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Invited Review

Modeling local coronavirus outbreaks

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\section{Introduction}

The novel coronavirus SARS-CoV-2, the causal virus that unleashed COVID-19 pandemic, first appeared in December 2019 in Wuhan, China. The resulting pandemic has led to nearly 90 million diagnosed cases and 2 million deaths as of mid-January 2021 (https://www.worldometers.info/coronavirus/) and has led countries around the world to shut down their economies – businesses, education, entertainment, transportation – to try and slow the spread of coronavirus. Preventing infections during the first year of the COVID-19 pandemic has best been accomplished using the most basic public health principles: hand hygiene, mask wearing, prevention of large gatherings, social distancing, and societal lockdowns. Testing and identifying infectious individuals to separate them from non-infectious persons via isolation and quarantine has perhaps been the most effective way to prevent infections, but large scale testing is expensive while in most locations testing (and contact tracing) capacity has been limited (though with some important exceptions as noted below). Vaccination only became a realistic infection control tool starting in mid-December 2020 with the completion of Phase III clinical trials for coronavirus vaccines produced by Pfizer (https://www.pfizer.com/products/product-detail/pfizer-biontech-covid-19-vaccine), Moderna (https://www.modernatx.com/covid19vaccine-eua/), and AstraZeneca (https://www.astrazeneca.com/covid-19.html), and additional vaccines are expected to receive approval during the spring of 2021.

The COVID-19 pandemic also rekindled interest in epidemic models as forecasting tools in the statistical sense, but more importantly as prospective policy tools to discern the impacts of potential actions. Indeed, early modeling studies were decisive in readying local and national governments the world over to adopt suppressive lockdown strategies in the face of failed early containment efforts (Ferguson, Laydon, & Gemma, 2020; Kissler, Tedijanto, Lipsitch, & Grad, 2020). Given the limited public health tools available coupled with the rapid worldwide spread of disease, communities around the world were faced with the problem of trying to control SARS-CoV-2 outbreaks. Modeling such local outbreaks is the subject of this paper.

The paper proceeds as follows: in the next section, we introduce the age-of-infection transmission intensity function, and use this to define the reproductive number $R_0$ and summarize early
transmission dynamics focusing on the well-known epidemic characteristic of exponential growth in new infections at the beginning of an outbreak; this leads to the famous Euler-Lotka equation (3). We build on this approach in Section 3 where the renewal epidemic model is formally stated using one integral and one differential equation (Eqs. (4) and (5)). In Section 4 we introduce a random lag \( L_F \) known as the forward generation time, and re-express the current incidence of infection at a given time in terms of the expected value of the incidence \( L_F \) time units earlier (Eq. (8)). We show how this approach reproduces the more commonly used Susceptible-Infectious-Recovered (SIR) and Susceptible-Exposed-Infectious-Recovered (SEIR) models. We review numerous applications of this random lag approach in Section 5, including: direct calculation of the final size of an unmitigated outbreak (Section 5.1); a new understanding of herd immunity in an unmitigated outbreak as the solution to an optimization problem while illustrating the results of different approaches to herd immunity owing to the timing of vaccination (Section 5.2); aligning observable epidemic indicators such as cases, hospitalizations, deaths and the concentration of coronavirus RNA in sewage sludge with the unobserved incidence of transmission to estimate key epidemic quantities (Section 5.3); approximating the effective reproduction number \( R_0 \) by combining the indicator alignment approach with first-order approximations of the underlying renewal model (Section 5.4); extending the model to accommodate any intervention based on isolating infectious individuals due to testing, contact tracing or self-recognition of symptoms (Section 5.5); and repeat asymptomatic testing programs of the form employed by some universities, sports teams and businesses (Section 5.6). We conclude the paper with a summary of the modeling approach and key results in Section 6.

2. Early outbreak transmission dynamics

The models in this paper all build from the following simple idea: early in an outbreak a person who has been infected for duration (or infection age) \( a \) and is otherwise surrounded by individuals susceptible to infection transmits new infections according to a nonhomogeneous Poisson process with rate function \( \lambda (a) \) (the notation of this paper is summarized in Table 1). This transmission intensity function captures the product of an infectious individual’s contact rate with their age-of-infection conditional probability of transmission. Early in an outbreak, essentially all of an infectious individual’s contacts are with susceptible persons, which makes \( \lambda (a) = \lambda \) equivalent to the expected number of infections transmitted by an infectious individual in the interval \((a, a + da)\). Consequently, at the start of an outbreak, the expected total number of infections transmitted by an infected person, known as the reproduction number \( R_0 \), is given by

\[
R_0 = \int_0^\infty \lambda (a) da. \tag{1}
\]

Another epidemic principle states that at the beginning of an epidemic, the rate of new infections (that is, the incidence rate) approximates exponential growth. Letting \( r \) denote the exponential growth rate, at the start of an outbreak, new infections grow as \( ke^{rt} \) where \( k \) is the initial infection rate at time 0. Combining approximate exponential growth in the rate of infections with the transmission intensity function leads to the approximation

\[
ke^{rt} \approx \int_0^\infty ke^{r(t-u)} \lambda (u) du + \lambda_0 \lambda (t), \quad t > 0 \tag{2}
\]

where \( \lambda_0 \) is the fraction of the population initially infected at time 0. At time \( t \), the rate of new infections is the cumulation of the product of past infection rates with the associated age-of-infection transmission rate at time \( t \). Dividing both sides by \( ke^{rt} \) and presuming \( e^{-rt} \lambda (t) \to 0 \) as \( t \to \infty \), yields

\[
\int_0^\infty e^{-ru} \lambda (u) du = 1 \tag{3}
\]

which is recognized as the Euler-Lotka equation (Britton & Tomba, 2019; Kaplan, 2020a; Wallinga & Lipsitch, 2007). Eq. (3) reveals the source composition of current infections (Kaplan, 2020a): among persons newly infected, \( e^{-ru} \lambda (u) \Delta u \) is the fraction whose infectors were infected between \( u \) and \( u + \Delta u \) time units ago.

3. Dynamic transmission model

To this point we have only modeled the early phase of an outbreak corresponding to exponential growth in the incidence of new infections per unit time. As infections mount, however, it is no longer the case that the contacts of infectious individuals can be presumed to be susceptible to infection. As in Chang, Crawford, & Kaplan (2020), let \( s(t) \) denote the fraction of the population that is susceptible to infection at time \( t \). Following the logic of Eq. (2) we model the incidence of infection at time \( t \) (in units of infections per capita per unit time), \( \pi (t) \), as

\[
\pi (t) = s(t) \int_0^\infty \pi (t - a) \lambda (a) da. \tag{4}
\]

The number of susceptibles in the population depletes as they become infected, which yields

\[
\frac{ds(t)}{dt} = -\pi (t). \tag{5}
\]

The initial conditions of this model are given by the function \( \pi (a) \) for \( a < 0 \), which implies that the fraction susceptible at time 0 is given by

\[
s(0) = 1 - \int_{-\infty}^0 \pi (a) da. \tag{6}
\]

As a practical matter, \( s(0) \approx 1 \) as the fraction of the population that has already been infected at time 0 is negligibly small. Since the integral Eq. (4) for the incidence function may be regarded as a renewal equation, this model falls into the class of renewal equation epidemic models (Britton & Tomba, 2019; Choparden & Dushoff, 2015; Heesterbeek & Dietz, 1996; Wallinga & Lipsitch, 2007) that have found application to SARS-Cov-2.

4. Random lag representation

An alternative representation admits a probabilistic interpretation of this deterministic model that illuminates model properties while greatly aiding model interpretation. Define the forward generation time density \( f(a) \) by

\[
f(a) = \frac{\lambda (a)}{R_0}, \quad a > 0 \tag{7}
\]

and associate the random variable \( L_F \) (the forward generation lag) with this probability density. This random variable denotes the timing of infectious transmission from the time persons become infected. Multiplying and dividing Eq. (4) by \( R_0 \) yields an alternative expression for Eq. (4) as

\[
\pi (t) = R_0 s(t) \int_0^\infty \pi (t - a) f(a) da = R_0 s(t) \int_0^\infty \pi (t - a) f(a) da \approx R_0 s(t) \left[ \frac{\pi (t - \mu_F)}{R_0} \right] \tag{8}
\]

where

\[
\mu_F = \int_0^\infty a f(a) da \tag{9}
\]
is the mean forward generation lag, and the final approximation in Eq. (8) follows from a first order Taylor expansion of \( \pi(t - L_F) \) about \( \mu_F \). We refer to the second line of Eq. (8) and similar expectations with respect to \( L_F \) as the random lag representation of the renewal epidemic model, and rely on this new formulation subsequently.

To first order then, incidence at time \( t \) is a multiple \( R_0 S(t) \) of incidence at time \( t - \mu_F \). This approximation is not intended to be used constructively, that is, we are not suggesting that one could accurately predict the incidence of infection by iterating this first order relationship over time (though the approximation should work well if the function \( \pi(t - a) \) is approximately linear over a range of ages \( a \) around \( \mu_F \) having high probability of containing \( L_F \)). Rather, we use this relationship to understand the fundamental time lag separating successive generations of infection within an outbreak. This will be especially important in Sections 5.3 and 5.4 when we consider how to relate the incidence of infection to observable indicators of such.

This model generalizes better-known epidemic models widely in use. For example, Susceptible-Infectious-Recovered (SIR) models presume constant transmission at rate \( \beta \) during an infectious period of random duration \( D \) having an exponential distribution with mean \( 1/\nu \) (Anderson & May, 1991). In the renewal model this corresponds to the transmission intensity function

\[
\lambda_{SIR}(a) = \beta \Pr[D > a] = \beta e^{-\nu a}
\]

so that \( R_0 = \beta/\nu \), \( f(a) = \nu e^{-\nu a} \) and \( \mu_F = 1/\nu \). Noting that \( S(t) \) in the SIR model is the same as \( s(t) \) in the renewal model, applying Eq. (4) to the SIR model yields

\[
\pi(t) = \beta S(t) \int_0^\infty \pi(t - a) e^{-\nu a} da.
\]

Since the probability that an infection that occurs at time \( u < t \) is still infectious at time \( t \) is \( e^{-\nu(t-u)} \), the last integral can be recognized as accumulating all previous infections that remain infectious at time \( t \) to obtain \( I(t) \), the prevalence of infection (the fraction of the population infected at time \( t \)), as

\[
I(t) = \int_{-\infty}^t \pi(u) e^{-\nu(t-u)} du = \int_0^\infty \pi(t - a) e^{-\nu a} da = \int_0^\infty \pi(u) e^{-\nu u} du.
\]

Combining the resulting equality \( \pi(t) = \beta S(t)I(t) \) with (5) gives the first of the well known differential equations representing the SIR model,

\[
\frac{dS(t)}{dt} = -\beta S(t)I(t),
\]

and the second differential equation comes from differentiating (12) to obtain

\[
\frac{dI(t)}{dt} = \frac{d}{dt} \left( e^{-\nu t} \int_{-\infty}^t \pi(u) e^{\nu u} du \right)
\]
\[ \begin{align*}
&= -v e^{-vt} \int_{-\infty}^{t} \pi(u) e^{\nu u} du + e^{-vt} \pi(t) e^{vt} \\
&= -v I(t) + \pi(t) \\
&= -v I(t) + \beta S(t) H(t).
\end{align*} \]

Applying the Taylor expansion from Eq. (8) to Eq. (11) gives the approximation
\[ \pi(t) = S(t) H(t) \approx R_0 S(t) \pi(t - \mu_F) \]
and substituting \( R_0 = \beta / \nu \) and \( \mu_F = 1/\nu \) gives
\[ I(t) \approx \pi(t - \mu_F) \times \mu_F \]
which is a local form of Little’s Theorem (Little, 1961) that states the number of infected persons approximately equals the number newly infected \( \mu_F \) time units ago times the mean duration of infectiousness.

Similarly, Susceptible-Exposed-Infectious-Recovered (SEIR) models have been widely applied to model SARS-CoV-2 transmission (Ferguson et al., 2020; Kissler et al., 2020; Morozova, Li, 
& Crawford, 2020; Patel, Zheng, 
& Walensky, 2020). In such models, newly infected but not yet infectious persons enter an exposed state for an exponentially distributed length of time with mean \( 1/\nu_1 \), after which they become infectious for an exponentially distributed duration of mean \( 1/\nu_2 \) during which transmission again occurs at constant rate \( \beta \). Letting \( D_1 \) and \( D_2 \) denote the duration of time after infection spent in the exposed and infectious states, early transmission in this model can be captured by
\[ \lambda_{SEIR}(a) = \beta \mathbb{P}(D_1 \leq a < D_1 + D_2) \]
\[ = \frac{\beta \nu_1}{\nu_1 - \nu_2} e^{-\nu_1 a} - e^{-\nu_2 a} \]
\[ = \frac{\beta \nu_1 \nu_2}{\nu_1 \nu_2 - \nu_2} e^{-\nu_1 a} - e^{-\nu_2 a} \]
where \( R_0 = \beta / \nu_2 \), \( f(a) = \frac{\nu_1}{\nu_1 - \nu_2} (e^{-\nu_2 a} - e^{-\nu_1 a}) \) and \( \mu_F = 1/\nu_1 + 1/\nu_2 \) (if \( \nu_1 = \nu_2 = \nu \), then \( R_0 = \beta / \nu \) and \( f(a) \) reduces to a gamma density \( \nu^2 a e^{-\nu a} \) with mean \( \mu_F = 2/\nu \).

Beyond SIR and SEIR models, epidemiologists have approximated generation time distributions directly from contact tracing data (data that link infectious to those individuals they have infected), and several such studies have been conducted using early SARS-CoV-2 outbreak data from China (see Park et al., 2020 for a summary). The generation times are often presumed to follow gamma distributions, as the latter provide a flexible statistical model for the time between the onset of symptoms for infector/infectee pairs within a transmission chain (the serial interval), and the distribution of serial intervals is taken as an estimate of the unobservable times between infections (which the generation time density \( f(a) \) is meant to represent).

The renewal model represented by Eqs. (4)–(6) describes an unmitigated outbreak, but it can be modified to account for public health interventions such as lockdown, testing and isolation, and infection control (Kaplan, 2020b).

### 5. Insights and applications to epidemic monitoring and control

The models discussed thus far address uncontrolled local outbreaks, and as such describe what epidemics can do to populations absent intervention. In this section of the paper, we use the models developed earlier to examine control measures for interrupting transmission, and monitoring measures for ascertaining the state of an outbreak that also can be used to assess the effectiveness of interventions. We first address the number of persons infected over the duration of an unmitigated outbreak; the resulting final size represents the size of the worst-case local outbreak, and serves as a benchmark for evaluating interventions. We next model epidemic control by vaccination, show that the herd immunity threshold necessary to reduce transmitted infections per newly infected person below one is the solution to an optimization problem, and demonstrate that the approach to herd immunity matters as much as the actual herd immunity threshold in determining what fraction of the population is ultimately infected in local outbreaks controlled by vaccination. We then turn to monitoring outbreaks via aligning lagged epidemic indicators such as cases, hospitalizations and deaths with the incidence of new infection, and approximate the widely-reported effective reproductive number \( R_t \) as an application of this approach. We conclude this section on monitoring and control by modeling how SARS-CoV-2 testing and isolation programs, and especially repeat asymptomatic testing combined with isolation, reduce overall coronavirus transmission in a local outbreak.

#### 5.1. Worst case: final size of an unmitigated outbreak

In an outbreak characterized by Eqs. (4)–(5), define the final size, \( \phi \), as the limiting fraction of the population that is eventually infected, that is,
\[ \phi = \int_{-\infty}^{\infty} \pi(t) dt. \]
To find an equation that characterizes \( \phi \) more explicitly, note that (5) and (8) give
\[ \frac{d}{dt} \log(s(t)) = \frac{s^\prime(t)}{s(t)} = -\pi(t) = -R_0 E[\pi(t - L_F)]. \]
so that, assuming \( \lim_{t \to \infty} s(t) = 1 \), we obtain
\[ \log(s(u)) = -R_0 \int_{-\infty}^{u} E[\pi(t - L_F)] dt. \]
Letting \( u \to \infty \) in (20) and identifying \( \lim_{u \to \infty} s(u) \) with \( 1 - \phi \) gives
\[ \log(1 - \phi) = -R_0 E\left[ \int_{-\infty}^{\infty} \pi(t - L_F) dt \right] = -R_0 \phi. \]
that is,
\[ \phi = 1 - e^{-R_0 \phi}. \]
We will use this result later in the paper.

#### 5.2. Control by vaccination and herd immunity

A fundamental concept in epidemiology is herd immunity, which is that point in an outbreak where a newly infected person is only able to transmit a single infection in expectation over the course of their infection. More formally, in an unmitigated outbreak, herd immunity is reached at that time \( t^* \) when \( R_0 \delta(t^*) = 1 \), as any person newly infected at time \( t^* \) would transmit at most 1 infection on average over all time after \( t^* \) since \( s(t) \) is a decreasing function of time (as is clear from Eq. (5)). From Eq. (8), we immediately see that at the time \( t^* \) at which herd immunity is reached,
\[ \pi(t^*) = R_0 \delta(t^*) E[\pi(t^* - L_F)] \]
\[ = E[\pi(t^* - L_F)] \]
\[ \approx \pi(t^* - \mu_F). \]

This result is illustrated in Fig. 1 for a model with \( R_0 = 2.5 \), which is the Centers for Disease Control’s base case \( R_0 \) estimate for SARS-CoV-2 (CDC, 2020). The forward generation time density \( f(a) \) in this example is a gamma distribution with mean (standard deviation) 8.9 (4.0) days based on the study by Li, Guan, & Wu (2020) of early SARS-CoV-2 transmission dynamics in Wuhan,
China. In this example, herd immunity is reached when the fraction of the population that is susceptible falls to 40%, at which point it is clear that the incidence of infection at the time of herd immunity \( (\pi (t^*)) \) very closely approximates the incidence of infection one mean generation lag prior \( (\pi (t^* - \mu_F)) \). Many people are under the mistaken impression that reaching herd immunity effectively signals the end of an outbreak. As Fig. 1 shows however, this is not necessarily the case at all. Indeed, in Fig. 1, the fraction susceptible continues to drop from 40% to 10% at the end of the outbreak, meaning an additional 30% of the population is infected after herd immunity is reached.

Herd immunity can also be represented as the solution to an optimization problem. Define

\[
l_i^*(t) = E \left( \int_{t-t^*}^{t} \pi (a) da \right).
\]

This is the expected number of infections transmitted over a generation lag ending at time \( t \). What is the generation interval containing the largest fraction of the population infected over all generation intervals during an outbreak? The answer is given by selecting \( t \) to maximize \( l_i^*(t) \). Differentiating Eq. (23) with respect to \( t \) and equating to zero produces Eq. (22), which can now be understood as the first order condition associated with maximizing \( l_i^*(t) \). In an unmitigated outbreak then, herd immunity is reached at the end of the generation interval that is expected to contain the most new infections. This condition is also evident in Fig. 1, where the area under the incidence curve between \( t - \mu_F \) and \( t \) is maximal at \( t = t^* \) when herd immunity is reached. Note that for the SIR model,

\[
l_i^*(t) = E \left( \int_{t-t^*}^{t} \pi (a) da \right)
\]

\[
= E \left( \int_{t}^{t^*} \pi (t-a) da \right)
\]

\[
= E \left( \int_{0}^{\infty} \pi (t-a) 1_{[t^*-a]} da \right)
\]

\[
= \int_{0}^{\infty} \pi (t-a) Pr\{L_F > a\} da
\]

\[
= \int_{0}^{\infty} \pi (t-a)e^{-\nu a} da
\]

\[
= I(t)
\]

(24)

where the last equality follows from (12). As a consequence, in the SIR model, the prevalence of infection \( I(t) \) is also maximized at the time herd immunity is reached (as is also evident from setting Eq. (14) equal to zero). Similar arguments show that for the SEIR model, the sum of the population fraction exposed plus the fraction infectious is maximized when herd immunity is reached.

As is often stated, where one ends up in life is less meaningful than the journey taken to get there. So it is with herd immunity: how population susceptibility falls from its initial value to the herd immunity level \( 1/R_0 \) matters more than simply reaching the target. This is especially relevant when considering the role of vaccination against coronavirus. To illustrate, suppose that a fraction \( \theta \) of the population is inoculated with a perfect immunizing vaccine at the start of an outbreak with no other interventions in place. This has two immediate effects: a direct effect of protecting that fraction \( \theta \) from infection, and an indirect effect of protecting the remaining susceptible in the population. To understand this latter effect, focus on the fraction of the population that remains susceptible after vaccination. Presuming that infectious persons are just as likely to come into contact with vaccinated as unvaccinated persons, the reproduction number experienced by the unvaccinated population is reduced from \( R_0 \) to \( R_0(1 - \theta) \) (as a fraction \( \theta \) of the contacts emanating from infectious persons will be with persons already vaccinated). Thus, presuming no other interventions are in place, unvaccinated individuals will experience an unmitigated outbreak but with reproduction number \( R_0(1 - \theta) \), and thus the fraction of unvaccinated persons who will become infected over the duration of the outbreak, \( \phi_0 \), follows Eq. (21), that is

\[
\phi_0 = 1 - e^{-R_0(1 - \theta) \phi_0}.
\]

(25)

Over the entire population, let \( q(\theta) \) be the fraction that acquire infection. As those vaccinated cannot become infected, whereas of those who are not vaccinated the proportion \( \phi_0 \) are infected, we see immediately that

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**Fig. 1.** Herd immunity in the basic renewal model \((R_0 = 2.5, \mu_F = 8.9, s(t^*) = 0.4)\).
Suppose that \( \theta \) is sufficiently large that the overall fraction \( q(\theta) \) of the population that becomes infected is sufficiently small for
\[
1 - e^{-R_0 q(\theta)} \approx R_0 q(\theta).
\]
Substituting this back into Eq. (26) yields
\[
q(\theta) \approx (1 - \theta) R_0 q(\theta) \implies R_0 (1 - \theta) = 1.
\]
which shows that instantaneous vaccination of the herd immunity fraction \( \theta = 1 - 1/R_0 \) of the population essentially eradicates the infection and thus avoids an outbreak.

Unfortunately, instantaneous vaccination is unrealistic, so instead imagine vaccinating the susceptible population at rate \( \eta \) for \( w \) time units, and for simplicity again consider a perfect vaccine. This circumstance can be represented by modifying Eq. (5) to
\[
\frac{ds(t)}{dt} = \begin{cases} 
-\pi(t) - \eta & 0 < t \leq w \\
-\pi(t) & t > w
\end{cases}
\]
and retaining Eqs. (4) and (6) to track the epidemic. In particular, this allows one to see the influence of \( \eta \) and \( w \) on the time until herd immunity is reached along with the resulting fractions of the population that are vaccinated, infected, or remain susceptible.

To illustrate these results, consider different outbreaks under the same conditions as Fig. 1 with the following three provisos:

1. 60% of the population is vaccinated prior to the importation of an infection from elsewhere (that is, herd immunity is induced at time 0);
2. Susceptibles are vaccinated at a rate of \( \eta = 0.15 \) per month over \( w = 4 \) months (so 60% of the original susceptible population would be vaccinated by the end of four months);
3. No susceptibles are vaccinated, leading to the unmitigated outbreak of Fig. 1.

Fig. 2 plots the fraction of the population that remains susceptible over time. In the first case (blue line), herd immunity is reached before any infections have been transmitted, which keeps the fraction of the population that is susceptible essentially equal to 40%. In the second case (orange curve), some people are getting infected while others are getting vaccinated. When the herd immunity threshold is reached after 72 days, the susceptible population continues to decline until eventually 60% will have been vaccinated, 37% infected, and 3% remain susceptible. In the third case of an unmitigated outbreak, herd immunity is reached sooner at 70 days, but at a terrible cost: fully 90% of the population is infected while 10% remain susceptible.

### 5.3. Aligning epidemic indicators for monitoring local outbreaks

The current status of local coronavirus outbreaks is indirectly measured by lagging indicators of infection such as the number of COVID cases (that is positive test results), hospitalizations and deaths, because repeat representative testing of the population to directly estimate the incidence of SARS-CoV-2 is almost never possible (though there are some exceptions such as repeat testing of college students as discussed subsequently). Epidemiological studies have produced estimates of the probability distribution for the time from infection until the observation of indicators such as hospitalization or death along with the fractions of those infected who are hospitalized or die on account of COVID (CDC, 2020; Kaplan et al., 2020; Lewnard et al., 2020; MIDAS, 2020). Other indicators such as SARS-CoV-2 RNA concentration in sewage sludge, seroprevalence of SARS-CoV-2 antibody (which represents the fraction of the population infected to date), or changes in observed viral loads (concentration of coronavirus) among samples of those testing positive are community-wide rather than individually tracked (Havers, Reed, & Lim, 2020; Peccia et al., 2020; Walker et al., 2020).

The random lag approach to modeling infection indicators involves two steps. The first step in this approach focuses on the delay with which infections contribute to a lagging indicator denoted by \( Y = Y(t) \). Suppose this delay is characterized by a random variable \( L \) having probability density function \( f_L(a) \), so that an infection at time \( u \) makes an expected contribution at a rate proportional to \( f_L(a) \) to the indicator \( Y \) at time \( u + a \). For example, if \( Y(t) \) is the rate of hospital admissions at time \( t \) due to prior
infection, then $L_t$ would represent a random time interval from infection to hospitalization. Retaining the notation $\pi(t)$ for the modeled incidence of coronavirus infection as determined by Eq. (8), we define a model-scale indicator $y(t)$ by

$$y(t) = \int_0^\infty f_{L_t}(a) \pi(t - a) \, da$$

$$= E_{L_t}[\pi(t - L_t)]$$

$$(29)$$

where $\pi_Y = E(\pi_Y)$ is the mean indicator lag. The randomly delayed infections accumulated in the model-scale indicator capture the overall timing with which the modeled infections are expected to contribute to the lagging indicator, on the scale of the modeled infections rather than in units of the indicator $Y$. Eq. (29) clarifies that the model-scale indicator at time $t$ equals the expected value of SARS-CoV-2 incidence $L_t$ time units into the past. To first order, the model-scale indicator at time $t$ is just the incidence of infection at time $t - \mu_Y$; as before, this approximation should work well if the function $\pi(t - a)$ is approximately linear over a range of ages $a$ around $\mu_Y$ having high probability of containing $L_t$.

Continuing to the second step, we assume that the expected value of the lagging indicator $Y(t)$ is proportional to the model-scale indicator, so that

$$E[Y(t)] = k_Y y(t).$$

(30)

The scaling factor $k_Y$ simultaneously accounts for population size (that is, changing infections per capita to total infections), process thinning (e.g. fraction of infections that lead to hospitalization or death), and process unit conversion (e.g. from new infections per capita to concentration of coronavirus RNA in sewage sludge). The second step also provides a basis for statistically estimating the scaling constant $k_Y$ along with other key model quantities.

As an example, Kaplan et al. (2020) reported daily measurements of SARS-CoV-2 RNA concentration in sewage sludge from the local wastewater treatment plant serving the towns of New Haven, East Haven, Hamden and Woodbridge, Connecticut, USA from March through May 2020. They also recorded COVID admissions to the local hospital emanating from these same four towns. Working with previously estimated probability distributions for the time from infection until hospitalization (Lewnard et al., 2020) and the forward generation time to represent the time course of viral shedding (Li et al., 2020; Park et al., 2020; Kaplan et al. (2020)) applied Eqs. (5), (8), (29) and (30) to produce a model linking coronavirus incidence to expected hospitalizations and sludge viral RNA concentrations. This enabled the construction of two likelihood functions – a Poisson likelihood for hospitalizations, and a normal likelihood for viral RNA concentration. Jointly maximizing these likelihoods not only estimated the necessary scaling constants from Eq. (30), but also enabled estimation of the reproduction number $R_0$ and the fraction of the population that was susceptible at the start of data collection. The estimated 95% confidence interval for the reproduction number was $2.4 \pm 0.2$, placing $R_0$ for this local outbreak squarely in the middle of the range of reproduction numbers that have been estimated for SARS-CoV-2 outbreaks worldwide (CDC, 2020; MIDAS, 2020; Park et al., 2020). Additional insights deduced from this analysis include that an estimated 9.3% of the 200,000 local population was infected during this outbreak, while the state government’s social distancing and stay-at-home restrictions in force during this time protected 89% of the population from becoming infected (Kaplan et al., 2020; Lamont, 2020a).

5.4. The effective reproductive number $R_t$ as an example of epidemic monitoring via indicator alignment

Thus far the epidemic model underlying the incidence of infection over time has been given by Eq. (8) as augmented by Eq. (5) to account for the depletion of susceptibles. A more general view of an epidemic offered by the renewal framework that facilitates empirical estimation of current transmission status is given by

$$\pi(t) = R_t E[\pi(t - L_t)]$$

$$= R_t \pi(t - \mu_Y)$$

(31)

where a new term, $R_t$, has replaced the product $R_0 \pi(t)$ in Eq. (8). $R_t$ is referred to as the effective reproduction number (Cori, Ferguson, Fraser, & Cauchemez, 2013; Gostic et al., 2020), and is meant to represent the expected number of new infections that would be transmitted by persons newly infected at time $t$ over the course of their infectiousness if the fraction of susceptibles remained constant at $s(t)$. The effective reproduction number is thus used as a signpost for whether the current status of an outbreak is growing or declining, with empirical estimates of $R_t > 1$ taken as a danger sign while if $R_t < 1$, the epidemic is slowing down. Many public sites report estimated values of $R_t$ based on different numerical implementations of Eq. (31); for examples see https://rtlive/. https://covidestim.org/ and https://alfred.shinyapps.io/ estR0/. While simple in appearance, there is a difficulty in that the literal application of (31) requires knowledge of the incidence $\pi(t)$. Estimating incidence thus requires the use of some model linking new infections to observable indicators such as cases, hospital admissions, or deaths, and indeed this is the approach taken by sites such as those referenced above, which makes estimating $R_t$ a common instance of epidemic indicator alignment.

To first order, one can use the approximations in Eqs. (29) and (31) to illustrate the alignment problem. From Eq. (29) we write

$$\pi(t) \approx y(t + \mu_Y).$$

(32)

Substituting into Eq. (31) then yields

$$y(t + \mu_Y) \approx R_t y(t + \mu_Y - \mu_Y).$$

(33)

Now the model scale indicator $y(t)$ is itself not observable, but the actual indicator $Y(t)$ is, and via Eq. (30) and using the observed data to estimate $E(Y(t))$ yields

$$E[Y(t + \mu_Y)] \approx R_t E[Y(t + \mu_Y - \mu_Y)]$$

(34)

as follows from multiplying both sides of Eq. (33) by the scaling constant $k_Y$ (though note that one need not know the value of $k_Y$). Eq. (34) clarifies the first-order lags that determine $R_t$ from indicator data, namely the mean forward generation time $\mu_Y$ and the mean indicator lag from infection $\mu_Y$.

To illustrate, we will compare three approaches to estimating $R_t$ for the State of Connecticut: covidestim.org (Chitwood et al., 2020); rtlive; and $R_t$ estimates based on Eq. (34), where $Y(t)$ represents observed total Connecticut hospitalizations for patients with COVID-19 as reported by the Connecticut Hospital Association to the state of Connecticut (https://data.ct.gov/stories/s/q5as-kyim). Implementing Eq. (34) requires the two constants $\mu_Y$ and $\mu_Y$ in addition to the observed data $Y(t)$. Here we assume $\mu_Y \approx 9$ days as discussed in Kaplan et al. (2020). Determining $\mu_Y$ requires additional work. A person who became infected at time $0$ will be found in the hospital at time $t$ if they were admitted to the hospital between $0$ and $t$ and have not yet been discharged. Letting $L_t$ denote the time from infection until hospital admission (for those who are hospitalized) and $L_{LOS}$ denote the length-of-stay in the hospital for a COVID-19 patient, the probability that a person infected at time $0$ would be found in the hospital at time $t$ is given by

$$Pr[\text{Hospitalized \ t units after infection}]$$

$$= \int_0^t f_{L_H}(x) \Pr[L_{LOS} > t - x] \, dx$$

(35)

where $f_{L_H}(x)$ is the probability density function for the random variable $L_H$, and we have assumed that $L_H$ and $L_{LOS}$ are independent. To turn this hospitalization probability into the appropriate indicator lag for COVID-19 hospitalizations requires scaling
Eq. (35) to represent a probability density function. This is achieved by dividing the equation above by $E[L_{LOS}]$, which immediately turns Eq. (35) into a probability density for the sum of the time from infection to hospitalization ($t_H$) and $t_{LOS}$, the backwards recurrence time spent in the hospital. The backwards recurrence time is the elapsed time from admission to the moment of sampling for a randomly selected patient in the hospital, and has probability density function $Pr[t_{LOS} > x] / E[t_{LOS}]$. Consequently the appropriate model-scale indicator $y(t)$ is lagged from infection with the lag $L_Y$ having probability density

$$f_{L_Y}(t) = \int_0^\infty f_{L_Y}(x) \frac{Pr[t_{LOS} > t - x]}{E[t_{LOS}]} \, dx$$

(36)

and mean lag $\mu_Y$ given by

$$\mu_Y = E[t_{LOS}] + E[t_{LOS}^2]$$

(37)

where

$$E[t_{LOS}^2] = \frac{E[t_{LOS}^2]}{E[t_{LOS}]}$$

(38)

as is well known from renewal theory (e.g., Cox, 1962).

Lewnard et al. (2020) estimated that the mean time from infection until hospitalization was 13.5 days, and also reported that the length of stay for COVID-19 patients was well-estimated by a Weibull distribution with 50% probability coverage running from 5.3 to 16.8 days, and 95% probability coverage running from 0.9 to 34.5 days. These values imply a Weibull distribution with a mean and second moment of 12.3 days and 232.9 days$^2$ respectively, which via Eqs. (38) and (37) imply estimates of $E[t_{LOS}^2] \approx 9.5$ days and $\mu_Y \approx 13.5 + 9.5 = 23$ days.

Fig. 3 reports the values for $R_i$ as estimated by covidestim.org and rt.live for Connecticut from March 18, 2020 to December 8, 2020. Also shown is our first-order estimate based on Eq. (34) using observed statewide Connecticut hospitalizations for patients with COVID-19, a lowess smooth (Cleveland, 1979) of those estimates, and the actual numbers of hospitalized COVID-19 patients in Connecticut. With the exception of the first week during which covidestim.org estimates higher values of $R_i$, the correspondence among these estimated $R_i$ series is striking. Note that neither covidestim.org nor rt.live use hospitalization data in their algorithms. This figure illustrates the 23 day mean lag ($\mu_Y$) separating the incidence of infection from hospitalizations. Initial high values of $R_i$ from early- to mid-March presaged the rapid rise in hospitalizations that peaked during the third week of April. Note that $R_i$ had already started to decline before Connecticut governor Ned Lamont issued stay-at-home orders on March 23, effectively locking down most of Connecticut except for essential workers (Lamont, 2020a).

By mid-April, $R_i$ had already fallen well below unity, leading to the decline in hospitalizations seen over the late spring and summer, during which Governor Lamont issued orders enabling the partial reopening of the Connecticut economy (Lamont, 2020b). $R_i$ was again increasing above unity by the end of the summer, but this did not translate into increases in hospitalizations until mid-fall. From mid-November onwards, $R_i$ again declined while remaining above or near one, but by this time observed hospitalizations were again on the rise.

Returning to modeling issues, while the covidestim.org and rt.live curves are much smoother than the first order estimates based on hospitalization data, which is a testament to the careful fitting and noise-cancellation features employed by those algorithms, the first order estimates have the advantage of ease of understanding based on two time lags – the mean forward generation time $\mu_F$ and the mean indicator lag $\mu_Y$ – and can be applied rapidly to a variety of indicator data. Statistical smoothing of the first order estimates, as illustrated by the lowess smooth in Fig. 3, also helps reveal the qualitative trends in $R_i$.

5.5. Outbreak control via testing and isolation

Consider a newly infected person and continue to denote the rate of transmission of new infections at infection age $a$ by $\lambda(a)$. In the absence of testing and isolation, our model assumes that the infected person will infect susceptibles according to a Poisson process with intensity function $\lambda$. However, if the infected person receives a positive test result, let us assume the person will be isolated, preventing transmission of further infections after being iso-
lated. Letting \( N_t \) denote the number of events in a Poisson process with intensity function \( \lambda(t) \) that occur in an interval \( I \) and letting \( T \) denote the age of the infection at the time of isolation, the number of infections that are prevented by the positive test can be written as \( N_{(T, \infty)} \). Thus, the test reduces the expected number of infections from the reproduction number \( R_0 = E(N_{(0, \infty)}) \) to \( E(N_{(0,T)}) \), which we will refer to as \( R_{\text{test}} \), the reproduction number induced by testing and isolation.

To rewrite \( R_{\text{test}} \) to gain additional insight, suppose that whether or not isolation happens by infection age \( t \) is independent of the Poisson process of infections after age \( t \). For example, this assumption allows the isolation time to be influenced by when infections occur before that time, as is natural in a contact tracing context. Then in calculating the number of prevented infections as \( E(N_{(T, \infty)}) = \int_0^\infty E(N_{(T, \infty)} | T = t) f_T(t) dt \), the independence assumption allows the simplification \( E(N_{(T, \infty)} | T = t) = E(N_{(T, \infty)} | T = t) = E(N_{(T, \infty)}) \), so that

\[
E(N_{(T, \infty)}) = \int_0^\infty E(N_{(T, \infty)} | T = t) f_T(t) dt = \int_0^\infty \int_t^\infty \lambda(a) da f_T(t) dt = \int_0^\infty \int_0^a f_T(t) dt \lambda(a) da = \int_0^\infty P(T \leq a) \lambda(a) da.
\]

and subtracting the last equation from \( R_0 = \int_0^\infty \lambda(a) da \) we obtain

\[
R_{\text{test}} = \int_0^\infty P(T > a) \lambda(a) da.
\]

In this sense, the testing and isolation at time \( T \) reduces the infection rate function from \( \lambda(a) \) to an effective transmission rate defined by \( \lambda(a)P(T > a) \). As depicted in Fig. 4, conditional on the isolation age \( T \), out of the full area \( R_0 \) under the \( \lambda \) curve, the testing and isolation prevents an expected number of infections shown by the gray area, and \( R_{\text{test}} \) is the expected value of the red area over the random isolation age \( T \).

The relationship (40) quantifies how detecting and isolating infected people as soon as possible after they are infected, to make \( P(T > a) \) as small as possible, helps reduce \( R_{\text{test}} \). As a useful first-cut analysis of the effectiveness of a testing program one could ask whether it is capable of reducing \( R_{\text{test}} \) to below 1. As a rather artificial example admitting simple closed form calculations, suppose that the isolation age \( T \) has an exponential distribution with rate \( \rho \), and the forward generation time distribution is in the gamma family so that the transmission rate function is of the form

\[
\lambda(a) = R_0 \frac{\beta}{T(\alpha)} a^{\alpha-1} e^{-\beta a} \quad \text{for } a > 0, \quad \text{and 0 otherwise.}
\]

Then \( R_{\text{test}} \) is easily be calculated to be

\[
R_{\text{test}} = R_0 \left( \frac{\beta}{\beta + \rho} \right)^\alpha.
\]

so that the rate of testing required to achieve \( R_0 = 1 \) is \( \rho = \beta (R_0^{-1}) \). For example, if we assume values \( \alpha = 4.866 \) and \( \beta = 0.549 \) to be consistent with Li et al. (2020), the rate of testing required to decrease the reproduction number from \( R_0 = 2.0 \) to \( R_{\text{test}} = 1 \) is \( \rho = 0.084 \), which would correspond to testing on average every \( \frac{1}{\rho} = 11.9 \) days. The previous example is not realistic in several ways including the assumed exponential distribution of the time to isolation and the lack of consideration of imperfect sensitivity of tests. The next section treats these and other issues more carefully in the context of recently implemented intensive screening programs used by universities and other organizations.

5.6. Repeat asymptomatic screening for local outbreak control

A number of institutions of higher education, including our own home institution Yale University, have implemented intensive asymptomatic screening programs in order to prevent and reduce outbreaks (Chang & Kaplan, 2020). For example such a program might aim to test each student on campus twice per week. The modeling framework and ideas about testing described above are helpful in analyzing such programs and addressing questions about how various factors such as the frequency of testing, the sensitivity of tests, or the delay in receiving the results of tests would be expected to affect the prevalence of the disease on campus over time (Chang et al., 2020; Paltiel et al., 2020).
In modeling the effectiveness of repeated testing, we recognize that the test sensitivity $\sigma$, that is, the probability that a test given to an infected person will return a positive result, depends on the age $a$ of the infection at the time the test was administered. We denote this sensitivity function by $\psi_z = \psi(a)$, and in our model we can make use of current estimates such as that of Kucirka, Lauer, Laeyendecker, Boon, & Lessler (2020), which is approximated by

$$
\psi_z (a) = \begin{cases}
  \frac{e^{x^2/(1 + e^x)}}{1} & \text{if } 0 \leq a < 21 \\
  \frac{6.88 - 2.44 \log(a)}{a > 21}
\end{cases}
$$

where $\psi_z$ is the logistic function defined by $\psi_z (a) = \frac{e^{x^2/(1 + e^x)}}{1}$; a plot of this function is shown in Fig. 5.

We assume that repeated tests on a given individual are administered at regularly spaced times with constant time $\delta$ between tests with a random start time, so that for a given person, tests are administered at ages $t_0, t_0 + \delta, t_0 + 2\delta, \ldots$., with $t_0 \sim \text{Unif}(0, \delta)$. Assuming that different tests on an infected person are independent with the probability of a positive result for each test given by the sensitivity function evaluated at the infection age at the time that test was administered, it turns out (Chang et al., 2020) that the age of the infection at the time of administration of the first positive test on an infected person has probability density function given by

$$
f_r(a) = \frac{\sigma(a)}{\delta} \prod_{k=1}^{\left\lfloor \frac{a}{\delta} \right\rfloor} (1 - \sigma(a - k\delta)) I_{(a,\infty)}(a).
$$

The isolation age $T$ is obtained from the infection age $\tau$ at administration of the first positive test by adding some delay or lag, $\ell$, capturing the additional time for the positive test result to be returned and the student to enter isolation. For example if we model $\ell$ as a constant, then the tail probability $P(T > a)$ that is the key ingredient in capturing the effect of the testing program is given by

$$
P(T > a) = \int_a^\infty f_r(t-\ell) dt + P(T = \infty) = 1 - \int_0^a f_r(t-\ell) dt,
$$

where $\{T = \infty\}$ represents the event that a person never tests positive. An additional ingredient that turns out to be important to include in modeling infections of students is "imported" infections arising from exposure to infected individuals who are not members of the student population. Incorporating a per capita rate of imported infections denoted by $v(t)$ into our dynamic model, and taking the effective transmission rate to be $\lambda(a)P(T > a)$ the incidence Eq. (4) becomes

$$
\pi(t) = \pi(t-\ell) \lambda(a)P(T > a)
$$

Given specified assumptions for an initial condition $\{\pi(t) : t \leq 0\}$ which induces the initial susceptibility $s(0) = 1 - \int_0^\infty \pi(t) dt$, infection rate function $\lambda(a)$ in the absence of testing, interval between repeated tests $\delta$, sensitivity function $\sigma(z)$, isolation lag $\ell$, and an assumption about imported infections, we can use (46) to generate projections for the incidence of infection $\pi(t)$ over times $t > 0$.

Other aspects of a repeat testing program and quantities of interest can be added to this model or tracked more explicitly. For example, assuming students are not susceptible while in isolation, they should be subtracted from the susceptible pool $s(t)$ when they enter isolation. Whether or not a student just released from isolation is added back to the susceptible pool should depend on whether the positive test result was a true positive or false positive. For current tests the false positive rate is small, but in regular asymptomatic screening of all students, the number of tests performed is so large that the false positives could amount to a substantial fraction of the students who are isolated. If we want to model previously infected and recovered students as being immune from subsequent infection, when students are released from isolation, students who received false positives would return to the susceptible pool while students who received true positives would not. Such assumptions may be incorporated in a straightforward manner into the evolution of the susceptibility $s(t)$ over time so that we can still use (46) to update projected infections $\pi(t)$, which in turn may be used to calculate expected numbers of true and false positive tests, as well as the number of students in isolation over time. Having generated projections of these quantities, some further bookkeeping can produce projections for other quantities of interest, such as the number of undetected infected students over time, as detailed in Chang et al. (2020). These calculations are implemented in a web app available at https://jtwchang.shinyapps.io/testing/
Fig. 6. Model projections for the number of infections in 80 days as a function of the testing interval \( \delta \) for a student body of size 3500 in a scenario described by (i)-(iv) in the text.

Model projections along these lines can be used to investigate design issues and potential scenarios with regard to repeat testing programs. As an illustration, all else being equal it is clear that more frequent testing, that is, a lower value for the testing interval \( \delta \), leads to quicker isolation of infected students, which in turn decreases the expected number of infections. However more frequent testing is more costly, and in order to weigh this tradeoff quantitatively it is useful to investigate how projected numbers of infections increase with the testing interval. Fig. 6 plots the number of infections projected over a period of 80 days for a hypothetical student body of size 3500, as a function of the testing interval \( \delta \), for an example scenario specified as follows:

(i) The reproduction number in the absence of the contemplated repeat testing program is \( R_0 = 2.0 \), with the Li et al. (2020) forward generation time distribution.
(ii) For each student tests are repeated regularly every \( \delta \) days with sensitivity characterized by the function estimated by Kucirka et al. (2020).
(iii) For a student who tests positive, after the test is given it takes a delay of \( t = 1 \) day for the positive test result to be returned and the student to be isolated.
(iv) At time \( t \) imported infections are added to this student population according to \( n(t) = \frac{0.25}{350} \), this corresponds to adding \( s(t) \) infections to the student population every 4 days, where \( s(t) \) is the proportion of students who are susceptible.

In this case one might judge that the additional cost of testing twice per week rather than once per week is worthwhile if it reduces the anticipated number of infections from around 300 to around 100.

6. Summary

This paper has reviewed a renewal equation approach to modeling local coronavirus outbreaks. The models emphasize how the incidence of infections in the past drives the current rate of new infections. The modeling lends itself well to parameterization based on epidemiological data such as the early exponential growth rate in infections, the forward generation lag linking past and present infections as estimated from contact tracing data, and the basic reproduction number \( R_0 \), enabling quick analysis of local outbreaks. The model also generates important insights such as the final size of unmitigated “worst case” outbreaks, and the depletion of susceptibles (whether by infection or vaccination) necessary to achieve herd immunity. Given the central role of the forward generation lag in the model structure, the approach lends itself naturally to aligning epidemic indicators. These in turn can be used to estimate important epidemic quantities such as the basic reproduction number, initial fraction of the population infected in an outbreak, and the effective reproduction number \( R_e \) from indicator data. The model also lends itself quite naturally to analyzing the effectiveness of isolation policies to separate infectious from susceptible individuals. Focusing on the distribution of the time from infection to isolation shows how the basic reproduction number can be attenuated as isolation times shorten. A very important application of this idea is to the repeat testing of students, athletes or employees by universities, sports teams or businesses to identify and isolate infectious individuals. Here the modeling has proven crucial to determining the testing frequency required to ensure that repeat asymptomatic screening reduces the spread of infection to manageable levels. With the advent of vaccines and better medical treatments for COVID-19, additional policy questions arise that can be addressed with the assistance of epidemic models such as those in this paper.

Much of the analysis in this paper was developed in real time as part of the response to the local coronavirus outbreak at our university as well as in our surrounding New Haven community and home state of Connecticut (Kaplan 2020b). The pressure to conduct timely analyses was felt most acutely when developing recommendations for repeat asymptomatic screening and outbreak monitoring via aligning epidemic indicators. Working in this context heavily influenced our approach to modeling local outbreaks, as we needed approaches that were true to basic epidemiological principles while remaining simple enough to implement in the time available. While there remain many opportunities for researchers to contribute to the modeling and control of local infec-
tious disease outbreaks, in deciding how to construct such models, it is important to consider the reasons for pursuing such analyses in the first place. Indeed, as we hope we have demonstrated in this article, relatively simple models can contribute a great deal to decision-making in situations where time and other resources are in short supply.

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