty = \lim_{t \rightarrow \infty} g(t), \quad \hat{g} = \int_0^\infty g(t) dt \leq \infty.$$

Integration of the equation for $(S + L + I)'$ gives

$$S_0 + L_0 + I_0 - S_\infty = \alpha \hat{I},$$

and integration of the equation for I' gives

$$\alpha \hat{I} = \kappa \hat{L} + I_0.$$

Now, using

$$\epsilon \hat{L} + \hat{I} = \left(\frac{1}{\alpha} + \frac{\epsilon}{\kappa} \right) \alpha \hat{I} - \frac{\epsilon I_0}{\kappa},$$

integration of the equation for S'/S gives

$$\begin{aligned} \ln \frac{S_0}{S_\infty} &= \frac{a}{N_0} (\epsilon \hat{L} + \hat{I}) \\ &= \frac{a}{N_0} \left(\frac{1}{\alpha} + \frac{\epsilon}{\kappa} \right) \alpha \hat{I} - \frac{\epsilon a I_0}{\kappa N_0} \\ &= \frac{\mathcal{R}_0}{N_0} \alpha \hat{I} - \frac{\epsilon a I_0}{\kappa N_0} \\ &= \mathcal{R}_0 \left(1 - \frac{S_\infty}{N_0} \right) - \frac{\epsilon a I_0}{\kappa N_0}. \end{aligned}$$

Observe that if $I_0 = 0$, the final size relation takes the neater form (3). If there are members of the population present at $t = 0$ who are beyond the first infective stage,

there is an initial term in the final size relation corresponding to the infections that these members fail to cause by missing the first infective stage.

This example can be viewed as an age-of-infection model with

$$\varphi = \varepsilon L + I.$$

In order to use the age-of-infection interpretation, we need to determine the kernel $A(\tau)$ in order to calculate its integral. We let $u(\tau)$ be the fraction of infected members with infection age τ who are not yet infective and $v(\tau)$ the fraction of infected members who are infective. Then the rate at which members become infective at infection age τ is $\kappa u(\tau)$, and we have

$$\begin{aligned} u'(\tau) &= -\kappa u(\tau), & u(0) &= 1 \\ v'(\tau) &= \kappa u(\tau) - \alpha v(\tau), & v(0) &= 0 \end{aligned}$$

The solution of this system is

$$u(\tau) = e^{-\kappa\tau}, \quad v(\tau) = \frac{\kappa}{\kappa - \alpha} [e^{-\alpha\tau} - e^{-\kappa\tau}].$$

Thus we have

$$A(\tau) = \varepsilon e^{-\kappa\tau} + \frac{\kappa}{\kappa - \alpha} [e^{-\alpha\tau} - e^{-\kappa\tau}],$$

and it is easy to calculate

$$\int_0^\infty A(\tau) d\tau = \frac{1}{\alpha} + \frac{\varepsilon}{\kappa}.$$

This gives the same value for \mathcal{R}_0 as was calculated directly. The calculation depends on the “memoryless property” of the exponential function.

The age-of-infection model also includes the possibility of disease stages with non-exponential distributions [4, 5]. For period distributions that are not exponential, the calculation is considerably more complicated, but it is possible to calculate

$$\int_0^\infty A(\tau) d\tau$$

without having to calculate the function $A(\tau)$ explicitly [10]. It should be noted that while the final size relation determines the final size of an epidemic in terms of the basic reproduction number, there are other important epidemiological quantities depending on the period distributions, such as the maximum epidemic size, the initial growth rate of the epidemic, and the duration of the epidemic [4, 5].

4. Models with disease deaths. We have been assuming that there are no disease deaths, so that the total population size remains constant. If there are disease deaths, it is necessary to add an equation for $N(t)$ to the model (1). It is reasonable to assume that the contact rate a is a density dependent saturating function with $a(N)$ a non-decreasing function of N and $a(N)/N$ a non-increasing function of N .

The model is now

$$\begin{aligned} S' &= -\frac{a(N)}{N} S\varphi & (7) \\ \varphi(t) &= \varphi_0(t) + \int_0^t [-S'(t-\tau)] A(\tau) d\tau, \end{aligned}$$

together with an equation for the total population size N . We assume that the disease survival rate is at least f , $0 \leq f \leq 1$. Disease deaths do not affect the

reproduction number, which, for the model (7), is

$$\mathcal{R}_0 = a(N_0) \int_0^\infty A(\tau) d\tau.$$

If there are no disease deaths, N is constant and the model is equivalent to (1). If there are disease deaths, N decreases over the time period of the epidemic, and it is easy to show that

$$\begin{aligned} N_0 &\geq N(t) \geq N_\infty \geq fN_0 \\ \frac{a(N_0)}{N_0} &\leq \frac{a(N(t))}{N(t)} \leq \frac{a(N_\infty)}{N_\infty} \leq \frac{a(fN_0)}{f} \leq \frac{a(N_0)}{f}. \end{aligned}$$

Since the total population size is not constant, the final size relation is an inequality and can not be used to calculate the limiting susceptible population size precisely. To derive the final size relation, we integrate the equation for S'/S in (7),

$$-\frac{S'(t)}{S(t)} = \frac{a(N(t))}{N(t)}\varphi_0(t) + \frac{a(N(t))}{N(t)} \int_0^t [-S'(t - \tau)]A(\tau) d\tau,$$

obtaining

$$\ln \frac{S_0}{S_\infty} = \frac{a(N^*)N_0}{N^*} \hat{A} \left(1 - \frac{S_\infty}{N_0} \right),$$

where N^* is an average population size given by

$$\begin{aligned} \int_0^\infty \frac{a(N(t))}{N(t)}\varphi_0(t) dt + \int_0^\infty \frac{a(N(t))}{N(t)} \int_0^t [-S'(t - \tau)]A(\tau) d\tau dt \\ = \frac{a(N^*)N_0}{N^*} \int_0^\infty \left[\varphi_0(t) + \int_0^t [-S'(t - \tau)]A(\tau) d\tau \right] dt \end{aligned}$$

with

$$N_0 \geq N^* \geq fN_0.$$

In particular,

$$\begin{aligned} \ln \frac{S_0}{S_\infty} &\leq \frac{a}{N_\infty} [N_0 - S_\infty] \int_0^\infty A(\tau) d\tau + \frac{a}{N_\infty} \int_0^\infty [\varphi_0(t) - (N_0 - S_0)A(t)] dt, \\ \ln \frac{S_0}{S_\infty} &\geq \mathcal{R}_0 \left[1 - \frac{S_\infty}{N_0} \right] + \frac{a}{N_0} \int_0^\infty [\varphi_0(t) - (N_0 - S_0)A(t)] dt. \end{aligned}$$

Since the right side of the first inequality is bounded, it follows that $S_\infty > 0$.

We wish to obtain an estimate for the limiting susceptible population size, which we denote by $S_\infty(f)$. With no disease deaths, the limiting susceptible population size is $S_\infty(1)$, and it is given implicitly by

$$\ln \frac{S_0}{S_\infty} = a(N_0)\hat{A} \left(1 - \frac{S_\infty}{N_0} \right).$$

Much as in Section 2, we define the function

$$g(x, a) = \ln \frac{S_0}{x} - a\hat{A} \left[1 - \frac{x}{N_0} \right].$$

It is easy to verify that

$$g(0+, a) > 0, \quad g(S_0, a) < 0,$$

and that $g'(x, a) < 0$ if and only if

$$0 < x < \frac{N_0}{a\hat{A}}.$$

Since $g(x, a)$ decreases from a positive value at $x = 0+$ to a minimum and then increases to a negative value at $x = N_0$, there is a unique zero $x(a)$ of $g(x, a)$ with

$$x(a) < \frac{N_0}{a\hat{A}}.$$

In fact, since

$$g\left(\frac{S_0}{a\hat{A}}, a\right) < 0,$$

we actually have

$$x(a) < \frac{S_0}{a\hat{A}}.$$

It is also easy to verify that if $a_1 \geq a_2$, then $x(a_1) \leq x(a_2)$. Now,

$$S_\infty(1) = x(a(N_0)), \quad S_\infty(f) = x\left(\frac{N_0}{N^*}a(N^*)\right).$$

The assumption that the function $a(N)/N$ is non-increasing and the fact that $N^* \geq N_\infty \geq fN_0$ imply that

$$\frac{N_0}{N^*}a(N^*) \leq \frac{a(fN_0)}{f}. \quad (8)$$

Since $a(N)$ is non-decreasing, $a(fN_0) \leq a(N_0)$, and

$$\frac{N_0}{N^*}a(N^*) \leq \frac{a(N_0)}{f}. \quad (9)$$

Thus, (9) gives

$$S_\infty(f) = x\left(\frac{N_0}{N^*}a(N^*)\right) \geq x\left(\frac{a(N_0)}{f}\right),$$

and $x\left(\frac{a(N_0)}{f}\right)$ is the zero of $g(x, \frac{a(N_0)}{f})$. This is the limiting susceptible population size for an epidemic with reproduction number

$$\frac{a(N_0)}{f}\hat{A} = \frac{\mathcal{R}_0}{f}$$

and no disease deaths. We have established the following result.

THEOREM 4.1. *The limiting susceptible population size for an epidemic with reproduction number \mathcal{R}_0 and a disease survival rate of at least f is no less than the limiting susceptible population size for an epidemic with reproduction number \mathcal{R}_0/f and no disease deaths.*

The final size relation (3) may be viewed as expressing S_∞ as a continuous function of \mathcal{R}_0 . Thus if f is close to 1, the limiting susceptible population size with disease deaths is close to the limiting susceptible population size with no disease deaths. To illustrate the use of the estimate, we give final size estimates calculated for various survival rates f in a population with $N_0 = 1000$, $S_0 = 995$ and $\mathcal{R}_0 = 1.4$, $\mathcal{R}_0 = 1.5$. We also give the “true” values of S_∞ obtained by dynamic simulation of an *SIR* model with standard incidence (a constant) and exponential period distributions. It should be remembered that a lower bound for S_∞ gives an upper bound for the epidemic size, and is thus a safe estimate for prediction.

TABLE 2. $\mathcal{R}_0 = 1.4$, $N_0 = 1000$, $S_0 = 995$

f	$S_\infty(f)$	true S_∞	Epidemic size
1.0	481.4	481.4	518.6
0.99	470.7	478.6	521.4
0.98	460.1	475.8	524.2
0.95	428.8	467.1	532.9
0.92	398.2	458.2	541.8
0.90	378.3	452.0	548.0

TABLE 3. $\mathcal{R}_0 = 1.5$, $N_0 = 1000$, $S_0 = 995$

f	$S_\infty(f)$	true S_∞	Epidemic size
1.0	411.7	411.7	588.3
0.99	402.2	408.9	591.1
0.98	392.9	406.1	593.9
0.95	365.2	397.4	602.6
0.92	338.3	388.5	611.5
0.90	320.7	382.4	617.6

With mortality rates of 1% or 2% the approximation is quite good. However, it is worth noting that even with considerably higher mortality rates the limiting value obtained assuming no disease mortality is a very good approximation, better than that given by Theorem 1. With a larger value of \mathcal{R}_0 , such as $\mathcal{R}_0 = 2.5$, similar results are obtained, as is shown by Table 4.

TABLE 4. $\mathcal{R}_0 = 2.5$, $N_0 = 1000$, $S_0 = 995$

f	$S_\infty(f)$	true S_∞	Epidemic size
1.0	106.6	106.6	893.4
0.99	103.4	105.2	894.8
0.98	100.2	103.8	896.2
0.95	91.0	99.7	900.3
0.92	82.2	96.0	904.0
0.90	76.5	93.6	906.4

If we use (8) instead of (9), we obtain an improved, but more complicated, estimate than Theorem 1, namely that the limiting susceptible population size is no less than the limiting population size for an epidemic with no disease deaths and reproduction number

$$\frac{a(fN_0)}{fa(N_0)}\mathcal{R}_0.$$

For mass action incidence, this estimate is \mathcal{R}_0 and for standard incidence, it is the same as the estimate in Theorem 1. For saturating incidence, it is a sharper estimate than that in Theorem 1.

5. Discussion. The age-of-infection model is useful for unifying models with an arbitrary number of stages, including latent stages with or without infectivity, asymptomatic stages, and stages for treatment, quarantine, or isolation. In addition, it

includes nonexponential distributions for stay in a stage. Once the reproduction number is calculated, the size of the epidemic is given by the final size relation. If there are disease deaths, the size of the epidemic is not given exactly, but an upper bound for the size of the epidemic is given in terms of the final size of an epidemic with a larger reproduction number. It should be remembered, however, that there are important aspects of an epidemic such as the maximum number of infectives, the initial growth rate, and the duration of the epidemic not determined by the final size relation.

The age-of-infection model studied here assumes homogeneous mixing. It should be possible to extend the analysis to an age-of-infection model for a population with interacting groups. This would be useful for modeling epidemics in a population in which some members have been vaccinated prior to a disease outbreak and thus have different model parameters or in a population stratified by activity levels.

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