The probability of epidemic burnout in the stochastic SIR model with vital dynamics

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Edited by Alan Hastings, University of California, Davis, CA; received August 9, 2023; accepted November 17, 2023

We present an approach to computing the probability of epidemic “burnout,” i.e., the probability that a newly emergent pathogen will go extinct after a major epidemic. Our analysis is based on the standard stochastic formulation of the Susceptible-Infectious-Removed (SIR) epidemic model including host demography (births and deaths) and corresponds to the standard SIR ordinary differential equations (ODEs) in the infinite population limit. Exploiting a boundary layer approximation to the ODEs and a birth-death process approximation to the stochastic dynamics within the boundary layer, we derive convenient, fully analytical approximations for the burnout probability. We demonstrate—by comparing with computationally demanding individual-based stochastic simulations and with semi-analytical approximations derived previously—that our fully analytical approximations are highly accurate for biologically plausible parameters. We show that the probability of burnout always decreases with increased mean infectious period. However, for typical biological parameters, there is a relevant local minimum in the probability of persistence as a function of the basic reproduction number \( R_0 \). For the shortest infectious periods, persistence is least likely if \( R_0 \approx 2.57 \); for longer infectious periods, the minimum point decreases to \( R_0 \approx 2 \). For typical acute immunizing infections in human populations of realistic size, our analysis of the SIR model shows that burnout is almost certain in a well-mixed population, implying that susceptible recruitment through births is insufficient on its own to explain disease persistence.

epidemics | stochastic processes | SIR model | extinction

It is well known that solutions of the standard ordinary differential equations (ODEs) describing a Susceptible-Infectious-Removed (SIR) epidemic with host births and deaths (aka “vital dynamics” or “demography”) eventually converge on a globally asymptotically stable equilibrium (1). Approach to the endemic equilibrium (EE) typically occurs via damped oscillations, motivating the use of the SIR model with demography as a basis for models of observed recurrent epidemics of childhood infections such as measles (2–6). For many biologically reasonable parameter values and population sizes, however, the troughs of these oscillations pass through infectious-host densities corresponding to a small fraction of an individual—the so-called “attofox problem” (7)—calling into question the appropriateness of the deterministic SIR model.

Here, we estimate the probability that a pathogen disappears at the end of a major epidemic in a stochastic individual-based SIR model, in a population of finite size. In the large population limit, the densities of each type \((S, I, R)\) are asymptotically deterministic and governed by the standard SIR ODEs (8). We will refer to pathogen extinction soon after introduction as fizzle, whereas if the pathogen escapes fizzle, we will refer to extinction at the end of a major epidemic as epidemic burnout, following the terminology of Dushoff (9). We will say that the pathogen persists if it has a subsequent epidemic wave, although it is worth mentioning that we always expect eventual extinction in a stochastic model with a finite population (10); the time to extinction of a pathogen that has survived to a state near the endemic equilibrium is considered in, e.g., refs. 11–13. Fig. 1 shows sample paths of the proportion of infectious individuals for the stochastic SIR model (together with the trajectory obtained from the ODE), illustrating fizzle, burnout, and persistence.

Significance

If a new pathogen causes a large epidemic, then it might “burn out” before causing a second epidemic. The burnout probability can be estimated from large numbers of computationally intensive simulations, but an easily computable formula for the burnout probability has never been found. Using a conceptually simple approach, we derive such a formula for the standard SIR epidemic model with vital dynamics (host births and deaths). With this formula, we show that the burnout probability is always smaller for diseases with longer infectious periods, but is bimodal with respect to transmissibility (the basic reproduction number). Our analysis shows that the persistence of typical human infectious diseases cannot be explained by births of new susceptibles, clarifying an important epidemiological puzzle.

*While “fade-out” (or “fadeout”) is commonly used to describe this extinction, e.g., ref. 4, §2.3, we find it conceptually useful to follow ref. 9 in distinguishing between extinction after a first major epidemic versus that occurring after multiple epidemics, and reserve the term fadeout for the latter.

Author contributions: All authors contributed to the conception of the research; T.L.P. and D.J.D.E. carried out the analysis, simulations, and figure creation, with input from B.M.B. and J.D.; T.L.P. and D.J.D.E. wrote the manuscript; and all authors revised the manuscript and approved the final version. The authors declare no competing interest.

This article is a PNAS Direct Submission.

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Published January 22, 2024.
The problem of epidemic burnout has been of ongoing interest (4, 14, 15), e.g.,

“The question ‘will the agent go extinct after the first outbreak?’ cannot be answered within the context of a deterministic description. So we would like to be able to switch back to a stochastic description at the end of the epidemic outbreak. While it is well known how to calculate the probability of extinction from a branching process in a constant environment…, it seems difficult to do so when environmental quality (from the point of view of the agent, i.e., the presence of susceptibles!) is improving linearly at a certain rate.” (14, p. 42)

and has been previously approached via perturbation methods (16, 17) and by hybrid analytical-numerical approaches (18):

1. van Herwaarden (16) (henceforth vanH) starts from a large population diffusion approximation to the Markov chain formulation of the SIR model (Model). Under the assumption that the individual mortality rate is low, a highly accurate approximation to the solution of the infinite-population limit SIR ODEs is obtained, which is in turn used to estimate the point of entry to a boundary layer where the number of infectious individuals is very small. In the boundary layer, the backward equation for the diffusion approximation \(^1\) is tractable and is used to obtain an analytical approximation to the burnout probability [vanH, Eq. (5.13)], which requires the numerical evaluation of an integral. It is, to quote Dickmann and Heesterbeek (14, p. 42), “an ingenious piece of work,” although it is challenging to interpret for non-experts.

2. By contrast, Meerson and Sasorov (17) (henceforth MS) retain the discrete population model. They estimate the probability of extinction as the probability of reaching the state with only one infective individual (weighted by the expected number of returns to this state)\(^2\) times the probability that a single infective recovers before transmitting to any other individuals. They approximate this probability by the product of the expected total time (summed over multiple returns) in the state with a single infective individual and the disease recovery rate (which is the rate of going extinct given that there is only one infectious individual). The time in the single-infective state is characterized by linear equations obtained by integrating the forward equations (see, e.g., ref. 19, §14.2) for all transient states over all time, for which an approximate solution is found via a WKB ansatz (see, e.g., ref. 22, Chapter 10) in the large population limit (i.e., a diffusion approximation is introduced implicitly). Under these assumptions, the burnout probability is shown to decay exponentially in the population size, with a constant of proportionality that is approximated analytically in the parameter regime where the initial exponential growth rate of infectious individuals greatly exceeds the per capita turnover rate (equivalent to \(\beta - \gamma \gg \mu\) in our formulation below). While providing coarser estimates than vanH, this approach yields a deterministic approximation to the most probable trajectory to pathogen extinction via a Hamiltonian formalism (see, e.g., refs. 23 and 24, Exercise 5.7.36). Like vanH, the approximation of MS involves an integral that cannot be evaluated analytically and presents a non-trivial numerical problem due to singularities in the integrand.

3. More recently, after identifying discrepancies between the analytical results of vanH and MS and the results of simulations, especially at smaller values of the expected population size, vanH (in ref. 18) introduced a computational approach that scales as \(O(n^2)\). As in the previous approaches, Ballard et al. (18) use the solution of the SIR ODEs—now evaluated numerically and summed with a higher-order Gaussian correction (8, Theorem 11.2.3)—to identify the point of entry into a boundary layer, where a simplified form of the Markov chain is then simulated to estimate the probability of burnout.

The approximations of vanH and MS are summarized in §2.3 of ref. 18. We compare the performance of these approximations with that of an analytical approximation that we have derived in the spirit of the quote from ref. 14 above. Like vanH and ref. 18, we use the SIR ODEs to approximate the stochastic SIR trajectories outside a boundary layer. Then, inside the boundary layer, we use a time-inhomogeneous birth-and-death process that approximates the true stochastic dynamics more accurately than the diffusion approximation of vanH (in Boundary Layer Independent Estimates, we obtain the expression from vanH as an approximation to ours). Our approach is simpler and more intuitive than the diffusion approximation, and—in contrast to all previous work—we obtain fully analytical expressions that are numerically stable and can be computed without recourse to numerical evaluation of integrals. Our approach yields expressions for the probability of persistence after any

\(^1\)See, e.g., refs. 19 or 20 for a discussion of the forward and backward diffusion equations; ref. 21 is an excellent introduction to boundary-layer methods for Markov chains.

\(^2\)In practice, there is negligible probability of returning to the state with one infective after an excursion to a state with many infectives.
number of epidemic waves and is also more amenable to
generalizations than singular perturbation analysis of diffusion
approximations; indeed, while we do not discuss the matter in
detail here, the boundary-layer diffusions of vanH correspond to
large population approximations for the branching processes we
consider here (similar to limits in refs. 25 and 26).

Approach and Analysis

Model. We consider the spread of an infectious disease in a
discrete population in which births balance deaths on average, so
there is a well-defined expected population size \( n \). We consider
a sequence of models indexed by \( n \), and for the \( n \)-th model denote
by \( S_n(t), I_n(t) \) and \( R_n(t) \) the numbers of individuals at time \( t \)
who are susceptible, infectious, and removed, respectively. The
total population size is

\[
N_n(t) = S_n(t) + I_n(t) + R_n(t).
\]

Births and immigration of new susceptible individuals occur
at constant rate \( \mu n \), while deaths occur at per capita rate \( \mu \),
independent of disease status. Thus, at every time \( t \), we have

\[
E[N_n(t)] = n
\]

where the expectation is taken over realizations of the stochastic
process. Infectious individuals recover at rate \( \gamma \), and new
infections occur according to the law of mass action in a well-
mixed population, i.e., at rate

\[
\frac{\beta S_n(t) I_n(t)}{n}.
\]

Since the demographic and epidemiological rates depend only
on the state of the system at the current time, our sequence is an
ensemble of Markov chain models (indexed by the expected total
population size \( n \)).

Following a common convention in probability theory, we
use upper case for functions and lower case for indices and the
functions as \( n \rightarrow \infty \), the frequencies \( \{X_n(t), Y_n(t), Z_n(t)\} \)
converge [almost surely on finite time intervals \((8)\)] to the solution
\( \{X(t), Y(t), Z(t)\} \) of the ODEs,

\[
\frac{dX}{dr} = \mu (1 - X) - \beta XY, \quad [5a]
\]

\[
\frac{dY}{dr} = (\beta X - \gamma - \mu) Y, \quad [5b]
\]

\[
\frac{dZ}{dr} = \gamma Y - \mu Z. \quad [5c]
\]

Formally, to make this connection, one must be careful to have
a sensible relationship between the initial conditions for the
stochastic processes and the initial conditions for the ODEs.
For example, given an initial state \( \{X(0), Y(0), Z(0)\} \) for
the ODEs, if one takes

\[
\frac{X_n(0)}{n}, \frac{Y_n(0)}{n}, \frac{Z_n(0)}{n} = \frac{1}{n}\left([nX(0)], [nY(0)], [nZ(0)]\right), \quad [6]
\]

then the theorem applies. More generally, one must choose initial
conditions \( \{X_n(0), Y_n(0), Z_n(0)\} \) for the stochastic processes
such that the limits \( \lim_{n \rightarrow \infty} X_n(t) \), etc. exist, and one must
take these limits as initial conditions for the ODEs (see
Theorem 11.2.1 in ref. 8, p. 456); Example B on p. 453 of Ethier &
Kurtz (8) illustrates how the SIR model without demography
relates to the hypotheses of the theorem, and Chapter 5 in ref.
27 provides a pedagogical introduction to Kurtz’s results in the
context of epidemic models.

The trajectories of the deterministic SIR model (Eq. 5) always
converge to a globally asymptotically stable (GAS) equilibrium point,
which can be shown via a combination of the Poincaré
Bendixson Theorem and Dulac’s criterion (28) or via a Lyapunov
function (29). The nature of the asymptotic state is determined by
the basic reproduction number (the expected total number of
new infections caused by a single infective individual introduced
into a naïve population),

\[
R_0 = \frac{\beta}{\gamma + \mu}. \quad [7]
\]

If \( R_0 \leq 1 \), then the GAS fixed point is the disease free
equilibrium, \( (x, y) = (1, 0) \), whereas if \( R_0 > 1 \), then all solutions
converge—either via damped oscillations or monotonically—to an
endemic equilibrium,

\[
(x_*, y_*) = \left(\frac{1}{R_0}, \epsilon \left(1 - \frac{1}{R_0}\right)\right), \quad [8]
\]

where

\[
\epsilon = \frac{\mu}{\gamma + \mu} \quad [9]
\]
gives the mean infectious period as a fraction of the mean host
lifetime. Our analysis requires that \( \epsilon \) is small but not too small.

<table>
<thead>
<tr>
<th>Event type</th>
<th>Rate</th>
<th>Transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth/immigration</td>
<td>( \mu n )</td>
<td>( S_n \rightarrow S_n + 1 )</td>
</tr>
<tr>
<td>Transmission</td>
<td>( \beta S_n R_n / n )</td>
<td>( S_n \rightarrow S_n - 1, I_n \rightarrow I_n + 1 )</td>
</tr>
<tr>
<td>Recovery</td>
<td>( \gamma I_n )</td>
<td>( I_n \rightarrow I_n - 1, R_n \rightarrow R_n + 1 )</td>
</tr>
<tr>
<td>Susceptible death</td>
<td>( \mu S_n )</td>
<td>( S_n \rightarrow S_n - 1 )</td>
</tr>
<tr>
<td>Infectious death</td>
<td>( \mu I_n )</td>
<td>( I_n \rightarrow I_n - 1 )</td>
</tr>
<tr>
<td>Removed death</td>
<td>( \mu R_n )</td>
<td>( R_n \rightarrow R_n + 1 )</td>
</tr>
</tbody>
</table>

Table 1. Event types in the stochastic SIR model

Fig. 2. Compartmental model for an SIR epidemic with vital dynamics. Labels on the arrows correspond to individual jump rates between states. For simplicity, the model is defined so that births/immigrations on average balance deaths, so that the expected total population size \( E[N_n(t)] = n \) is fixed.
\( \left( \frac{1}{2} \ll \varepsilon \ll 1 \right) \), which is true for a wide variety of common acute infectious diseases (Table 2). The upper bound \( \varepsilon \ll 1 \) is essential so we can justify perturbation expansions in \( \varepsilon \). The lower bound \( \frac{1}{2} \ll \varepsilon \) is equivalent to \( ne \gg 1 \), which ensures that the number of infectives at equilibrium \( (\eta_\varepsilon) \) is substantially greater than 1 (from Eq. 8, \( \eta_\varepsilon \sim ne \)). The ODEs continue to provide a good approximation to the epidemic dynamics until the prevalence \( y \) (the proportion of hosts that are infectious) becomes small; we take “small” to mean that \( y \) is less than the equilibrium prevalence \( y_* \) (Eq. 8). Thus, we take the boundary layer—within which the dynamics must be treated stochastically—to be the region of the phase plane where \( y \ll y_* \) (in Boundary Layer Independent Estimates, we also give approximations independent of the specific choice of boundary layer).

The need to analyze the dynamics differently within the boundary layer is especially clear if we consider the introduction of a single infectious individual into a fully susceptible population. If \( R_0 > 1 \), then in the ODE system (Eq. 5) \( Y(t) \) will deterministically increase, whereas in the stochastic model, \( Y_\varepsilon(t) \) will fizzle with probability \( 1/R_0 \) (30); i.e., the ODE (Eq. 5) fails to capture the dynamics of the stochastic model (Fig. 2) when there are few infectives. We therefore use a birth-and-death process to approximate the dynamics of the number of infectious hosts when the number is small (in contrast, susceptibles can be assumed to remain sufficiently abundant that we can always use the deterministic approximation \( X(t) \)).

**Birth-and-Death Process Heuristic.** New infections occur at rate

\[
\frac{\beta S_n(t)}{n} I_n(t) = \beta X_n(t) I_n(t) \approx \beta X(t) I_n(t),
\]

while the number of infectious hosts decreases by one due to recovery or death at rate

\[
(y + \mu) I_n(t).
\]

When there are few infectious hosts \( (I_n(t) \ll n \eta_* \) we approximate \( I_n(t) \) by a linear birth and death process with time-inhomogeneous per capita rates \( \beta(t) \) and \( \gamma(t) \), where

\[
\beta(t) = \beta X(t),
\]

\[
\gamma(t) = \gamma + \mu.
\]

Note that when \( X(t) \) equals \( x_* \) (the classical herd immunity threshold), \( \beta(t) = \gamma(t) \), and the birth and death process transitions from subcritical to supercritical. Unlike in models without demography, the birth of new susceptible individuals ensures that a population will eventually cross the herd immunity threshold. Therefore, even if the number of infectious hosts initially declines it can eventually grow exponentially, if the infection survives until \( X(t) > x_* \).

We can estimate the survival probability for this branching process, and thus, the persistence probability, using the following result.

**Theorem 1 [Kendall (31)].** Let \( K(t) \) be a birth and death process with time-inhomogeneous per-capita birth rate \( \beta(t) \) and death rate \( \gamma(t) \). The probability of eventual extinction starting from one individual at time 0 is

\[
q = \left( 1 + \frac{1}{\int_0^\infty e^{-\int_0^t [\beta(s) - \gamma(s)] ds} ds} \right)^{-1}.
\]

The extinction probability starting from \( k \) individuals is \( q^k \).

Consequently, the probability of indefinite persistence (a branching process will either go extinct or grow indefinitely), starting from \( k \) individuals at time 0, is

\[
\mathbb{P}(K(\infty) > 0) = 1 - q^k.
\]

To complete our persistence probability estimate, we need an expression for the proportion susceptible at time \( t \) \( X(t) \) in Eq. 12). As suggested visually by the example shown in Fig. 1, inside the boundary layer \( (y < y_* \) both the deterministic and the stochastic trajectories spend most of their time at prevalences much lower than \( y_* \) [note the log scale in the subfigures (B) and (E)]. Consequently, we can approximate \( X(t) \) by solving (Eq. 5) with \( Y(0) = 0 \). Thus, we set

\[
\frac{dX}{dt} \approx \mu(1 - X),
\]

and solve this approximate equation as if it were exact to obtain

\[
X(x_0, t) \approx 1 - (1 - x_0) e^{-\mu t}.
\]

Here, \( x_0 \) is the fraction susceptible at the initial time \( t = 0 \), and we write \( X(x_0, t) \) to emphasize the dependence on the initial state. We also write \( q(x_0) \) for the value of \( q \) in Eq. 14 obtained by taking \( \beta(t) = \beta x_0(t) \). We first apply this branching process approximation to a population at the disease-free equilibrium (DFE). Thus, we set \( x_0 = 1 \) in (Eq. 17), which yields \( X(1, t) \equiv 1 \); hence, we have a time-homogeneous branching process in this case, and the integral in (Eq. 14) is easily evaluated and yields \( q(1) = \frac{1}{R_0} = x_* \). Considering a small number of initially infective individuals, \( I_n(0) = k \), we recover the classical expression for the establishment probability (30), that is, the probability that the pathogen does not fizzle:

\[
p_k = 1 - x_*^k.
\]

We now use Kendall’s \( q \) (Eq. 14) to compute the burnout probability. Assuming that the pathogen does not fizzle, the number of infectious hosts will rapidly exceed \( n \eta_* \) individuals,\(^5\) at which point the densities of both susceptible and infectious hosts are well approximated by the ODEs (Eq. 5). To proceed, we need a formula for the fraction of hosts that are susceptible when the trajectory enters the boundary layer at the end of an epidemic; we denote this fraction \( x_{in} \) to emphasize that it refers to the susceptible proportion upon entry into the boundary layer (the point \( (x_{in}, y_*) \)) is indicated by a heavy yellow dot in Fig. 1). In ref. 34, assuming \( \varepsilon \) is small,\(^6\) we derive an approximate expression for the fraction susceptible, \( X(y, x_1) \), as a function of the fraction infectious \( y \) and the initial fraction susceptible \( x_1 \). Using that approximation, we have

\[
x_{in} = X(y_*, x_1) \approx -x_* W_0 \left( -R_0 x_1 e^{-R_0 (x_1 - y_*)} \right) + e^{R_0 x_1} (E_1 (R_0 x_1) - E_1 (R_0 x_1 - R_0)).
\]
Here, $W_0$ denotes the principal branch of the Lambert $W$-function\(^8\) (35), $E_1(x) = \int_x^{\infty} \frac{e^{-t}}{t} \, dt$ is the exponential integral function (36, §8.2.1) and $Y_0$ is the peak prevalence in the limit $\varepsilon \to 0$ (i.e., $\mu \to 0$), i.e., the maximum fraction infectious in the SIR model without vital dynamics,

$$Y_0 = x_1 - x_e \left(1 + \ln \left(x_1/x_e\right)\right).$$ \[21\]

(See e.g., ref. 37 for a derivation of $Y_0$.) Taking $x_1 = 1$ corresponds to the invasion of a novel pathogen into an epidemiologically naive population (i.e., at the DFE). Later (Subsequent Epidemic Waves), we give an iterative scheme for $x_{j+1}$, an “effective initial fraction susceptible” that—substituted for $x_1$ in Eqs. 19 and 21—gives the fraction susceptible at the end of the $j$th epidemic wave after invasion at the DFE. We compare our approximation of $x_{n+k}$ for $x_1 = 1$ to the value obtained by numerically integrating the SIR ODEs (Eq. 5) in Fig. 3 and discuss its domain of applicability below (The Domain of Applicability of the Approximation (Eq. 19) to $x_{n+k}$).

If we now take $t = 0$ to be the end of a major epidemic, i.e., the time when the infectious host density falls below $y_a$, and $x_0 = x_{n+k}$, then the density of infectious hosts is small, and the density of susceptible hosts is well approximated by $X(x_{n+k}, t)$ (we are preparing a rigorous treatment of these results; here, we will content ourselves with showing that our analytical results closely match the results of individual-based simulations). We can thus estimate the conditional burnout probability—i.e., the probability of burnout conditional on not fizzling—by

$$q(x_{n+k}) = q^*(x_{n+k}).$$ \[22\]

and the conditional persistence probability by

$$1 - q(x_{n+k}).$$ \[23\]

Fig. 3. Susceptible proportion ($y_a$) as a function of $R_0, \varepsilon$ (A) $y_a$, as a function of $R_0$ (Eq. 7) (B) $y_a$, as a function of $\varepsilon$ (Eq. 9). The exact value of $y_a$ (obtained by numerically solving the SIR ODEs (Eq. 5)) is shown with solid curves, our approximation (Eq. 19) is shown with dashed curves, and the approximation of $y_{n+k}$ is shown with dotted curves. Based on Eq. 42, the minimum $R_0$ for which our approximation of $x_{n+k}$ (Eq. 19) is valid is $\approx e^{\varepsilon_0}$ (i.e., $1.020027$ for $\varepsilon = 0.01$ and $1.00002027$ for $\varepsilon = 0.001$).

Below (Computing the Epidemic Burnout Probability), we compute an exact expression for $q(x_{n+k})$,

$$q(x_{n+k}) = \left(1 + \frac{\varepsilon}{e^{-a} - 1}\right)^{-1} \approx \left(1 + \frac{\varepsilon}{e^{-a} - 1}\right)^{-1} \left(1 + \frac{1}{\varepsilon^2} \right)$$ \[24a\]

where

$$z = \frac{R_0}{\varepsilon} (1 - x_w),$$ \[24b\]

and

$$a = \frac{R_0}{\varepsilon} (1 - x_e).$$ \[24c\]

Here, $\gamma$ denotes the lower incomplete gamma function\(^9\) (36, §8.2.1); we use the nonstandard notation $q$ to avoid confusion with our recovery rate parameter $\gamma$. Below (Asymptotics for Small $\varepsilon$), we derive an approximation for $q(x_{n+k})$ that is extremely accurate for small values of $\varepsilon$.

$$q(x_{n+k}) \approx \left(1 + \frac{1}{\varepsilon^2} \right)$$ \[25\]

We emphasize that this expression is elementary and numerically stable.

Thus, the burnout probability—i.e., the probability of not fizzling (Eq. 18) but disappearing after an epidemic—is

$$p_k (q(x_{n+k}), y_a),$$ \[26\]

where $n$ is the expected total population size, $y_a$ is the equilibrium prevalence (Eq. 8), $q$ is the probability of eventual extinction (under post-epidemic conditions) starting from one infectious individual (Eq. 14), and $k$ is the initial number of infectious individuals. Our exact expression for $q(x_{n+k})$ is given in (Eq. 24).

Similarly, the persistence probability—i.e., the probability of not burning out after a first epidemic (Eq. 23)—is

$$P_1 (R_0, \varepsilon, n, k) = p_k (1 - q(x_{n+k}), y_a).$$ \[27\]

More generally, the probability of persisting beyond the $m$th epidemic wave is

$$P_m (R_0, \varepsilon, n, k) = p_k \prod_{j=1}^m (1 - q(x_{n+j}, y_a)).$$ \[28\]

where

$$x_{n+j} = X(y_a, x_{n+j}).$$ \[29\]

(see Eq. 19 and Subsequent Epidemic Waves). For biologically reasonable values of $\varepsilon$, $R_0$, and $n$, we find that the difference between $P_1 (R_0, \varepsilon, n, k)$ and $P_m (R_0, \varepsilon, n, k)$ is negligible, because $q(x_{n+j}) \ll 1$ for $j \geq 2$. Intuitively, because the troughs between epidemics get shallower and shallower, an invading disease that survives burnout is almost certain to persist through many more cycles.

Thus, in Results, we focus on burnout after the initial epidemic when a novel disease invades a fully susceptible population. There, we use our accurate, numerically stable, and computationally efficient approximation for $q(x_{n+k})$ (Eq. 25), obtained via Eqs. 19 and 37a, to compute the probability of burnout.

\(^{8}\)If $W(z) = ze^z$, Lambert’s W-function $W(z)$ (35) solves the “left-sided” inverse relation $W(W(z)) = z$. This equation has countably many solutions, each corresponding to branches $W_i$ of the W-function; we will need the two real branches, $W_0$ which maps $[-\infty, -1] \to [-\infty, 1]$, and $W_1$, which maps $[-\infty, 0] \to (-\infty, -1]$. For these two branches, $W_1(z)$ is a “partial” “right-sided” inverse function for $W(z)$:

$$W_1(z) = \frac{z}{e^z} - 1 \quad \text{if} \quad z \leq -1$$

$$W_0(z) = \frac{z}{e^z} - 1 \quad \text{if} \quad z \geq -1.$$ \[20\]

\(^{9}\)If $\gamma(z) = \int_0^\infty e^{-t} t^{z-1} \, dt$ is proportional to the cumulative distribution function for the gamma distribution. We use this fact to compute $\gamma(a, z)$ accurately in our burnout R package, mentioned in footnote **.
Results

Fig. 4 shows that our analytical approximation for the persistence probability (Eq. 27) agrees very well with the same probability estimated from large numbers of simulations. The probability is shown as a function of the basic reproduction number ($R_0$) with fixed mean infectious period ($\epsilon = 0.01$). The panels differ only in the underlying expected population size (ranging from $n = 10^4$ to $10^7$). For each value of $R_0$, the simulation-based persistence probability was estimated from $10^7$ individual-based stochastic realizations of the model (Fig. 2 and Table 1). Note that $\epsilon = 0.01$ corresponds to an infectious period that is 1% of the average lifetime, far longer than is realistic for most acute immunizing infections; however, our approximation only improves for smaller $\epsilon$. We use $\epsilon = 0.01$ in Fig. 4 so that discrepancies between the simulations and analytical results are visible.

Our simple approximation for Kendall’s $g$ (Eq. 25) allows us to easily and quickly explore the conditional and unconditional probability of pathogen extinction across the entire range of biologically plausible values of $R_0$ and $\epsilon$. Fig. 5 shows a contour plot of the persistence probability (this graph would have required years of computer time to produce from simulations). As was observed previously (18, 38), Fig. 5 indicates that the burnout probability is non-monotone in $R_0$ for $\epsilon \leq 0.016$. In this range of $\epsilon$, the probability of persistence is lowest for basic reproduction numbers in the range $2 \leq R_0 \leq 2.57$, and increases rapidly with increasing $R_0$. Below (The $R_0$ Maximizing the Probability of Burnout), we compute a linear approximation to the value of $R_0$ at which the persistence probability is minimized. The upper limit of 2.57 for the persistence-minimizing range of $R_0$ is the limit as $\epsilon \to 0$ in Eq. 63; Fig. 5 shows that this linear approximation performs very well over the range where the persistence probability is non-monotonic. Less intuitively, the persistence probability increases for small $R_0$ (below the red curve in Fig. 5) as $R_0$ decreases to one. We note, however, that except for very large expected population size $n$, the secondary peak in the persistence probability—which occurs for $1 < R_0 \simeq 2$—remains small (cf. Fig. 4), except for pathogens with extremely long infectious periods. Fig. 5 also suggests that for fixed $R_0$, the probability of persistence always increases with increasing $\epsilon$, which we confirm analytically below (The Burnout Probability is a Decreasing Function of $\epsilon$). Note that $\beta = R_0(\gamma + \mu) = \frac{R_0\gamma}{1-\epsilon}$, so varying $\epsilon$ while holding $R_0$ constant simultaneously varies the infectious period and contact rate by a factor of $O(\epsilon)$.

Discussion

The problem of infectious disease persistence following a major epidemic (4, p. 20; 14, p. 42; 47, p. 451; 9, 15, 38) is important for identifying characteristics of pathogens that can successfully invade, and is related to the notion of a “critical community size” required for a disease to persist in the long term (30).
Given sufficient computing resources, it is possible to estimate the persistence probability for a given model from large numbers of stochastic, individual-based simulations. The gray curves in Fig. 4 show this probability estimated from simulations of the SIR model. Fig. 4 also shows the probability estimated using previous analytical methods (16, 17) (blue and orange curves) and our approximation (black curves). All three analytical approaches yield similar results,** and differences in the estimated probabilities can be seen only on a logarithmic scale in the limit as $R_0 \to 1^+$ (e.g., for $R_0 \leq 1.05$ in Fig. 4), where all of these approximations†† are technically invalid: in a stochastic, finite population model, as $R_0 \to 1^+$ there is no phase during which the deterministic model is a good approximation, and the distinction between fizzle, burnout, and fadeout breaks down (48). Analysis of the limit $R_0 \to 1^+$ could improve understanding of the process of eradication as the magnitude of control measures is increased, but for the burnout problem on which we focus here, the limit $R_0 \to 1^+$ is of limited interest.

While our approximation agrees closely with previous work (16, 17) for ranges of $R_0$ that are biologically relevant, there are several important theoretical and practical advantages of our approach; our analysis

- is simpler and easier to understand, since it is based directly on the underlying stochastic process rather than on a diffusion approximation (and is consequently easier to apply to models that are more complex than the SIR model considered here);
- yields fully analytical approximations that are numerically stable, unlike the previous analytical approaches (16, 17), which depend on non-trivial numerical integrations with singular integrands;
- predicts the persistence probability after an arbitrary number of epidemic waves.

We expand on these points below.

We have obtained useful analytical estimates (Eqs. 24, 25, 27, and 28) of the SIR epidemic burnout and persistence probabilities in a well-mixed population, via a hybrid use of ODEs when prevalence is high and time-dependent branching processes when prevalence is low. As noted after Eq. 28, the probability of burning out in each subsequent epidemic trough after persisting through the first is negligibly small for the SIR model.

Our time-dependent branching process approach (Birth-and-Death Process Heuristic) also yields analytical results that are more amenable to computation than previous approximations (16, 17). Our application of Laplace’s method to approximate the integral in Kendall’s $q$ (Eq. 14) is particularly useful. Eq. 25 for the conditional burnout probability provides a fully analytical formula—not requiring the numerical evaluation of integrals as in previous approaches (16, 17)—that can be evaluated without numerical instabilities and agrees very well with numerical simulations across a wide range of biologically plausible values of $R_0$ and $\epsilon$. The convenience and speed of our simple analytical expression for the persistence probability (Eq. 27) also allows us to obtain results for larger population sizes than are tractable via hybrid numerical methods (18) and facilitates efficient exploration of more of the parameter space (though with less accuracy at smaller population sizes).

As is suggested visually by Fig. 5, and proved below (The Burnout Probability is a Decreasing Function of $\epsilon$), the persistence probability increases with infectious period ($\epsilon$) across all values of $R_0$. For any given infectious period, one viable life history strategy for persistence is a high $R_0$ (dark gray shading in Fig. 5). In addition to this high $R_0$ strategy, for a limited range of longer infectious periods ($\epsilon \lesssim 0.016$), there is a second life-history strategy that promotes persistence: $R_0$ close to but greater than one.

We use our analytical results to compute a linear approximation to the value of $R_0 > 1$ at which the burnout probability is maximized (see Eq. 63 in The $R_0$ Maximizing the Probability of Burnout). This approximation shows excellent agreement with the numerical results over the range of $\epsilon$ for which the secondary peak exists and the burnout probability is numerically distinguishable from 1 (in Fig. 5, the dotted red curve is the approximation and the solid red curve is the numerically computed exact value). Intriguingly, with the exception of the ancestral strain of SARS-CoV-2—which has been replaced by variants with much higher $R_0$—the endemic infectious diseases of humans listed in Table 2 roughly divide into high and low $R_0$ strategies.

These life history strategies can be interpreted in terms of the herd immunity threshold, $x = x_\star = \frac{R_0}{1 + R_0}$, i.e., the minimum proportion susceptible at which the epidemic can grow from a small number of infections. When $R_0$ is large, the herd immunity threshold $x_\star$ is low, allowing the fraction susceptible to rapidly reach the threshold. When $R_0$ is low, there is a larger reservoir of susceptible hosts at the end of the first major epidemic, which reduces the wait until the herd immunity threshold is crossed. In either case, a longer infectious period (larger $\epsilon$) allows the pathogen to “wait out” the period of herd immunity. This non-monotonicity of the burnout probability as a function of $R_0$ was previously observed (18, 38), and the maximum burnout probability was conjectured to occur for $R_0 \approx 3$ (38) or $R_0 = 2$ (18).

We have shown that, in fact, the value of $R_0$ at which the probability is maximized is a decreasing function of $\epsilon$ (solid red curve in Fig. 5). The probability-maximizing $R_0$ varies from $R_0 \approx 2.57$ for $\epsilon \to 0$ (Eq. 63) to $R_0 \approx 2$ for $\epsilon \approx 0.016$; for larger $\epsilon$, the persistence probability increases monotonically with $R_0$.

These results also have evolutionary implications: reduced virulence may be associated with longer infectious periods.

**We have implemented all three approximations in an open-source R package, which we used to create our figures. The package is available at https://github.com/davidearn/burnout.

†† Differences between our approximation and those of refs. 16 and 17 as $R_0 \to 1^+$ arise at least in part because they use $\mu$ rather than $v$ as the small parameter, and consequently predict persistence for $\mu/v > 1$ rather than $\mu/(\mu + v) > 1$.

Table 2. Representative parameters for acute immunizing infections (and HIV for comparison)

<table>
<thead>
<tr>
<th>Disease</th>
<th>$R_0$</th>
<th>$\tau_{\text{lat}}$ [days]</th>
<th>$\tau_{\text{inf}}$ [days]</th>
<th>$\epsilon \times 10^2$</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>17</td>
<td>8</td>
<td>5</td>
<td>0.71</td>
<td>(4)</td>
</tr>
<tr>
<td>Pertussis</td>
<td>17</td>
<td>8</td>
<td>14</td>
<td>1.2</td>
<td>(4)</td>
</tr>
<tr>
<td>Mumps</td>
<td>12</td>
<td>15</td>
<td>6</td>
<td>1.1</td>
<td>(4)</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>11</td>
<td>10</td>
<td>5</td>
<td>0.82</td>
<td>(4)</td>
</tr>
<tr>
<td>COVID-19 (Delta)</td>
<td>6.8</td>
<td>5.8</td>
<td>14</td>
<td>1.1</td>
<td>(39)</td>
</tr>
<tr>
<td>Rubella</td>
<td>6.5</td>
<td>10</td>
<td>7</td>
<td>0.93</td>
<td>(4)</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>5.5</td>
<td>1.5</td>
<td>18</td>
<td>1</td>
<td>(4)</td>
</tr>
<tr>
<td>Smallpox</td>
<td>4.5</td>
<td>15</td>
<td>7</td>
<td>1.2</td>
<td>(40)</td>
</tr>
<tr>
<td>COVID-19 (ancestral)</td>
<td>3</td>
<td>3.7</td>
<td>14</td>
<td>0.97</td>
<td>(39)</td>
</tr>
<tr>
<td>HIV</td>
<td>2.2</td>
<td>87</td>
<td>270</td>
<td>19</td>
<td>(41)</td>
</tr>
<tr>
<td>Influenza (1918)</td>
<td>1.8</td>
<td>2</td>
<td>2.5</td>
<td>0.25</td>
<td>(42, 43)</td>
</tr>
<tr>
<td>Ebola</td>
<td>1.6</td>
<td>9.3</td>
<td>7</td>
<td>0.89</td>
<td>(43)</td>
</tr>
<tr>
<td>Pneumonic plague</td>
<td>1.3</td>
<td>4.3</td>
<td>2.5</td>
<td>0.37</td>
<td>(44)</td>
</tr>
</tbody>
</table>

The basic reproduction number ($R_0$), mean latent period ($\tau_{\text{lat}}$), and mean infectious period ($\tau_{\text{inf}}$) are taken from the cited sources. The dimensionless parameter $\epsilon$ is defined in Eq. 9 in terms of the recovery rate ($\gamma$) and birth-death rate ($\mu$) in the SIR model. We associate $1/\gamma$ with the mean generation interval of the SEIR model, i.e., $1/\gamma = T_{\text{lat}} + T_{\text{inf}}$ (45, 46), set $\mu = 0.02$ year$^{-1}$ to mimic human birth and death rates, and compute $\epsilon = \mu/(\mu + \gamma)$. Where original sources present a range, we have listed the midpoint. Many of the estimates come from Anderson and May (4) ($R_0$ is taken from Table 4.1 (4, p. 70); the mean latent and infectious periods come from Table 3.1 (4, p. 31)). All the diseases listed in this table are shown in Fig. 5.

PNAS 2024 Vol. 121 No. 5 e2313708120 https://doi.org/10.1073/pnas.2313708120 7 of 12
Computing the Epidemic Burnout Probability. To apply Kendall’s $\mu$ (Eq. 14) to the problem of epidemic burnout, we need to compute the integral

$$I(x_n) = \int_0^\infty \int_{\mu}^\infty e^{-\int_0^t \beta(x_n, s)(y + \mu) \, ds} (y + \mu) \, dt$$

where, in the second line, we use the mean duration of infection ($1/(y + \mu)$) as the time unit and write $\sigma = (y + \mu) s$, $\tau = (y + \mu) t$. Recalling Eq. 17, we can write

$$X(\sigma) = X_k(\mu, \sigma) = (1 - x_n) \exp(-\sigma)$$

and hence

$$X'(\sigma) = \epsilon(1 - x_n) \exp(-\sigma) = \epsilon(1 - X(\sigma)).$$

Now, to evaluate the inner integral in Eq. 30a, we make a change of variables, using $x = X(\sigma)$ as the variable of integration:

$$\int_0^\tau \left[ R_0 x \left( \frac{x_n - \frac{\sigma}{\tau + \mu}}{\gamma + \mu} \right) - 1 \right] \, d\sigma = \int_0^{X(\tau)} \frac{R_0 x - 1}{(1 - x)} \, dx = -\frac{R_0}{\epsilon} (X(\tau) - x_n) - \frac{R_0}{\epsilon} (1 - x_n) \ln \frac{1 - X(\tau)}{1 - x_n}.$$  \hspace{1cm} [33]

Changing variables in a similar way, we have

$$\int_0^\tau e^{-\int_0^\tau \left[ R_0 x \left( \frac{x_n - \frac{\sigma}{\tau + \mu}}{\gamma + \mu} \right) - 1 \right] \, d\sigma} \, d\tau$$

We are interested in the probability of ultimate extinction, which corresponds to taking the limit as $T \to \infty$, or, equivalently, $X(T) \to 1$, giving us

$$I(x_n) = \int_0^1 e^{\frac{R_0 x}{\epsilon}(x - x_n)} \left( \frac{1 - x}{1 - x_n} \right) \frac{R_0}{\epsilon}(1 - x_n) \, dx$$

where we recall $\mathcal{G}$ denotes the lower incomplete gamma function. Eq. 24 follows immediately.

Asymptotics for Small $\epsilon$. We may also write $I(x_n)$ (Eq. 35) as

$$I(x_n) = \frac{1}{\epsilon} \int_{x_n}^{1} \frac{1}{1 - x} e^{\frac{R_0}{\epsilon}(x - x_n) \ln \frac{1 - x}{1 - x_n}} \, dx$$

for $h(x) = \frac{1}{1 - x}$ and $\phi(x) = R_0 \left( x - x_n + (1 - x_n) \ln \frac{1 - x}{1 - x_n} \right)$. Assuming $\epsilon$ is small, we can apply Laplace’s method (22, §6.4): provided $x_n \leq x_*, \phi(x)$ has its maximum at $x = x_*$, so

$$I(x_n) \sim \frac{1}{\epsilon} \frac{2\pi \epsilon}{\phi'(x_*)} h(x_*) e^{\phi(x_*)}$$

yielding Eq. 25.

**Remark 1:** Note that, since $x_n < x_*$,

$$0 < -R_0 \int_{x_n}^{x_*} \ln (1 - t) \, dt$$

$$< R_0 \left( x_* - x_n + (1 - x_n) \ln (1 - x_n) - (1 - x_n) \ln (1 - x_n) \right)$$

$$\phi(x_n) = \phi(x_*)$$

so the Laplace approximation and thus the original integral (Eq. 35a) are both exponentially large in $\epsilon^{-1}$.  

Materials and Methods

Computing the Epidemic Burnout Probability.
Subsequent Epidemic Waves. In ref. 34, we derive an iterative scheme to compute "effective initial conditions" for every epidemic wave following initial disease invasion. Writing \( x_{ij} \) for the fraction susceptible at the start of the \( j \)th epidemic wave, we find our trajectory approximations agree very closely with the "exact" value obtained by solving the SIR ODEs (Eq. 5) numerically, starting from the DFE.

Setting \( x_{ij,1} = 1 \), we iteratively obtain \( \overline{y}_{0j} \) and \( x_{ij+1} \) (Eq. 19) from \( x_{ij} \) by computing

\[
\begin{align*}
x_{ij} &= -x_* W_0(\xi (-x_{ij}/x_*)), \quad \text{[39a]} \\
\overline{y}_{0j} &= x_{ij} - x_* \left( 1 + \ln \left( x_{ij}/x_* \right) \right), \quad \text{[39b]} \\
x_{ij+1} &= 1 + (1 - x_*) W_0 \left( -\frac{1 - x_{ij}}{1 - x_*} \right), \quad \text{[39c]}
\end{align*}
\]

Note that \( x_{ij} \) and \( \overline{y}_{0j} \) are the final fraction susceptible (i.e., when the pathogen has gone extinct) and maximal fraction infectious, respectively, for the SIR model without vital dynamics (\( \epsilon = 0 \)) with initial condition \( x_{ij,0} \).

The Domain of Applicability of the Approximation (Eq. 19) to \( x_{in} \). The refined trajectory approximation that yields Eq. 19 is derived in ref. 34 under the assumption that \( R_0 \) is large. Despite this, we find that the approximation to \( x_{in} \) obtained from it (Eq. 19) performs very well for all but values of \( R_0 \) very close to 1 or very large values of \( \epsilon > 0 \) (Fig. 3). In particular, \( W_0(\epsilon) \) is undefined for \( \epsilon < -\epsilon^{-1} \), so we must have

\[
-\epsilon^{-1} \leq x_{in} \leq 1.
\]

or, expanding and rearranging using Eq. 8,

\[
\epsilon < 1 - \ln \frac{R_0}{R_0 - 1} + x_* \ln x_*.
\]

Alternatively, we can find an approximate lower bound for \( R_0 \),

\[
R_0 > \epsilon^{2x},
\]

by observing that for any \( x \geq 1 \), \( 1 - \ln x \leq 1 \). To derive this latter inequality, note that both sides approach a limit of 0 as \( x \to 1 \), whereas

\[
\frac{d}{dx} \left( 1 - \ln x \right) = \frac{1}{x - 1} < \frac{1}{x - 1/2} \leq 0.
\]

Again, \( \ln x - \frac{x^2 - 1}{2x} \) vanishes at \( x = 1 \), whereas

\[
\frac{d}{dx} \left( \ln x - \frac{x^2 - 1}{2x} \right) = -\frac{2x^2 - 1}{2x} \leq 0,
\]

so \( \ln x - \frac{x^2 - 1}{2x} \leq 0 \) for \( x > 1 \), and thus

\[
\frac{d}{dx} \left( 1 - \ln x + \frac{1}{2} \ln x \right) \leq 0,
\]

proving the desired inequality.

Boundary Layer Independent Estimates. Thus far, we have computed the burnout probability via a specific, but arbitrary choice of boundary \( x_* \) and explicit solutions for \( x_{in} \), the fraction susceptible when first entering the boundary layer under the ODE approximation (Eq. 5). Here, we consider an alternative approach, using results from refs. 34 and 59 to implicitly characterize \( x_{in} \). In conjunction with Eq. 35, this allows us at the cost of a small loss of precision—to give expressions for the extinction and persistence probabilities that are independent of the precise choice of threshold, provided the threshold is \( \mathcal{O}(\epsilon) \). In addition to being of interest in and of themselves, we use them to compute the value of \( R_0 \) maximizing the burnout probability (the \( R_0 \) Maximizing the Probability of Burnout) and also to show how one derives the result of ref. 16 as an approximation to Eq. 24 (Boundary Layer Independent Estimates).

In refs. 34 and 59, we use the method of matched asymptotic expansions (60, 61) to derive analytical approximations to the phase-plane trajectories of the SIR model with vital dynamics, i.e., expressions \( Y(x) \) and \( X(y) \) expressing the density of infectious hosts as a function of the density of susceptible hosts and vice versa. In the boundary layer, we obtain lowest- and first-order approximations to \( Y(x) \): the lowest-order approximation (34) is

\[
Y(x) \approx W_0 \left( \frac{R_0}{e^x - 1} \right) e^{R_0(x-x_*)},
\]

whereas the refined estimate (59) is

\[
Y(x) \approx \left( \frac{x - x_*}{x_*} \right) \left( \frac{1 - x_*/x}{1 - x} \right) e^{R_0(x-x_*)}.
\]

Thus

\[
Y(x) \approx \left( \frac{x - x_*}{x_*} \right) \left( \frac{1 - x_*/x}{1 - x} \right) e^{R_0(x-x_*)},
\]

where

\[
x_i = -x_* W_0(-R_0 e^{-R_0}),
\]

is the final size of the SIR epidemic without vital dynamics (62) and

\[
\mathcal{X}_{x_i}(1) = \int_{x_i}^{1} \left( \frac{x - x_*}{x_*} \frac{1 - x_*/x}{1 - x} \right) e^{R_0(x-x_*)} \approx \left( \frac{x - x_*}{x_*} \frac{1 - x_*/x}{1 - x} \right) \left( \frac{1 - x}{x_*} \right).
\]

A very closely related expression (using \( \mu \) rather than \( \epsilon \) as the small parameter) is derived in ref. 16.

Recalling that, \( Y(x_{in}) = y_* \), evaluating either of Eq. 45 or 46 at \( x = x_{in} \) gives us a relation between \( x_{in}, x_i \), and \( y_* \). From the former (Eq. 45), we have

\[
\frac{1}{1 - x_{in}} \frac{R_0}{e^{x_{in}}} e^{-\frac{R_0}{x_{in}}} \approx y_*
\]

whereas the latter (Eq. 46) gives us

\[
\frac{1}{1 - x_{in}} \frac{R_0}{e^{x_{in}}} e^{-\frac{R_0}{x_{in}}} \approx y_*,
\]

Substituting Eq. 49 into the integrand in Eq. 35a and proceeding as above gives

\[
\mathcal{X}(x_{in}) \approx \frac{y_*}{y_0} \int_{x_{in}}^{1} \frac{R_0}{e^{x_{in}}} e^{-\frac{R_0}{x_{in}}} \frac{dx}{(1 - x)} = \frac{1}{y_*} \int_{x_{in}}^{1} \frac{R_0}{e^{x_{in}}} e^{-\frac{R_0}{x_{in}}} \frac{dx}{(1 - x)}
\]

\[
\times \left( \frac{R_0}{e^{x_{in}}} \right) \left( \frac{1 - x_{in}}{x_*} \right) = \frac{1}{y_*} \frac{R_0}{e^{x_{in}}} e^{-\frac{R_0}{x_{in}}} \frac{dx}{(1 - x)}.
\]

Set \( \zeta = \frac{R_0}{e^{x_{in}}} (1 - x) \). Then, \( \zeta \) (Eqs. 24b and 24c) and \( \zeta = \frac{R_0}{e^{x_{in}}} (1 - x) \) are fixed, while as \( \epsilon \to 0, a \to \infty \) and \( g(a, z) \sim \Gamma(a) - 2^{a-2} \Gamma(a) - 2^{a-2} \) (see ref. 36, §8.11.6) and similarly for \( g(a, z) \). Thus

\[
\left( \frac{2}{z} \right)^a 2^{a-z} \Gamma(a) - \Gamma(a, z) \sim \left( \frac{2}{z} \right)^a 2^{a-z} - 1.
\]
and the error in replacing $x_{in}$ by $x_j$ in the incomplete gamma function in Eq. 51b is equal to
\[ \frac{1}{x_j} \frac{x_j - x_{in}}{1 - x_j} \left( \frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}} - \frac{\gamma(1; x_{in})}{x_{in}} \right) \]
\[ = \frac{1}{x_j} e^{\gamma(1; x_j - x_{in})} \left( \frac{1 - x_j}{x_{in}} \right) \ln \left( \frac{1 - x_j}{x_{in}} \right) \]
\[ = \frac{1}{x_j} e^{\gamma(1; x_j - x_{in})} \left( \frac{1 - x_j}{x_{in}} \right) \ln \left( \frac{1 - x_j}{x_{in}} \right) \]
\[ \approx \frac{1}{x_j} e^{\gamma(1; x_j - x_{in})} \left( \frac{1 - x_j}{x_{in}} \right) \ln \left( \frac{1 - x_j}{x_{in}} \right) \]
\[ \approx e^{-n(1-x_j)} \left( \frac{1}{\sqrt{2\pi \sigma^2}} \right) e^{-\left( z^2 - \frac{1}{4} \right)} \frac{1}{x_j} \left( x_{in} - x \right)^{\frac{3}{2}} \gamma \left( a, z \right) \]

Both $x_{in} - x_j$ and $x_j - x_{in}$ are $O(\epsilon)$, whereas $\frac{x_j - x_{in}}{1 - x_j}$ is $O(1)$, so this error is $O(1)$. Thus, in absolute terms, the error is not small. However, as we observed above, $I(x_{in})$ is exponentially large in $e^{-1}$, so the error is negligible relative to this leading term (indeed, replacing the incomplete gamma function by $\Gamma \left( \frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}} \right)$ produces a similarly negligible error). We can also replace $x_{in}$ by $x_j$ in the Laplace approximation with negligible error:
\[ I(x_{in}) \approx I(x_j) \approx \frac{1}{\epsilon (1 - x_j)} \left( \frac{1 - x_{in}}{\epsilon (x_{in} - 1)} \right) e^{-z^2} \]

Similarly, repeating the same argument using the higher-order expression, Eq. 50, gives
\[ I(x_{in}) \approx \frac{1}{\epsilon (1 - x_j)} \left( \frac{1 - x_{in}}{\epsilon (x_{in} - 1)} \right) e^{-z^2} \]
\[ \times e^{z \left( \gamma(1; x_j - x_{in}) \right)} \]
\[ \approx \frac{1}{\epsilon (1 - x_j)} \left( \frac{1 - x_{in}}{\epsilon (x_{in} - 1)} \right) e^{-z^2} \]
\[ \times e^{z \left( \gamma(1; x_j - x_{in}) \right)} \]

Now, we recall from Eqs. 14 and 22 that the burnout probability is
\[ q(x_{in})^{\gamma(1; x_j - x_{in})} = \left( 1 + \frac{1}{I(x_{in})} \right)^{-\gamma(1; x_j - x_{in})} \]
\[ = e^{-\gamma(1; x_j - x_{in}) \ln \left( 1 + \frac{1}{I(x_{in})} \right)} \]
\[ = e^{-\gamma(1; x_j - x_{in}) \ln \left( 1 + \frac{1}{\frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}}} \right)} \]
\[ \approx e^{-\gamma(1; x_j - x_{in}) \ln \left( 1 + \frac{1}{\frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}}} \right)} \]

Above, we showed that $I(x_{in})$ is exponentially large in $e^{-1}$ as $\epsilon \to 0$ and, thus, that the error in making the last approximation (Eq. 56c) is exponentially small. Substituting any of the expressions Eq. 51b, 54, 55a, or 55b for $I(x_{in})$ in Eq. 56c, we see that the factors $y_j$ cancel, giving us an approximate expression for the burnout probability that does not depend on the specific choice of threshold, only upon its order of magnitude, $\epsilon$:
\[ q(x_{in})^{\gamma(1; x_j - x_{in})} \approx e^{-\frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}} \ln \left( 1 + \frac{1}{\frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}}} \right)} \]
\[ \approx e^{-\gamma(1; x_j - x_{in}) \ln \left( 1 + \frac{1}{\frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}}} \right)} \]

or
\[ q(x_{in})^{\gamma(1; x_j - x_{in})} \approx \exp \left[ -\frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}} \ln \left( 1 + \frac{1}{\frac{\gamma(1; x_j - x_{in})}{x_j - x_{in}}} \right) \right] \]

The $R_0$ Maximizing the Probability of Burnout. Using the simplified expression for the burnout probability (Eq. 57b), we can obtain an approximation to the value of $R_0$ that maximizes the probability of burnout linear in $n$ which is highly accurate across the range of values of $\epsilon$ for which the burnout probability is non-monotone. Eq. 57b is minimized when
\[ \frac{1}{\epsilon} \left[ \ln \left( \frac{R_0 + W_0 - R_0 e^{-R_0}}{\sqrt{R_0}} \right) \right] - \frac{1}{R_0} \]
\[ + \frac{\ln R_0}{2} \left( \frac{R_0 + W_0 - R_0 e^{-R_0}}{\sqrt{R_0}} \right) + \frac{1}{2 R_0^2} \left[ \ln R_0 \right] = 0. \]

An analytical closed-form solution does not appear to exist, but one can use a formal asymptotic series expansion $R_0 = \sum_{j=0}^{\infty} \epsilon^j$ to obtain a polynomial approximation in $\epsilon$ to arbitrarily large degree (here, we content ourselves with a linear approximation). Substituting this series into Eq. 60 and collecting terms of order $\epsilon^{-1}$ and order one, we obtain
\[ \ln \left( \frac{R_0 + W_0 - R_0 e^{-R_0}}{\sqrt{R_0}} \right) - \frac{1}{R_0} \]
\[ + \frac{1}{2 R_0^2} \left[ \ln R_0 \right] = 0. \]

We may solve Eq. 61 by Newton iteration to find the unique root $R_0 = 2.572692848$, which we use to solve Eq. 62 to find $I_1 = -27.71866282$ giving us the linear approximation
\[ \text{arg max } q(x_{in})^{\gamma(1; x_j - x_{in})} \approx 2.572692848 - 27.71866282 \epsilon. \]

We compare this linear approximation to the numerically determined minimum in Fig. 5.

The Burnout Probability is a Decreasing Function of $\epsilon$. In what follows, we show that $\frac{\partial q(x_{in})}{\partial \epsilon} \leq 0$, from which we conclude that $q(x_{in})$ is decreasing as $\epsilon$ increases, for all values of $R_0$. Using Eq. 24, we have
\[ \frac{\partial q(x_{in})}{\partial \epsilon} = -q(x_{in})^2 \left( \frac{1}{\epsilon} + \frac{\partial}{\partial \epsilon} \left( \frac{1}{\epsilon} \right) \right) \]
\[ = -q(x_{in})^2 \left( \frac{1}{\epsilon^2} \frac{\partial}{\partial \epsilon} \left( \frac{1}{\epsilon} \right) \right) \]

The first term in the large brackets on the right-hand side is always positive, so the result follows if one can show that $\epsilon^2 \frac{\partial}{\partial \epsilon} \left( \frac{1}{\epsilon} \right) \leq 0$. Applying the chain rule gives
\[ \epsilon \frac{\partial}{\partial \epsilon} \left( \frac{1}{\epsilon} \right) \leq 0 \]

respectively.

Remark 2: If in Eq. 58a we approximate $g(a, x')$ by $\Gamma(a)$ (i.e., if we approximate the integral up to $x' \gg 1$ by the integral over the whole real line, introducing an error of $O(\epsilon)$), we obtain an expression for the burnout probability equivalent to that from ref. 16 (up to minor differences resulting from using different small parameters, $\mu$ and $\epsilon$).
Then, the law of large numbers (67, §6) tells us that
\[
\lim_{m \to \infty} \frac{1}{m} \sum_{i=1}^{m} I_i = \mathbb{E}[I_1] = q.
\]

Thus, provided
\[
\frac{\partial}{\partial a}[e^{z^{-2}g(a,z)}] \approx \frac{\partial}{\partial z}[e^{z^{-2}g(a,z)}] - a \frac{\partial}{\partial a}[e^{z^{-2}g(a,z)}],
\]
Recalling that
\[
g(a,z) = \frac{f(t) e^{-a t}}{z} - \ell_d,\]
and
\[
\frac{\partial}{\partial x}[e^{z^{-2}g(a,z)}] = \frac{\partial}{\partial z}[e^{z^{-2}g(a,z)}] - z \frac{\partial}{\partial x}[e^{z^{-2}g(a,z)}],
\]
Integrating by parts in the rightmost term, this becomes
\[
\left(1 + R_0 \frac{\partial x}{\partial x}(a,t)\right) \frac{\partial}{\partial z}[e^{z^{-2}g(a,z)}] - \frac{\partial}{\partial x}[e^{z^{-2}g(a,z)}] - z \frac{\partial}{\partial x}[e^{z^{-2}g(a,z)}] - \frac{\partial}{\partial z}[e^{z^{-2}g(a,z)}] = 0.
\]

Now, \(g(a,z) \geq 0\), whereas \(\frac{\partial}{\partial x}[e^{z^{-2}g(a,z)}] \leq 0\), since \(x_n < x^*\), so \(1 - \frac{z}{a} \geq 0\) and, since \(g(a,z)\) is an increasing function of \(z\), we have
\[
\int_0^z \frac{\partial}{\partial z}[e^{z^{-2}g(a,z)}] \frac{\partial}{\partial x}[e^{z^{-2}g(a,z)}] \frac{\partial}{\partial z}[e^{z^{-2}g(a,z)}] \geq 0.
\]

Finally, from Eq. 19, we see that
\[
\frac{\partial}{\partial x}(a,t) = \lim_{\varepsilon \to 0} \varepsilon R_0 \sum_{x=1}^m \mathbb{E} \left[ R_0 \sum_{x=1}^m \mathbb{E} \left[ \frac{1}{x} \frac{\partial}{\partial z}[e^{z^{-2}g(a,z)}] \right] \right] \geq 0,
\]
since \(x^* \leq x_0\) and \(E(x)\) is a decreasing function of \(x\).

Simulations.

Stochastic simulation algorithm. Exact realizations of the stochastic SIR model (Fig. 2 and Table 1) can be obtained using the standard Gillespie algorithm (63, 64). If we denote the various event rates \(a_i\) (e.g., \(a_1 = \mu\), etc.), then the total event rate is \(a = \sum_{i=1}^k a_i\). The time to the next event is drawn from an exponential distribution with mean \(1/a_i\), and the event is taken to be of type \(i\) with probability \(a_i/a\). This algorithm scales with expected population size \(n\) and is prohibitively slow when running large numbers of simulations with \(n \geq 10^5\).

We therefore used the adaptive \(r\)-leaping approximation (65), as implemented in the adaptvetar R package (66). The key idea in this approach is to identify, at any point of the simulation, a time \(r\) over which the various event rates can be considered approximately constant, and then determine the number of events of each type that can be expected over this time interval. We then "leap forward" by time \(r\) rather than treating events individually.

Estimating the Required Number of Simulations. To determine the number of simulations required to estimate the epidemic burnout probability to a given accuracy, we use the central limit theorem. Suppose we run \(m\) independent simulations. Let
\[
I_i = \begin{cases} 1 & \text{if the } i\text{th simulation ends in burnout,} \\ 0 & \text{otherwise.} \end{cases}
\]

Then, the law of large numbers (67, §6) tells us that
\[
\lim_{m \to \infty} \frac{1}{m} \sum_{i=1}^m I_i = \mathbb{E}[I_1] = q.
\]
Data, Materials, and Software Availability. All study data are included in the main text. Our open-source R package, which we used to create our figures, is available at https://github.com/daviedearn/burnout (68).

ACKNOWLEDGMENTS. This project was partially supported by the CNRS International Emerging Actions (IEA) grant "Structured Populations, Epidemics, and Control Strategies (SPECs)." D.J.D.E., J.D., and B.M.B. were supported by the Natural Sciences and Engineering Research Council of Canada (NSERC).

We thank David Champredon, Michelle deJonge, Sarah Drohan, Karsten Hempel, Chai Molina, Irena Papst, and Dora Rosati for their contributions to the preliminary work that led to ref. 38.

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