

Interplay of generation time and spatial structure in epidemic dynamics and the reliability of reproduction ratio estimates

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(Received 12 September 2025; accepted 11 December 2025; published 9 February 2026)

The reproduction ratio R is a central metric for monitoring infectious disease epidemics and guiding public health interventions. It is typically inferred from population-level surveillance data, but such estimates can be biased by the spatial structure of the underlying population and by complexities in disease natural history. Here, we develop a theoretical framework to study how the distribution of the generation time (the time from primary to secondary infection) interacts with spatial network structure of the host population, to shape epidemic dynamics and the accuracy of R estimates. We show that the mean and dispersion of the generation time determine the contribution of subdominant epidemic modes, controlling the rate at which the system converges to its spatial equilibrium. Overdispersed generation times slow convergence near the epidemic threshold, whereas underdispersed distributions, common for respiratory pathogens, can markedly delay convergence at moderate and high transmissibility, producing long-lived biases in R . We evaluate the performance of an existing correction to incidence data that removes bias from spatial structure under simplified dynamical conditions. We demonstrate that it remains valid for arbitrary generation time distributions only if both mean and dispersion are accurately specified. Otherwise, substantial residual errors persist, especially when R is above the threshold. We extend the framework to short-lived perturbations, both exogenous (e.g., extreme weather, mass gatherings, and mobility restrictions) and endogenous (e.g., behavioral changes), and show that realistic dispersions can amplify their impact on spatial distributions and prolong bias on R far beyond the perturbation. We illustrate these mechanisms through a case study of a respiratory pathogen in Spain, using colocation-based mobility data, and identify the conditions under which surveillance-derived R is reliable and when precise measurements of the generation time distribution are critical.

DOI: [10.1103/32b8-x9z5](https://doi.org/10.1103/32b8-x9z5)

I. INTRODUCTION

The reproduction ratio R is a widely used indicator for monitoring the evolution of an infectious disease epidemic [1,2]. It quantifies the average number of secondary infections generated by one infected individual over the course of the infection. Estimates of the reproduction ratio underpin public health decisions and interventions, as they allow authorities to assess pathogen circulation and compare alternative scenarios [3–5].

The reproduction ratio is inferred, across a wide range of diseases and epidemics [5–9], from population-level data coming from epidemiological surveillance, such as incident cases, healthcare access (e.g., hospitalizations), or severe outcomes [10–12]. Such estimates, however, are sensitive both to the underlying epidemic dynamics and to the accuracy of the available data and of the measurements that are made on those data. Specifically, the reliability of the estimated value of R

is known to depend on the underlying parametrization of the distribution of the generation time [10,13,14]. The generation time is the time between the infection of an index case and the time at which that case infects someone else. The generation time, and its empirical distribution, is, too, typically inferred from epidemiological data [15–17]. Different diseases exhibit different generation time distributions, and even under similar epidemic conditions, these differences can lead to substantially different reproduction ratio estimates [18]. At the same time, in a recent study we showed that the estimates of R obtained through statistical inference on surveillance data are biased if one does not properly account for the spatial structure of the host population on which the disease spread [19]. This is due to the complex network structures describing contacts and emerging from host demographic, behavioral, and mobility patterns within and across spatial communities [20–25].

Available theoretical methods for estimating R from surveillance, however, either control for the heterogeneity in the generation time in spatially homogeneous populations [10] or address the complexity of the spatial structure but assume a fixed generation time [19]. The interplay between the two components, however, becomes relevant especially when changes in behavior (and so in the structure of contacts) occur, affecting the estimation of R [26,27]. Here, we study the interaction between these two aspects and analytically

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determine when they can be treated separately, and when instead their complex interplay has a nontrivial effect on epidemic dynamics and consequently the estimate of the reproduction ratio. Finally, we use the developed theory to study the effects of temporally localized perturbations on spatial epidemics dynamics and their effect on the estimate of epidemic trends. This applies to commonly observed phenomena such as extreme weather and natural disasters [28–31], public health interventions such as mobility restrictions [32–34], and seasonal patterns such as holidays [35,36].

II. THEORETICAL FORMALISM

We consider a population made of N distinct spatial communities. Let $I_i(t)$ be the number of incident (new) infections occurring among residents of community i during an infinitesimal time interval centered in t . Then, let ζ be the probability density function of the generation time: $\zeta(t) \geq 0$ and $\int_0^\infty dt \zeta(t) = 1$. $\mathbf{R}$ is the $N \times N$ reproduction operator as defined in Ref. [19]. This operator is similar to the well-known next-generation matrix [24,37,38] and encodes the transmission potential of the disease within and between communities. Specifically, R_{ij} is the expected number of secondary infections that a resident of j generates over the course of their infectious period among residents of i . The reproduction ratio of the system, called *reference* reproduction ratio henceforth following the nomenclature of Ref. [19], is then the largest eigenvalue of $R_{\text{ref}} = \rho[\mathbf{R}]$ [39,40], where $\rho[\cdot]$ is the spectral radius of the operator. This value is real and positive because $\mathbf{R}$ is non-negative and can be assumed irreducible [19]. Then, the evolution of the number of infections obeys the following Volterra integral equation:

$$I_i(t) = J_i(t) + \sum_j R_{ij} \int_0^t ds \zeta(t-s) I_j(s), \quad (1)$$

where $J_i(t)$ is a source term accounting for importation and exportation of infections from outside of the system. This modeling approach has been widely used [1,41–43] and offers the advantage of being able to consider completely general generation time distributions. It discounts, however, stochastic fluctuations and assumes that $\mathbf{R}$ remains approximately constant during the period in which we study the epidemic: This is a reasonable assumption if we are in the early phase of an epidemic when no acquired immunity or major public health interventions have been put in place (see Appendix G). It is also reasonable whenever the timescale of observation is shorter than typical timescales such as seasonality, vital dynamics, and immunity buildup and waning [19,44].

III. EVOLUTION OF THE DYNAMICS

Equation (1) admits the following as a general solution [45]:

$$\mathbf{I}(t) = \int_0^t ds \mathbf{G}(t-s) \mathbf{J}(s), \quad (2)$$

which we wrote in vector notation where $\mathbf{I}$ is simply the vector with I_i as components. The operator $\mathbf{G}(t)$ is the system

Green's function that solves the following equation:

$$\mathbf{G}(t) = \delta(t) + \mathbf{R} \int_0^t ds \zeta(t-s) \mathbf{G}(s). \quad (3)$$

Equation (3) admits a formal solution in Laplace space [46]:

$$\hat{\mathbf{G}}(a) = [1 - \hat{\zeta}(a) \mathbf{R}]^{-1}, \quad (4)$$

where $\hat{\cdot}$ denotes the Laplace transform and a the variable in the Laplace space. It can be written in the basis of eigenvectors of $\mathbf{R}$:

$$\hat{\mathbf{G}}(a) = \frac{1}{1 - \hat{\zeta}(a) R_{\text{ref}}} \mathbf{v} \mathbf{v}^* + \sum_{\beta} \frac{1}{1 - \hat{\zeta}(a) \Lambda_{\beta}} \mathbf{w}_{\beta} \mathbf{w}_{\beta}^*, \quad (5)$$

where $\mathbf{v}$ is the (right) Perron eigenvector associated with R_{ref} , $\mathbf{v}^*$ the corresponding covector in the conjugate base (left eigenvector), Λ_{β} are the other $N-1$ eigenvalues of $\mathbf{R}$ (repeated according to their multiplicities), and $\mathbf{w}_{\beta}$, $\mathbf{w}_{\beta}^*$ the corresponding eigenvectors and their conjugates. Vectors are normalized so that $\sum_i v_i = 1$, $\mathbf{v}^* \mathbf{v} = 1$, $\mathbf{v}^* \mathbf{w}_{\beta} = \mathbf{w}_{\beta}^* \mathbf{v} = 0$, and $\mathbf{w}_{\alpha}^* \mathbf{w}_{\beta} = \delta_{\alpha\beta}$. We can determine the evolution in time of $\mathbf{G}(t)$ from the singularities of $\hat{\mathbf{G}}(a)$ in Eq. (5). Asymptotically, at large time it will evolve as $\mathbf{G}(t) \sim e^{\Gamma_{\text{ref}} t} \mathbf{v} \mathbf{v}^*$ where Γ_{ref} is the solution of $\hat{\zeta}(a) R_{\text{ref}} = 1$ with largest real part (it will be itself real and positive); see Appendix A for details on the large-time evolution. This fact is a generalization of the link between the basic reproduction ratio and the epidemic growth rate, which is well known in the context of populations without spatial structure [10]. At shorter times, other modes will contribute too. Some come from other possible solutions of $\hat{\zeta}(a) R_{\text{ref}} = 1$, other from the subdominant modes of the spectral decomposition of $\mathbf{R}$: They are in the form $e^{t \Re \Gamma_{\beta}} \mathbf{w}_{\beta} \mathbf{w}_{\beta}^*$ where Γ_{β} is a solution of $\hat{\zeta}(a) \Lambda_{\beta} = 1$.

These considerations confirm, on the one hand, that in the large-time limit the spatial distribution of infections will reach an equilibrium distribution corresponding to $\mathbf{v}$, which was previously proven by assuming a constant generation time [19]. On the other hand, they show that the specific generation time distribution may strongly affect both the pathway and the rate at which the epidemic converges to that equilibrium distribution, by altering the relative rates of decay of the subdominant modes with respect to the leading one—which in turn determine our ability to estimate R_{ref} from surveillance.

IV. ESTIMATING THE REPRODUCTION RATIO FROM SURVEILLANCE DATA

As a first step, we study how the generation time distribution combined with the spatial network structure affects the estimate of the reproduction ratio. We define $I_{\text{tot}}(t) = \sum_i I_i(t)$ as the total incidence of infections and we also define the corrected incidence $I_{\text{corr}}(t) = \sum_i v_i^* I_i(t)$, as it was introduced in Ref. [19], to remove the bias on the estimate of the reproduction ratio induced by the spatial structure when the generation time was assumed constant. Furthermore, we introduce $J_{\text{tot}}(t) = \sum_i J_i(t)$ as the total source term and J_{corr} the corrected source term. The latter is $J_{\text{corr}}(t) = \sum_i v_i^* J_i(t)$ only if the source is perfectly known. We also introduce ζ_{estim} as the estimated generation time distribution, which is the one specified when estimating R_{ref} . The generation time

distribution may be correctly specified ($\zeta_{\text{estim}} = \zeta$) or not, if the estimated mean and/or dispersion do not match the true values. It is typically the parametrization of the generation time that is available either from similar epidemic contexts or as a best estimate on available data. We call $R_{\text{estim}}(t)$ and $R_{\text{corr}}(t)$ the reproduction ratios estimated from I_{tot} and I_{corr} , respectively. The former [$R_{\text{estim}}(t)$] is the surveillance-based reproduction ratio as customarily estimated by public health authorities without correcting from the spatial structure. Within our framework, they should instantly solve the following effective equations:

$$I_{\text{tot}}(t) = J_{\text{tot}}(t) + R_{\text{estim}}(t) \int_0^t ds \zeta_{\text{estim}}(t-s) I_{\text{tot}}(s), \quad (6)$$

$$I_{\text{corr}}(t) = J_{\text{corr}}(t) + R_{\text{corr}}(t) \int_0^t ds \zeta_{\text{estim}}(t-s) I_{\text{corr}}(s). \quad (7)$$

A. When the generation time is correctly specified

First, we will consider the case when the generation time and its distribution are accurately estimated and specified: $\zeta_{\text{estim}} = \zeta$. Applying $\mathbf{v}^*$ on both sides of Eq. (1), one gets

$$I_{\text{corr}}(t) = \mathbf{v}^* \mathbf{J}(t) + R_{\text{ref}} \int_0^t ds \zeta(t-s) I_{\text{corr}}(s). \quad (8)$$

Combining it with Eq. (7), one gets

$$R_{\text{corr}}(t) = R_{\text{ref}} + \frac{\mathbf{v}^* \mathbf{J}(t) - J_{\text{corr}}(t)}{\int_0^t ds \zeta(t-s) I_{\text{corr}}(s)}. \quad (9)$$

If importation and exportation of cases are perfectly known, then $R_{\text{corr}}(t) = R_{\text{ref}}$ at all times: The corrected incidence introduced in Ref. [19] correctly removes the bias induced by the spatial structure. If the latter condition does not hold, then importation and exportation will bias the estimate of the reproduction ratio with a factor proportional to the projection of the real source term $\mathbf{J}$ onto the equilibrium spatial distribution minus the assumed corrected source term. Nonetheless, this bias decays with time and $R_{\text{corr}}(t)$ will converge to R_{ref} even if the source is misspecified. However, the equilibrium distribution $\mathbf{v}^*$ often concentrates in densely populated communities (cities), which are also typically transportation hubs (and thus importation/exportation hubs). This may enhance the bias coming from source misspecification at the start of the epidemic (see Appendix G), when $\mathbf{v}^* \mathbf{J}$ may be comparable in magnitude to the incidence of internally generated infections [47–49].

To study the behavior of R_{estim} , we adopt the common approach of modeling the generation time distribution with a gamma distribution, parametrized in terms of its mean value τ , representing the average generation time, and the shape parameter k tuning the dispersion around the mean. $k = 1$ is an exponential distribution, with variance equal to the mean squared. An exponentially distributed generation time is common to the simplest compartmental models such as the Susceptible-Infectious-Susceptible (SIS) or the Susceptible-Infectious-Recovered (SIR). Values of $k > 1$ give distributions that are underdispersed with respect to the exponential distribution (variance smaller than τ^2), while $k < 1$ are overdispersed (variance larger than τ^2) and have broader tails than the exponential. More on this parametrization is available

in Appendix B. Estimates from observational data often lead to underdispersed distribution ($k > 1$): Figures 1(a) and 1(c) show the generation time distribution of COVID-19 (original strain in 2020) and pandemic H1N1 influenza from 2009, as estimated in Refs. [50,51], compared to alternative dispersion (k) values. Cases of overdispersed generation times, albeit rarer, have also been reported [52].

Using the Laplace transform (see Appendix B), we can establish the time evolution of $\mathbf{G}(t)$ through the exponential growth rates coming from each eigenmode of the spatial network $\mathbf{v}$, $\mathbf{w}_\beta$:

$$\Gamma_{\text{ref},m} = \frac{k}{\tau} (R_{\text{ref}}^{1/k} e^{i \frac{2\pi m}{k}} - 1), \quad (10)$$

$$\Gamma_{\beta,m} = \frac{k}{\tau} (|\Lambda_\beta|^{1/k} e^{i \frac{\arg \Lambda_\beta + 2\pi m}{k}} - 1), \quad (11)$$

where we have specified $\arg \Lambda_\beta$ to account for the fact that some eigenvalues of $\mathbf{R}$ may be negative or nonreal [19]. Appendix B proves that, for each mode, m runs over a finite set of indices, being $\{0, 1, \dots, k-1\}$ if $k \in \mathbb{N}$ or one subset of it if not. It also proves that the full dynamical evolution can be written as

$$\begin{aligned} \mathbf{G}(t) = & \frac{R_{\text{ref}}^{1/k}}{\tau} \left[\mathbf{v} \mathbf{v}^* \sum_m e^{i 2\pi m/k} e^{\Gamma_{\text{ref},m} t} + \sum_\beta |\lambda_\beta|^{1/k} \mathbf{w}_\beta \mathbf{w}_\beta^* \right. \\ & \times \sum_m e^{i(2\pi m + \arg \Lambda_\beta)/k} e^{\Gamma_{\beta,m} t} \left. \right] \\ & - \frac{\mathbf{R}^{-1}}{\tau} \frac{1}{\pi} k^{-k} \Gamma(1+k) \sin(\pi k) \left(\frac{t}{\tau} \right)^{-(1+k)} e^{-kt/\tau}. \end{aligned} \quad (12)$$

If $k \in \mathbb{N}$, Eq. (12) is exact and is the generalization to a spatially structured population of the series representation available in Ref. [43]. If $k \notin \mathbb{N}$, the last term is nonzero and is an additional contribution to each eigenmode, coming from the branch point of the generation time distribution. This contribution always decays in time (even above the epidemic threshold), and its weight is suppressed for underdispersed generation times ($k \gtrsim 2$). Nevertheless, it can become significant in the presence of very weak eigenmodes (small Λ_β) or for highly overdispersed generation times ($k \approx 1/2$). Further details on the computation of this and the other components of Eq. (12) are provided in Appendix B.

The term $\Gamma_{\text{ref},0} = \frac{k}{\tau} (R_{\text{ref}}^{1/k} - 1)$ dominates the asymptotic (large-time) dynamics of the system, and represents the well-known relationship between the reproduction ratio and the system asymptotic growth rate for a gamma-distributed generation time [10,43]. The limit $k = 1$ gives the familiar value of $\Gamma_{\text{ref},0} = (R_{\text{ref}} - 1)/\tau$ of the SIR and SIS models, and the limit $k \rightarrow \infty$ gives $\Gamma_{\text{ref},0} = \log R_{\text{ref}}/\tau$, which corresponds to the case of fixed generation time of Ref. [19]. The other modes $\Gamma_{\text{ref},m}$ and $\Gamma_{\beta,m}$ are subdominant and decay relative to $\Gamma_{\text{ref},0}$: The speed at which they decay determines the accuracy of R_{estim} [19]. This is because Eq. (12) describes the interaction between the spatial network linking the different communities and the generation time distribution in determining the epidemic dynamics and, as such, the accuracy in estimating the reproduction ratio. To study this dynamics, we can study

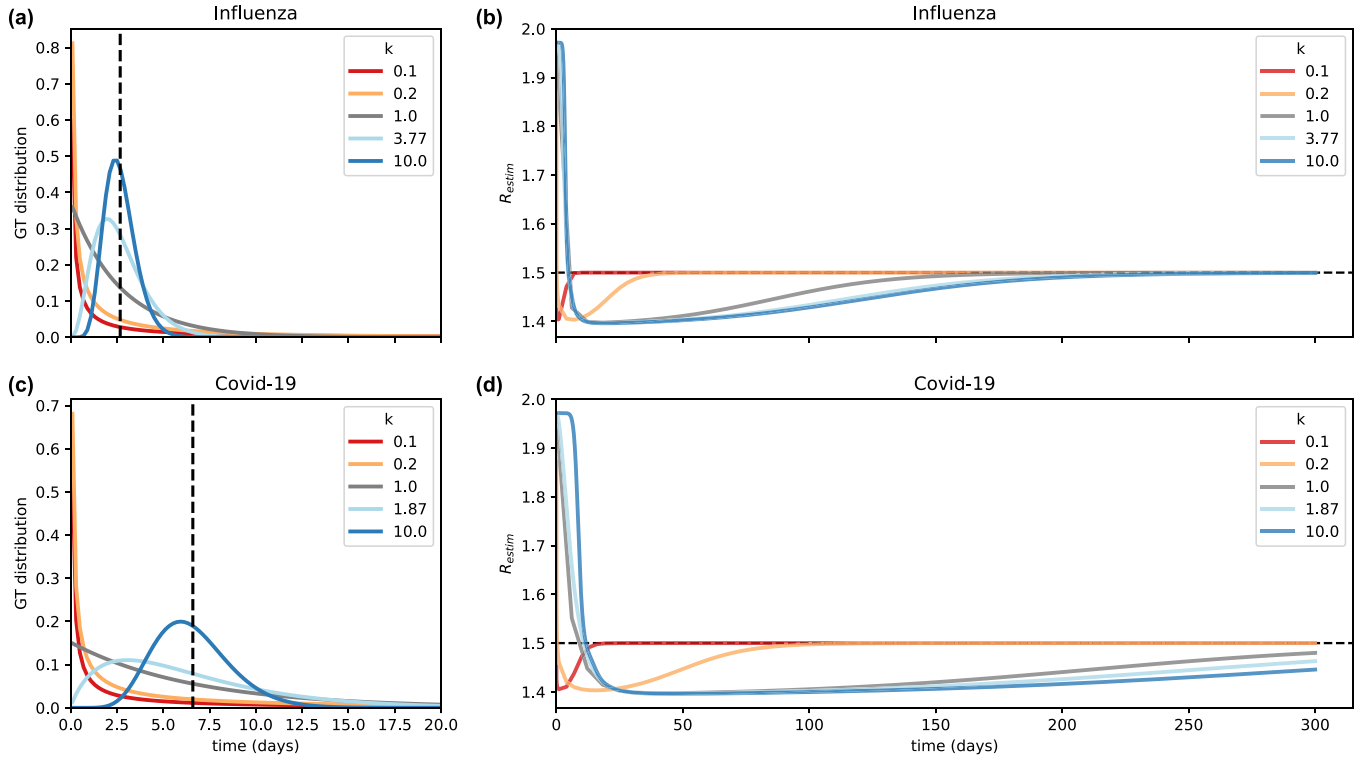


FIG. 1. In panels (a) and (c), a gamma distribution is shown with the mean (black dotted line) set to the estimated values for COVID-19 (original strain) [51] and the H1N1 influenza pandemic [50], respectively, while varying the shape parameter k . Panels (b) and (d) show the temporal evolution of R_{estim} , computed assuming a generation time distribution modeled as a gamma distribution with the same range of k values used, respectively, in panels (a) and (c). R_{ref} is represented as a dotted line.

the weight of each eigenmode and its speed of decay from Eq. (12). This shows that each subdominant eigenmode (barring the additional, k -suppressed one) of the spatial network contributes proportionally to $|\lambda_\beta|^{1/k}$ (where $\lambda_\beta = \Lambda_\beta/R_{\text{ref}}$), which is a growing function of k given that $|\lambda_\beta| < 1$. Two consequences follow. First, decreasing the dispersion of the generation time around its mean (i.e., increasing k) increases the weights of the subdominant spatial eigenmodes. Second, the relative difference between the weights of two distinct eigenmodes will also decrease as k grows, meaning that more eigenmodes may give a perceptible contribution to the epidemic evolution. Even more crucially, the generation time distribution impacts the rate at which the subdominant eigenmodes decay relative to the dominant one. To quantify this, we can compute the rates of this relative decay directly by subtracting the growth rate of each subdominant mode [Eq. (11)] from the growth rate of the dominant mode [Eq. (10)]. Specifically,

$$\begin{aligned} \delta_m &= \Gamma_{\text{ref},0} - \Re \Gamma_{\beta,m} \\ &= \frac{k}{\tau} R_{\text{ref}}^{1/k} \left[1 - |\lambda_\beta|^{1/k} \cos \left(\frac{\arg \Lambda_\beta + 2\pi m}{k} \right) \right]. \end{aligned} \quad (13)$$

Without loss of generality, we will consider now a generic

$$\delta = \frac{k}{\tau} R_{\text{ref}}^{1/k} (1 - \lambda^{1/k}), \quad (14)$$

thus assuming λ real and positive. If not, it suffices to correct it by the cosine in Eq. (13). Notice that Eq. (14) includes the

possible additional branching-point mode in Eq. (12) (when not suppressed by k), obtained simply by setting $\lambda = 0$. It is convenient to compute its limiting values:

$$\delta[k=1] = \frac{1}{\tau} R_{\text{ref}} (1 - \lambda), \quad (15)$$

$$\delta[k \rightarrow \infty] = \frac{1}{\tau} \log \frac{1}{\lambda}. \quad (16)$$

The first implication is that if the generation time has $k \approx 1$ (i.e., $\text{VAR}[\tau] \approx \tau^2$), then the subdominant eigenmodes will decay faster in more transmissible epidemics: The larger is R_{ref} , the faster R_{estim} converges to R_{ref} . Instead, when the dispersion of the generation time decreases (k increases) the decay rate of the modes no longer depends on the overall transmissibility of the disease [Eq. (16)]. Also, by imposing the condition $\delta[k \rightarrow \infty] < \delta[k=1]$ one finds a cutoff value

$$\lambda_{\text{cutoff}} = -\frac{W(-R_{\text{ref}} e^{-R_{\text{ref}}})}{R_{\text{ref}}}, \quad (17)$$

where W is the principal branch of the Lambert's $\mathcal{W}$ function: Increasing k will decrease the δ of the modes for which $\lambda > \lambda_{\text{cutoff}}$ (and thus increase the contribution of each eigenmode). It will instead decrease the contribution of those for which $\lambda < \lambda_{\text{cutoff}}$. Below the epidemic threshold ($R_{\text{ref}} < 1$), one has $\lambda_{\text{cutoff}} = 1$, meaning that underdispersed generation times (large k) will lead to faster convergence of R_{estim} to R_{ref} because all the modes are increasingly suppressed. Conversely, above the epidemic threshold, underdispersion will amplify

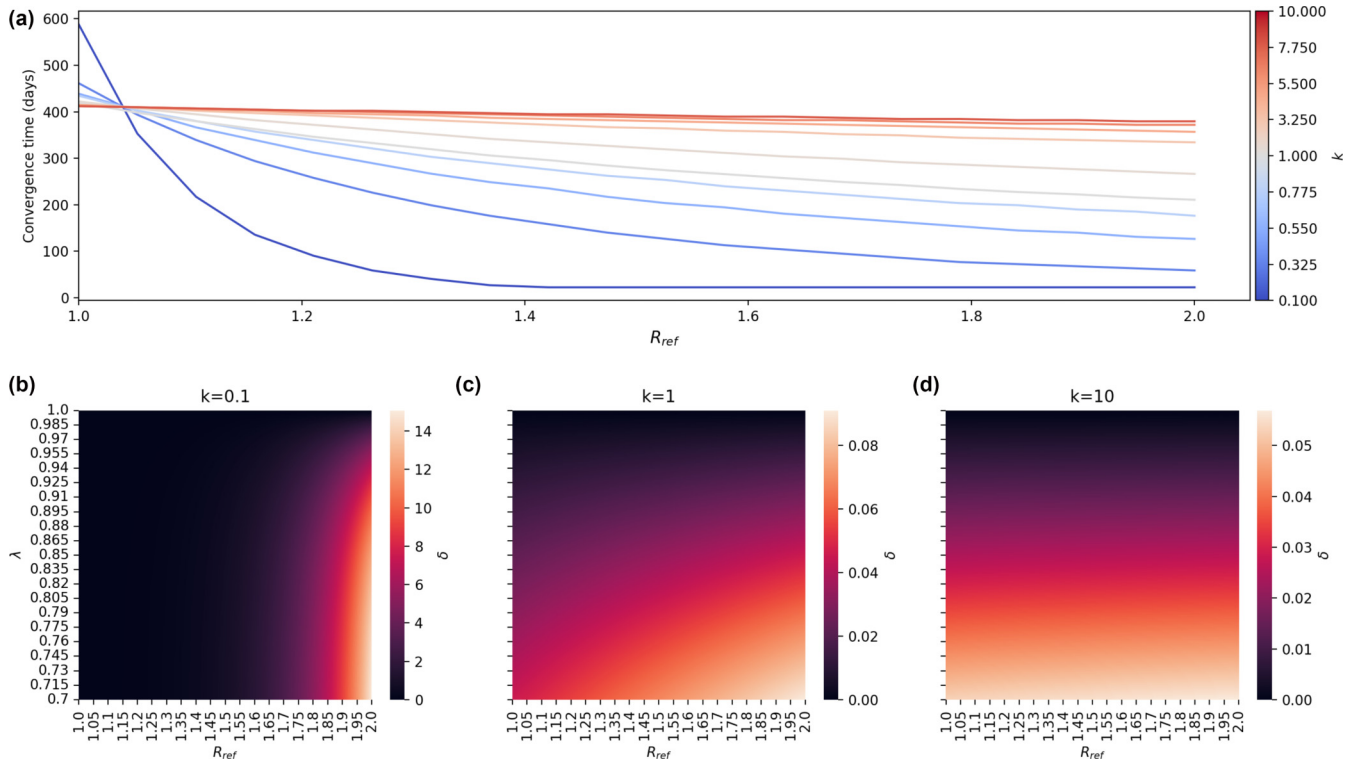


FIG. 2. In panel (a), the convergence time of R_{estim} toward R_{ref} is shown as a function of R_{ref} (see Appendix G and Fig. 7 for the convergence time plotted as a function of k). The generation time distribution is modeled as a gamma distribution with the mean set to the estimate for COVID-19 (original strain) [51] and varying shape parameter k . Panels (b)–(d) show heatmaps of the δ rate as a function of R_{ref} and the λ parameter for $k = 0.1$, $k = 1$, and $k = 10$, respectively.

the effect of many eigenmodes, as λ_{cutoff} is fairly small even for moderately big R_{ref} : for example, $\lambda_{\text{cutoff}} = 0.2$ for $R_{\text{ref}} = 2$. The behavior at small k (strong overdispersion) has an additional feature. $d\delta/dk$ is always negative close to $k = 0$ if $R_{\text{ref}} > 1$ so that very strong values of overdispersion will always decrease eigenmode contribution even if $\lambda < \lambda_{\text{cutoff}}$. Finally, the dispersion of the generation time can increase the number of relevant exponential terms for each eigenmode by interacting with the spatial network. Equation (13) shows that, when k is large, terms other than $m = 0$ can provide non-negligible contributions, as $\cos(2\pi/k)$ increases as k increases. Underdispersed generations thus further amplify the contribution of subdominant eigenmodes and slow the convergence of R_{estim} to R_{ref} , also increasing the number of relevant exponential terms, with increasing likelihood of seeing complex oscillatory behaviors of R_{estim} around R_{ref} .

To confirm and illustrate the effect of the distribution of the generation time on the dynamical convergence of the epidemic to its dominant eigenmode, we simulated the spread of a respiratory pathogen in Spain. We used Colocation Maps by Meta [53] to parametrize the operator $\mathbf{R}$ [19,29], identifying Spanish provinces as spatial communities. More details are available in Appendix D. Figures 1(b) and 1(d) compare the evolution in time of the value of the reproduction ratio estimated from surveillance (R_{estim}) and the reference value (R_{ref}) for two hypothetical epidemics started in Spain's capital Madrid. They were parametrized using COVID-19 (original strain) and pandemic H1N1, except for the dispersion parameter k that was explored, to show the previously discussed

slowdown of the convergence to R_{ref} due to an underdispersed generation time.

Figure 2 further explores the interaction between spatial dynamics and generation time. Specifically, Fig. 2(a) confirms the existence of the structural cutoff [Eq. (17)] by showing how the effect of k on the time of convergence to R_{ref} changes with the overall transmissibility, in the case of a COVID-19-like epidemic starting in Madrid. As R_{ref} is close to the epidemic threshold, convergence is faster for higher k values. However, as R_{ref} is slightly above the critical value, convergence slows down dramatically as k increases, as one or more subdominant modes in the Spanish network find themselves above λ_{cutoff} . The figure also confirms that at large k the time of convergence depends weakly on overall transmissibility [see Eq. (16)]. Figures 2(b)–2(d) explore the effect on time of convergence of a generic subdominant mode when it varies in magnitude. As $k = 1$ (exponential distribution), Fig. 2(c) shows the linear relationship between convergence and R_{ref} , λ found in Eq. (15). Figure 2(b) instead confirms that a highly overdispersed generation time [$k = 0.1$ in Fig. 2(b)] sharply flattens the contribution of all eigenmodes below λ_{cutoff} to zero dramatically slowing down convergence. However, as R_{ref} increases, those modes become larger than λ_{cutoff} and at that point their weight is sharply increased, abruptly decreasing convergence time. Here, convergence time is sensitive almost exclusively to R_{ref} , which determines—through λ_{cutoff} —whether the contribution of the subdominant modes is pushed toward zero or toward one. The situation is inverted in Fig. 2(d). When the generation time is underdispersed (large

k), we again see the effect of Eq. (16): The contribution of the subdominant modes does not depend on R_{ref} and the time of convergence is weakly sensitive to the overall transmissibility.

B. When the generation time is not correctly specified

We model this case by assuming that ζ_{estim} is a gamma distribution with mean τ_{estim} and k_{estim} that may be different from the “true” values τ, k . We will focus on R_{corr} , which we proved to be an unbiased estimator of R_{ref} if τ, k are correctly specified.

From Eq. (8), we can compute the scalar Green’s function for I_{corr} : $\hat{g}(a) = [1 - \hat{\zeta}(a)R_{\text{ref}}]^{-1}$, which is simply the component of Eq. (5) proportional to $\mathbf{v}$. Assuming, for simplicity, no source term beyond $t = 0$ [$J_{\text{corr}}(t) = \delta(t)j_0$], then

$$R_{\text{corr}}(t) = \frac{g(t)}{\int_0^t ds \zeta_{\text{estim}}(t-s)g(s)}. \quad (18)$$

The singularities of $\hat{g}(a)$ are those in Eq. (10), with each residue

$$\text{Res} \hat{g}|_{a=\Gamma_{\text{ref},m}} = -\frac{1}{R_{\text{ref}} \hat{\zeta}'(\Gamma_m)} = \frac{R_{\text{ref}}^{1/k}}{\tau} e^{i2\pi m/k}. \quad (19)$$

As in the case of the full Green’s function, we write

$$g(t) = \sum_m \frac{R_{\text{ref}}^{1/k}}{\tau} e^{i2\pi m/k} e^{\Gamma_m t} - \frac{1}{R_{\text{ref}} \tau} \sqrt{\frac{2}{\pi}} \sqrt{k} \times \sin(\pi k) e^{-k} \left(\frac{t}{\tau}\right)^{-(1+k)} e^{-kt/\tau},$$

where the second term accounts for the branch point discussed in Appendix B. Since this contribution, when present, always decays in time, we will neglect it in what follows. To estimate the denominator in Eq. (18), we first consider its Laplace transform: $\hat{\zeta}_{\text{estim}}(a)\hat{g}(a)$. We can neglect the singularities coming from the first factor $\hat{\zeta}_{\text{estim}}(a)$ as they decay fast: Their real part must be negative given that $\zeta_{\text{estim}}(t) \rightarrow 0$ as $t \rightarrow \infty$, being a probability density function. Therefore, the role of $\hat{\zeta}_{\text{estim}}$ is to correct the residues of the already considered singularities, giving the final formula

$$R_{\text{corr}}(t) = \frac{\sum_m e^{i2\pi m/k} e^{\Gamma_m t}}{\sum_m \hat{\zeta}_{\text{estim}}(\Gamma_m) e^{i2\pi m/k} e^{\Gamma_m t}}. \quad (20)$$

Note that when $k \in \mathbb{N}$ $\Gamma_m^* = \Gamma_{k-m}$ and $\Gamma_{k/2} \in \mathbb{R}$ when k is even, so that this expression is real. If $k \notin \mathbb{N}$, we know it to be an approximation so that residual imaginary terms may linger. As a safety check, one can set $\zeta_{\text{estim}} = \zeta$ in Eq. (20). Then, $\hat{\zeta}(\Gamma_m) = 1/R_{\text{ref}}$ by definition, so that $R_{\text{corr}}(t) = R_{\text{ref}}$ correctly at all time. When this is not the case, the combination of modes will bias the estimate of R_{ref} even when the incidence has been corrected by $\mathbf{v}^*$, with a possibly oscillating sign of the error (underestimation and overestimation of R_{ref}). However, most interesting is the asymptotic value of Eq. (20), when $t \rightarrow \infty$. There, only $m = 0$ counts, so that

$$R_{\text{corr}}(\infty) = \frac{1}{\hat{\zeta}_{\text{estim}}(\Gamma_0)} = \left[1 + \frac{\tau_{\text{estim}}}{\tau} \frac{k}{k_{\text{estim}}} (R_{\text{ref}}^{1/k} - 1) \right]^{k_{\text{estim}}}. \quad (21)$$

This value is generally different from R_{ref} , meaning that the bias coming from misestimating the generation time distribution does not decay to zero in time, unlike the one coming from neglecting or misestimating the spatial structure. This happens because unlike the structural bias that is self-correcting as the dynamics tends to the spatial equilibrium, the bias from the generation time is not. Its origin and magnitude, however, do vary according to dynamical parameters. Expanding Eq. (21) for $R_{\text{ref}} \approx 1$, i.e., when the epidemic is close to the epidemic threshold, gives the following:

$$R_{\text{corr}}(\infty) = R_{\text{ref}} + \left(\frac{\tau_{\text{estim}}}{\tau} - 1 \right) (R_{\text{ref}} - 1) + \mathcal{O}[(R_{\text{ref}} - 1)^2]. \quad (22)$$

This provides two important pieces of information: First, when the epidemic is close-to-critical ($R_{\text{ref}} \approx 1$), the error coming from misestimating the generation time is small regardless of the difference between τ and τ_{estim} , as it is suppressed linearly by the term $R_{\text{ref}} - 1$. Instead, at fixed R_{ref} , it grows linearly with the estimated mean generation time. Second, accurately knowing the average generation time is enough as Eq. (22) does not depend on k : This is notable because estimating the average generation time is easier than estimating its dispersion [54,55]. However, when R_{ref} is far from the critical point, Fig. 3 shows that knowing τ is not enough, and an accurate estimate of k is needed to ensure that R_{corr} measures R_{ref} .

Figure 4 shows the error made by estimating the reproduction ratio of one historical epidemic of respiratory pathogen, using the generation time parametrized from another epidemic. The magnitudes are substantial, and this is a problem because this is often done in the absence of reliable data [56,57].

V. PERTURBATIONS

We will now use the formalism developed so far to study the effect of a short-term change in the reproduction operator on the spatial dynamics, and on the estimate of the reproduction ratio. We assume that the system is governed for a long time by an unperturbed $\mathbf{R}$, so that the dynamics has evolved to the spatial equilibrium $\mathbf{v}$. Practically, this means that the system is prepared in the state $\mathbf{v}$ at $t = 0$. In the absence of perturbations, the spatial distribution of incident infections will remain $\mathbf{v}$ indefinitely. We wish to measure how much a perturbation changes the spatial distribution, and how long it takes for the system to revert back to $\mathbf{v}$ after the perturbation. This information is relevant because the distribution of infections describes the dynamics of the epidemic in space, and it impacts the ability of public health to correctly estimate epidemic evolution, as we have seen. Specifically, we will assume that the reproduction operator changes to $\mathbf{R}_p$ in the interval $t \in [0, t_p]$, and then reverts back to $\mathbf{R}$. This simplified system can model the effect of changes in the spatial mixing of communities due to exogenous perturbations: extreme weather [28–31], public health interventions such as mobility restrictions [33], and seasonal patterns such as holidays [35,36].

We identify the spectral structure of $\mathbf{R}_p$ with the subscript p , so that, for instance, its reference reproduction ratio and

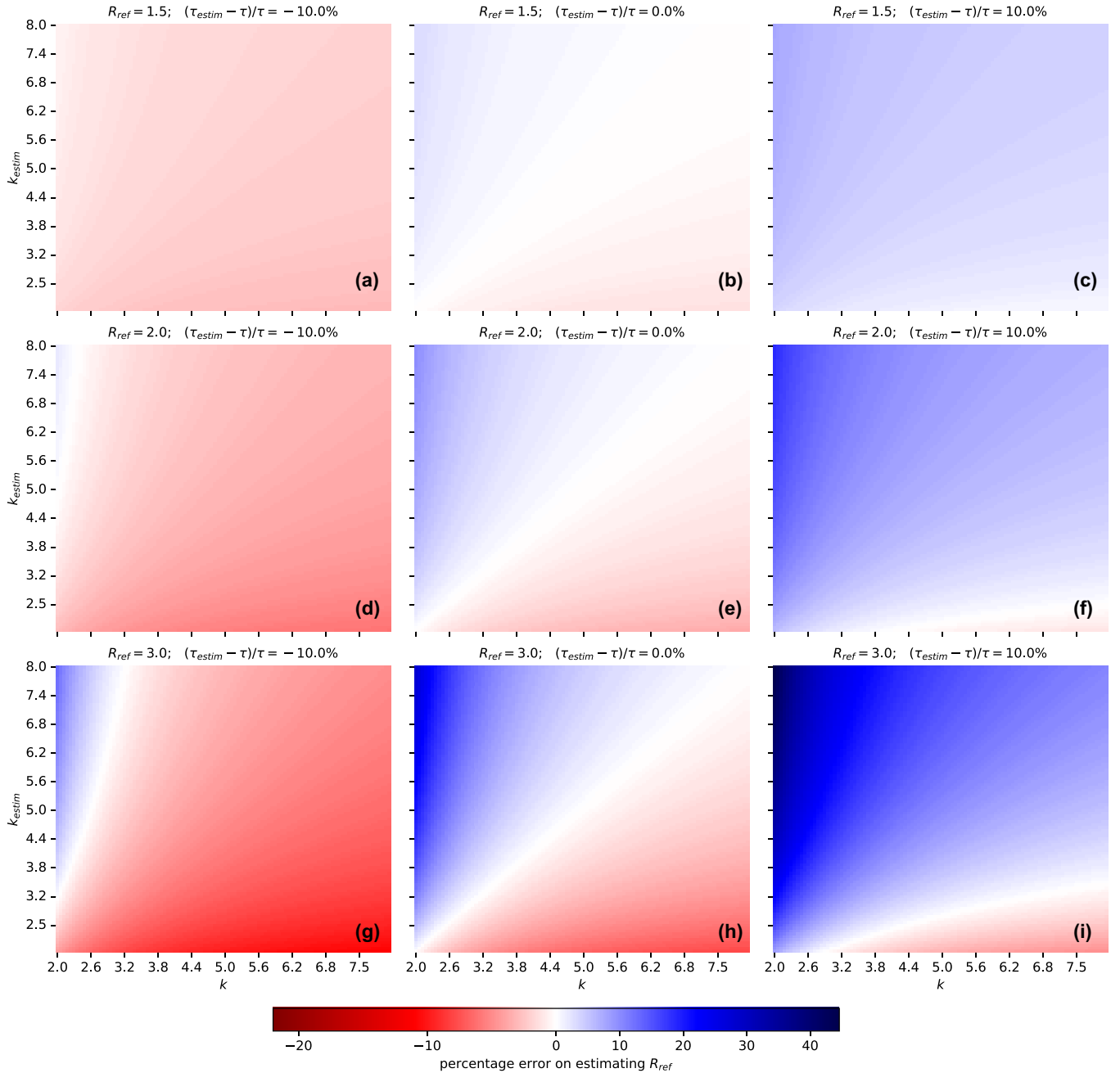


FIG. 3. Effect of inaccurately measuring the generation time distribution on the estimate of the reproduction ratio. Each panel shows the relative percentage error on the estimates of the reproduction ratio. Rows indicate the actual shape parameter k of the generation time distribution, columns the one used in the estimate. Panels have different values of the reference reproduction ratio R_{ref} and of the relative difference between the actual mean generation time and the one used to compute the reproduction ratio. The color bar shows the relative difference between the estimated reproduction ratio and R_{ref} asymptotically at large time.

spatial equilibrium (Perron eigenvector) are $R_{ref,p}$, $\mathbf{v}_p$. Analogously, we identify the Green's function of the perturbed evolution as $\mathbf{G}_p = [1 - \hat{\zeta}(a)\mathbf{R}_p]^{-1}$. We assume that the perturbation affects the overall transmissibility and spatial epidemic structure but does not change the generation time distribution.

Appendix E proves that the Laplace transform of $\mathbf{I}(t)$ after the perturbation is

$$\hat{\mathbf{I}}(a) = e^{at_p} \hat{\zeta}(a) \hat{\mathbf{G}}(a) \mathbf{R} \int_0^{t_p} ds e^{-sa} \mathbf{G}_p(s) \mathbf{v}. \quad (23)$$

The first exponential simply shifts the exponential growth to start at t_p . The term $\hat{\mathbf{G}}(a)$ is the only one contributing with singularities, correctly expressing the fact that the asymptotic behavior (large t) will be determined by the eigenmodes of the unperturbed propagation [45]: Each of them will decay at a relative rate given by Eq. (13). The last term in Eq. (23) encodes the effect of the perturbation as it computes the weight of each subdominant eigenmode attributable to the perturbation. To isolate each weight, we multiply from the left by $\mathbf{w}_\beta^*$ and, as before, compute the residue. Assuming again for simplicity real positive eigenvalues, for the mode $\Gamma_{\beta,m}$ the

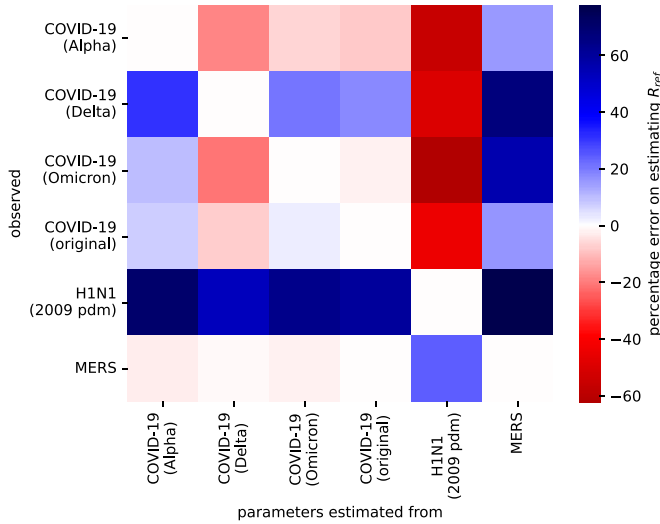


FIG. 4. Impact of sharing estimates of the generation time across epidemics. The figure shows the relative percentage error on the estimates of the reproduction ratio that is made when estimating R for the epidemic indicated in the column using parameters from the epidemic indicated in the row. The parameters used are $R_{\text{ref}} = 3.0$, $\tau = 6.60$, $k = 2.49$ for the original strain of COVID-19 [51,58], $R_{\text{ref}} = 4.5$, $\tau = 7.12$, $k = 2.53$ for its Alpha variant [59,60], $R_{\text{ref}} = 5.0$, $\tau = 6.52$, $k = 1.87$ for its Delta variant [59,61], $R_{\text{ref}} = 8.2$, $\tau = 6.84$, $k = 2.39$ for its Omicron variant [62], and $R_{\text{ref}} = 0.7$, $\tau = 6.80$, $k = 4.85$ for 2012–2013 Middle East Respiratory Syndrome [63]. The color bar shows the relative difference between the estimated reproduction ratio and R_{ref} asymptotically at large time.

residue is

$$\text{Res} \mathbf{w}_{\beta}^* \hat{\mathbf{I}}|_{a=\Gamma_{\beta,m}} = \frac{|\Lambda_{\beta}|^{1/k} - 1}{\tau} e^{i2\pi m/k} \int_0^{t_p} \times ds e^{(t_p-s)\Gamma_{\beta,m}} \mathbf{w}_{\beta}^* \mathbf{G}_p(s) \mathbf{v}. \quad (24)$$

The term $\Lambda_{\beta}^{1/k}$ is the familiar weight [Eq. (12)], while the last term is the contribution of the perturbation. It shows that the most disruptive perturbations are those whose propagators transform $\mathbf{v}$ into $\mathbf{w}_{\beta}$, where β is the one with the smallest decay rate δ . Note, however, that this transformation will never be exact as $\mathbf{w}_{\beta}$ is not a Perron vector and thus not a suitable spatial distribution, but will maximize the scalar product with $\mathbf{w}_{\beta}^*$. The simplest way to achieve it is that $\mathbf{R}_p$ contains a term approximately proportional to $\mathbf{w}_{\beta} \mathbf{v}^*$. Let us consider this term in the context of weakly coupled systems, whereby transmission occurs predominantly within communities or within clusters of communities, translating into diagonally dominant or blockdiagonally dominant reproduction operators ($R_{ii} > \sum_{j \neq i} R_{ji}$). There, each eigenvector is mostly concentrated into one or few communities, and the outer product $\mathbf{w}_{\beta}^* \mathbf{v}$ indicates, in the context of a perturbation, an anomalous increase (or decrease) in the transmission potential between the communities where $\mathbf{w}_{\beta}$, $\mathbf{v}$ are concentrated. This was observed, for example, in the aftermath of natural disasters where aid-driven mobility increases contacts among residents of communities that can be far apart [29], or in the time leading to a major movement restriction such as the first COVID-19-driven lockdown in France, when people spontaneously and massively

relocated outside major urban centers during the time between policy announcement and policy enforcement [33]. More routinely, it can also happen during holiday periods when people spend time in crowded destinations away from their normal residence [35,36]. These examples use administrative units as communities; similar effect may, however, occur across spatial scales, when perturbations change contacts between the distinct *mobility containers* that are known to exist at multiple scales [64].

As a final observation, we wish to determine the impact of the generation time distribution on the effect of the perturbation. To do this, we assume the perturbation to last for a relative short time and expand the perturbation term in t_p (see Appendix F). We find that for up to $k \approx 1$,

$$\int_0^{t_p} ds e^{(t_p-s)\Gamma_{\beta,m}} \mathbf{w}_{\beta}^* \mathbf{G}_p(s) \mathbf{v} \approx (\mathbf{w}_{\beta}^* \mathbf{v}_p)(\mathbf{v}_p^* \mathbf{v}) \left[1 + \frac{kt_p}{\tau} (R_{\text{ref},p}^{1/k} - 1) \right], \quad (25)$$

where, for clarity, we have kept only the leading mode of the perturbed propagation. For exponentially distributed generation times ($k = 1$), the effect of the perturbation grows linearly with the transmissibility during the perturbation, while overdispersed generation times ($k < 1$) enhance this through a sublinear relation with small argument.

For underdispersed generation times ($k \gg 1$),

$$\int_0^{t_p} ds e^{(t_p-s)\Gamma_{\beta,m}} \mathbf{w}_{\beta}^* \mathbf{G}_p(s) \mathbf{v} \approx (\mathbf{w}_{\beta}^* \mathbf{v})(\mathbf{v}_p^* \mathbf{v}_p) R_{\text{ref},p} \frac{e^k}{k^{3/2}} \left(\frac{t_p}{\tau} \right)^k. \quad (26)$$

The exponential dependency on k as well as the leading order t_p^k show that underdispersion substantially enhances the effect of the perturbation.

To sum up, this means that the interaction between generation time and spatial structure again affects epidemic dynamics by enhancing the effect of changes in spatial transmission patterns when τ is both underdispersed and overdispersed with respect to the exponential distribution. The fact that most epidemics of respiratory pathogens feature underdispersed generation times (see Fig. 4) and, more generally, generation times compatible with $k = 1$ are rarely observed, implies that the effect of perturbations, even if relatively short (weeks) [29,33,65], may substantially change the spatial structure of the epidemic and compromise our ability to correctly evaluate epidemic trends using surveillance data.

VI. CONCLUSION

In this study, we developed a theoretical framework linking the effect of the distribution of the generation time and the spatial contact structure on epidemic dynamics, and the implications for epidemiological surveillance.

We showed that the generation time distribution interacts nontrivially with the spatial coupling network to determine epidemic evolution and, in particular, the rate and manner in which the system approaches the equilibrium spatial distribution of infections. Our findings show that the dispersion of the generation time around its mean modulates the

contribution of subdominant epidemic modes, thereby altering the time required for surveillance-based estimates of R to converge to their reference value. For epidemics close to criticality, overdispersed generation times slow convergence, while for transmission well above the epidemic threshold, underdispersed generation times—typical of many respiratory pathogens—can markedly delay convergence, leading to long-lived bias in surveillance-derived R .

Furthermore, we found that the previously introduced correction to incidence data, which removes the bias due to the spatial structure, remains valid for arbitrary generation time distributions only if both the mean and the shape of the distribution are accurately known. When R is close to $R = 1$, errors from misspecifying the generation time are small and knowledge of the mean τ suffices. However, for R well above the critical point, misestimation of either the mean or the dispersion of the generation time induces systematic errors that are not removed by the spatial correction and do not decay in time.

Finally, we applied the framework to short perturbations in epidemic dynamics, such as those arising from exogenous factors (e.g., extreme weather events, mass gatherings, and sudden mobility restrictions) as well as endogenous changes (e.g., behavioural changes). We found that realistic dispersion values can substantially amplify the impact of such perturbations and increase the time needed by the epidemic to return to the unperturbed equilibrium. As a result, even in regimes where surveillance-based estimates R would otherwise be reliable, abrupt short-term changes can induce biases in R estimates that persist well beyond the duration of the perturbation.

We illustrated these effects in a case study of a respiratory pathogen in Spain, where colocation-based mobility data allowed us to quantify the interaction between generation time distribution and spatial structure, and their effects on the estimate of R , under realistic contact patterns.

In conclusion, these findings strengthen the theoretical foundation and provide operational criteria for public health practice on two levels. First, they inform the interpretation of surveillance-derived estimates of epidemic evolution. Second, they delineate the epidemiological and statistical conditions under which such estimates remain robust, as well as the circumstances in which corrective adjustments are necessary and available. The practical implications for public health are clear, and historical analyses of COVID-19 in Spain—our case study—provide concrete examples of this situation. Early estimates of the reproduction ratio assumed an exponential generation-time kernel and considered no spatial structure [66,67]. Others used more realistic generation time distributions but informed them with data from China [68]. While understandable given the data available at the time, these assumptions are precisely the conditions under which our framework predicts structural bias in surveillance-based estimates of the reproduction ratio.

ACKNOWLEDGMENT

This study was partially supported by Horizon Europe grant SIESTA (101131957) to E.V.

DATA AVAILABILITY

Meta Colocation Maps can be requested at [69]. Population data for Spain are publicly available at [70].

APPENDIX A: ASYMPTOTIC EVOLUTION

Equation (5) implies that, as $t \rightarrow \infty$, $\mathbf{G}(t) \sim e^{\Re \Gamma_{\max} t}$, where $\Gamma_{\max}$ is the singularity of $\hat{\mathbf{G}}(a)$ with the largest real part. The singularities solve the following equations:

$$\hat{\zeta}(\Gamma_{\text{ref}})R_{\text{ref}} = 1, \quad (\text{A1})$$

$$\hat{\zeta}(\Gamma_{\beta})\Lambda_{\beta} = 1, \quad (\text{A2})$$

whose explicit formula in the case of a gamma-distributed generation time appears in Eqs. (10) and (11). Here, however, we consider a completely general generation time distribution. This is a quite cumbersome proof of something apparently trivial, i.e., that the dominant eigenmode of $\mathbf{R}$ is indeed what determines the asymptotic epidemic behavior. We report it nonetheless, to prove that changes in the generation time distribution can change how the system approaches the asymptotic equilibrium spatial distribution $\mathbf{v}$ but cannot change it, as it is exclusively determined by the spatial network structure.

We prove here that $\Gamma_{\max}$ is the real solution of Eq. (A1). To do this, we study $\hat{\zeta}$. Clearly, $\hat{\zeta}$ is a real function for $a \in \mathbb{R}$. The requirement that $\zeta(t) \geq 0$ for $t \in \mathbb{R}_+$ implies that $\hat{\zeta}(a) \geq 0$ for $a \in \mathbb{R}_+$. $\hat{\zeta}$ is also monotonically decreasing on $\mathbb{R}_+$ because $\hat{\zeta}'(a) = -\int_0^\infty dt e^{-at} t \zeta(t) < 0$ for $a \in \mathbb{R}_+$. Its (possibly multivalued) inverse $\hat{\zeta}^{-1}(a)$ is thus also monotonically decreasing:

$$(\hat{\zeta}^{-1})'(a) = \frac{1}{\hat{\zeta}'(\hat{\zeta}^{-1}(a))} < 0. \quad (\text{A3})$$

Now, we need to prove that $\Re(\Gamma_{\beta}) < \Gamma_{\text{ref}} \forall \beta$.

Case 1: $\Lambda_{\beta} \in \mathbb{R}$. Since $\mathbf{R}$ is non-negative irreducible matrix, then $\Lambda_{\beta} < R_{\text{ref}}$ by Perron-Frobenius theorem:

$$\Lambda_{\beta} < R_{\text{ref}} \Rightarrow \frac{1}{R_{\text{ref}}} < \frac{1}{\Lambda_{\beta}}, \quad (\text{A4})$$

$$\Rightarrow \Gamma_{\text{ref}} = \hat{\zeta}^{-1}\left(\frac{1}{R_{\text{ref}}}\right) > \hat{\zeta}^{-1}\left(\frac{1}{\Lambda_{\beta}}\right) = \Gamma_{\beta}. \quad (\text{A5})$$

This proves that $\Gamma_{\text{ref}} > \Gamma_{\beta}$. We dropped $\Re$ because being $\hat{\zeta}^{-1}(a)$ is real if the argument is real.

Case 2: $\Lambda_{\beta} \in \mathbb{C} \setminus \mathbb{R}$. Given that $\hat{\zeta}(\Gamma_{\beta}) = 1/\Lambda_{\beta}$, then

$$\Re \hat{\zeta}(\Gamma_{\beta}) = \frac{\Re \Lambda_{\beta}}{|\Lambda_{\beta}|^2}. \quad (\text{A6})$$

We now prove the following inequality:

$$\Re \hat{\zeta}(\Gamma_{\beta}) < \hat{\zeta}(\Re \Gamma_{\beta}). \quad (\text{A7})$$

$$\Re \hat{\zeta}(\Gamma_{\beta}) = \Re \int_0^\infty dt e^{-t\Gamma_{\beta}} \zeta(t), \quad (\text{A8})$$

$$= \int_0^\infty dt e^{-t\Re \Gamma_{\beta}} \cos(t\Im \Gamma_{\beta}) \zeta(t), \quad (\text{A9})$$

$$< \int_0^\infty dt e^{-t\Re\Gamma_\beta} \zeta(t) = \hat{\zeta}(\Re\Gamma_\beta). \quad (\text{A10})$$

Combining Eqs. (A6) and (A7), one gets

$$\Re\Gamma_\beta < \hat{\zeta}^{-1}\left(\frac{\Re\Lambda_\beta}{|\Lambda_\beta|^2}\right). \quad (\text{A11})$$

Then, to prove that $\Gamma_{\text{ref}} > \Re\Gamma_\beta$ we just need to prove that $\Gamma_{\text{ref}} \geq \hat{\zeta}^{-1}\left(\frac{\Re\Lambda_\beta}{|\Lambda_\beta|^2}\right)$:

$$\Gamma_{\text{ref}} \geq \hat{\zeta}^{-1}\left(\frac{\Re\Lambda_\beta}{|\Lambda_\beta|^2}\right) \Rightarrow \hat{\zeta}(\Gamma_{\text{ref}}) \leq \frac{\Re\Lambda_\beta}{|\Lambda_\beta|^2}, \quad (\text{A12})$$

$$\Leftrightarrow R_{\text{ref}} \geq \frac{1}{\frac{1}{\Re\Lambda_\beta}} > \Re\Lambda_\beta. \quad (\text{A13})$$

APPENDIX B: GAMMA-DISTRIBUTED GENERATION TIME

We assume the generation time t to be distributed as a gamma distribution, defined on $[0, \infty)$ and with the following probability density function:

$$\zeta(t) = \frac{1}{\Gamma(k)} \left(\frac{k}{\tau}\right)^k t^{k-1} e^{-kt/\tau}. \quad (\text{B1})$$

τ is the mean generation time and k is the shape parameter tuning dispersion:

$$\mathbb{E}[t] = \tau, \quad (\text{B2})$$

$$\text{VAR}[t] = \frac{\tau^2}{k}. \quad (\text{B3})$$

This distribution has the following Laplace transform:

$$\hat{\zeta}(a) = \left(1 + \frac{\tau}{k}a\right)^{-k}. \quad (\text{B4})$$

1. Green's function

We study the time evolution of the Green's function $\mathbf{G}(t)$ from its Laplace transform in the case of gamma-distributed generation time. We define

$$f_\Lambda(a) = \left[1 - \Lambda\left(1 + \frac{\tau a}{k}\right)^{-k}\right]^{-1}, \quad (\text{B5})$$

which we can use as a generic term to rewrite the spectral decomposition of the Laplace transform of $\mathbf{G}$ in Eq. (5):

$$\hat{\mathbf{G}}(a) = f_{R_{\text{ref}}}(a)\mathbf{v}\mathbf{v}^* + \sum_\beta f_{\Lambda_\beta}(a)\mathbf{w}_\beta\mathbf{w}_\beta^*. \quad (\text{B6})$$

The contributions of different eigenspaces can be treated independently, so we will focus on the contribution from the generic $f_\Lambda(a)$. As customary, we will study and characterize its singularity, which will determine, in each eigenspace, its contributions to the evolution in time of $\mathbf{G}$. First, we define a shifted variable: $x = 1 + \tau a/k$ and a function $\tilde{f}_\Lambda$ such that

$$\tilde{f}_\Lambda(x) = f_\Lambda(a):$$

$$\tilde{f}_\Lambda(x) = \frac{x^k}{x^k - \Lambda}. \quad (\text{B7})$$

In general, $k \in \mathbb{R}$. Here, however, we will assume that $k \in \mathbb{Q}$. This causes no loss of generality as estimates of the dispersion of the generation time have always nonzero uncertainty, so they can always be approximated arbitrarily well with a rational number given that $\mathbb{Q}$ is dense in $\mathbb{R}$. Candidate singularities of $\tilde{f}_\Lambda$ are the solutions of $x^k - \Lambda = 0$ and $x = 0$, the latter existing only if $k \notin \mathbb{N}$ and being a branch point. We will first prove that the former singularities are a finite number of simple poles and compute their residue.

Let $k = p/q$ with $p, q \in \mathbb{N}$ coprime. Then, the solutions of $x^k - \Lambda = 0$ are a subset of the solutions of $x^p - \Lambda^q = 0$. These latter are

$$x_j = |\Lambda|^{1/k} \exp\left[i\left(\frac{\arg \Lambda}{k} + \frac{2\pi j}{p}\right)\right], \quad (\text{B8})$$

with $j = 0, 1, \dots, p-1$. Among these, x_j is a solution of $x^k - \Lambda = 0$ only if q divides j . This means that the solutions of $x^k - \Lambda = 0$ can be enumerated as follows:

$$x_m = |\Lambda|^{1/k} \exp\left(i\frac{\arg \Lambda + 2\pi m}{k}\right), \quad (\text{B9})$$

$$\Gamma_m = \frac{k}{\tau} \left[|\Lambda|^{1/k} \exp\left(i\frac{\arg \Lambda + 2\pi m}{k}\right) - 1 \right], \quad (\text{B10})$$

$$m = 0, 1, \dots, \left\lfloor \frac{p-1}{q} \right\rfloor. \quad (\text{B11})$$

Here, we also shifted the singularities back to a : $\Gamma_m = k(x_m - 1)/\tau$. Incidentally, these Γ_m are exactly the exponential growth rates appearing in Eqs. (10) and (11), as we are about to see.

Now, we identify the numerator and the denominator in Eq. (7): $\tilde{f}_{\Lambda,U}(x) = x^k$, $\tilde{f}_{\Lambda,D}(x) = x^k - \Lambda$. $\tilde{f}_{\Lambda,U}(x_m) \neq 0$ and $\tilde{f}_{\Lambda,D}(x) = kx_m^{k-1} \neq 0$ so $\tilde{f}_\Lambda$ has simple poles in x_m . Also,

$$\tilde{f}_\Lambda(x) = \frac{x_m}{k} \frac{1}{x - x_m} + \mathcal{O}(1). \quad (\text{B12})$$

Going back to a , this means that f_Λ has simple poles in Γ_m and

$$\text{Res } f_\Lambda(a)|_{a=\Gamma_m} = \frac{|\Lambda|^{1/k}}{\tau} \exp\left(i\frac{\arg \Lambda + 2\pi m}{k}\right). \quad (\text{B13})$$

By the properties of the Laplace transform, each of these simple poles contributes with an exponential growth to each term of $\mathbf{G}(t)$ with rate Γ_m and weight equal to $\text{Res } f(a)|_{a=\Gamma_m}$.

We now turn to the branch point in $x = 0$ or, equivalently, in $a = -k/\tau$. Close to the branch point, $\tilde{f} - \Lambda$ behaves as

$$\tilde{f} - \Lambda = -\frac{x^k}{\Lambda} + \mathcal{O}(x^{2k}). \quad (\text{B14})$$

Performing the inverse Laplace transform of this local expansion and shifting back to a , one finds that the branch point contributes to the time evolution of each term of $\mathbf{G}(t)$ with the following:

$$\rightarrow -\frac{1}{\pi} \frac{1}{\tau \Lambda} k^{-k} \Gamma(1+k) \sin(\pi k) \left(\frac{t}{\tau}\right)^{-(1+k)} e^{-kt/\tau}. \quad (\text{B15})$$

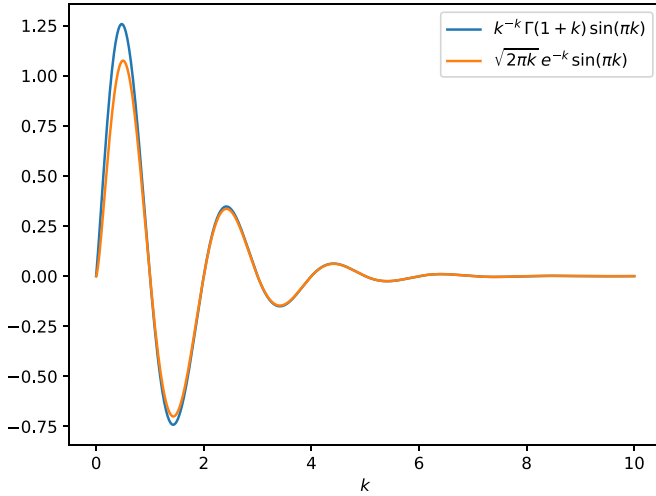


FIG. 5. Evaluation of the k -dependent term of the contribution from the branch point, both its exact form [Eq. (B15)] and with Stirling's approximation [Eq. (B16)].

Given that the branch point exists only if $k \notin \mathbb{N}$, the term $\sin(\pi k)$ correctly suppresses it when $k \in \mathbb{N}$. For $k \gg 1$, we can replace Euler's gamma with its Stirling approximation (see Fig. 5):

$$\rightarrow -\sqrt{\frac{2}{\pi}} \frac{1}{\tau \Lambda} \sqrt{k} \sin(\pi k) e^{-k} \left(\frac{t}{\tau}\right)^{-(1+k)} e^{-kt/\tau}, \quad (\text{B16})$$

which means that this contribution is exponentially suppressed at large k , as proven also by Fig. 5. This figure also shows that this contribution can be relevant basically for k around $1/2$ and possibly $3/2$, when the k -dependent coefficient peaks and the exponential decay in time $e^{-kt/\tau}$, whose rate depends linearly on k , is still small.

We now have identified all the singularities of $f_\Lambda(a)$, characterized them, and found their contribution to the evolution in time of $\mathbf{G}(t)$ [Eq. (12)], by their Laplace transform. We now can sum them together:

$$\begin{aligned} f_\Lambda \rightarrow & \sum_m \frac{|\Lambda|^{1/k}}{\tau} \exp\left(i \frac{\arg \Lambda + 2\pi m}{k}\right) e^{\Gamma_m t} \\ & - \frac{1}{\pi} \frac{1}{\tau \Lambda} k^{-k} \Gamma(1+k) \sin(\pi k) \left(\frac{t}{\tau}\right)^{-(1+k)} e^{-kt/\tau}. \end{aligned} \quad (\text{B17})$$

Then, summing together the contributions from the different eigemodes one gets Eq. (12). Note that the weight of the contribution coming from the branch point singularity [Eq. (B15)] for generic eigenmode Λ is equal to $1/\Lambda$ times something that is equal for all eigenmodes. This means that, when summing over the eigenmodes, one gets $(\mathbf{v}\mathbf{v}^*/R_{\text{ref}} + \sum_\beta \mathbf{w}_\beta \mathbf{w}_\beta^*/\Lambda_\beta)$ times the part that does not depend on the eigenvalues. This sum is clearly the spectral decomposition of $\mathbf{R}^{-1}$, and this explains why in Eq. (12) the contribution from the branch point singularity is written as $\mathbf{R}^{-1}$ times the time dependence.

APPENDIX C: AN IDENTITY WITH $\mathbf{G}$

Proof that

$$\hat{\zeta}(a) \hat{\mathbf{G}}(a) = \mathbf{R}^{-1} [\hat{\mathbf{G}}(a) - 1]. \quad (\text{C1})$$

Note that here $\mathbf{R}^{-1}$ can be formal if $\mathbf{R}^{-1}$ is not invertible as the inverse disappears at the end of the calculations.

$$\hat{\zeta}(a) \hat{\mathbf{G}}(a) = \hat{\zeta}(a) [1 - \hat{\zeta}(a) \mathbf{R}]^{-1}, \quad (\text{C2})$$

$$\begin{aligned} &= \mathbf{R}^{-1} \hat{\zeta}(a) \mathbf{R} \sum_{n=0}^{\infty} [\hat{\zeta}(a) \mathbf{R}]^n \\ &= \mathbf{R}^{-1} \sum_{n=1}^{\infty} [\hat{\zeta}(a) \mathbf{R}]^n, \end{aligned} \quad (\text{C3})$$

$$= \mathbf{R}^{-1} \left\{ \sum_{n=0}^{\infty} [\hat{\zeta}(a) \mathbf{R}]^n - 1 \right\}, \quad (\text{C4})$$

$$= \mathbf{R}^{-1} [\hat{\mathbf{G}}(a) - 1]. \quad (\text{C5})$$

APPENDIX D: NUMERICAL SIMULATIONS

1. Parametrization of the reproduction operator

To reconstruct the spatially structured reproduction operator, we use Colocation Maps from Meta, which quantify the probability p_{ij} that a randomly selected resident of community i and one of community j are found colocated during a 5-min interval within a given week. These maps allow us to stratify by type of contact (within household or community). For our purposes, we only focused on community contacts. These maps are provided at the administrative level of Spanish provinces in April 2023. Similarly to what we did in Refs. [19,29], we define the un-normalized contact rate matrix as $M_{ij} = p_{ij} N_j$, where N_i is the resident population of community i , obtained from census data [71]. Finally, we parametrize the entries of the reproduction operator as

$$R_{ij} = R_{\text{ref}} \frac{M_{ji}}{\rho[\mathbf{M}]}, \quad (\text{D1})$$

where ρ is the spectral radius, so that the scalar coefficient tuning $\mathbf{R}$ is exactly R_{ref} . This operator captures both within-community ($i = j$) and between-community ($i \neq j$) transmission potential.

2. Numerical solutions

We solved numerically the Volterra equations by discretizing it in a certain number of steps. We fixed a time step $dt = 0.04 d$, an initial condition $\mathbf{v}_0$ where we considered the first case reported to be introduced in the spatial community of Madrid and an observation interval T . We then solved the equation for every time step and for every community thus obtaining a vector of cases of dimensions $N \times T/dt$, where N is the number of spatial communities and T/dt is the number of time steps considered. To obtain R_{estim} , we computed the total incidence per time step as the sum across all communities at a specific one, $I_{\text{tot}}(t) = \sum_i I_i(t)$. From this, we exploited the relation

$$R_{\text{estim}}(t) = \frac{I_{\text{tot}}(t)}{\int_0^t ds \xi(t-s) I_{\text{tot}}(s)}. \quad (\text{D2})$$

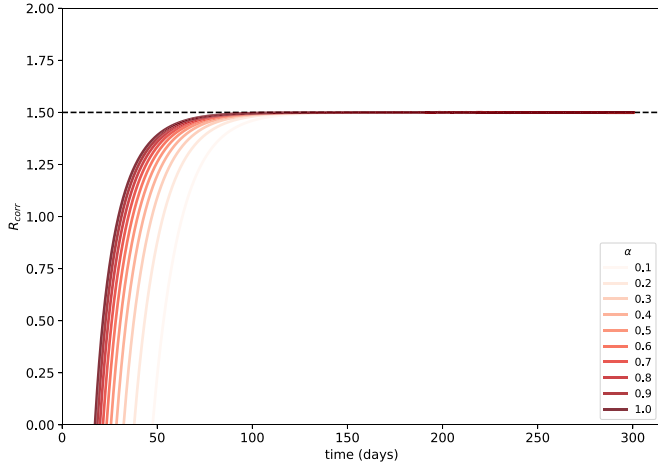


FIG. 6. Evolution of R_{corr} with time, assuming a bias in the estimation of the source function in Spain. Importation is modeled as a constant function, proportional to population: $J_i(t) = \alpha N_i / N_{\text{tot}}$, where N_i is the resident population in province i and N_{tot} is the total population of Spain. α tunes the overall importation flow and its value is explored in the legend. The misspecified importation term is an initial introduction in Madrid and no importation or exportation at $t > 0$.

To extract the time of convergence, we first computed the relative variation between R_{estim} and R_{ref} , called it $\Delta(t)$. Then, we defined the time of convergence as the smallest t^* for which $\Delta(t^*) < \epsilon$ where $\epsilon = 0.01$ arbitrarily. To ensure this value would be representative for the long-time convergence of the estimate, we disregarded any result before $t = 20 d$. Considering a gamma distribution as the generation time distribution, we explored these two values at varying shape and for different values of the mean.

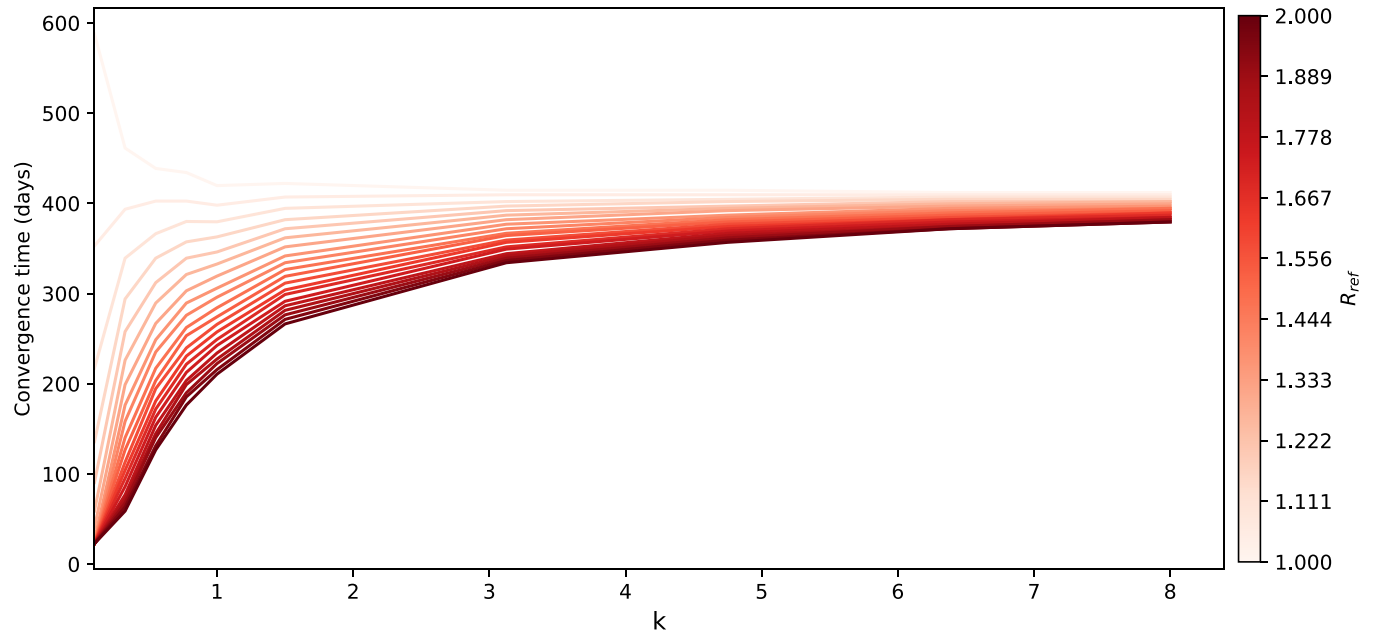


FIG. 7. Convergence time of R_{estim} toward R_{ref} shown as a function of the shape parameter k , according to different values of R_{ref} . The generation time distribution is modeled as a gamma distribution with the mean set to the estimate for COVID-19 (original strain) [51] and varying k . Data and initial conditions are the same as in Appendix D.

APPENDIX E: EVOLUTION AFTER SPATIAL PERTURBATION

The evolution of the epidemic with the perturbation is described by the following:

$$\mathbf{I}(t) = \delta(t)\mathbf{v} + \mathbf{R}_p \int_0^t ds \zeta(t-s)\mathbf{I}(s) \quad \text{for } t \leq t_p, \quad (\text{E1})$$

$$\mathbf{I}(t) = \mathbf{R} \int_0^t ds \zeta(t-s)\mathbf{I}(s) \quad \text{for } t > t_p. \quad (\text{E2})$$

Equation (E1) has the following solution: $\mathbf{I}(t) = \mathbf{G}_p(t)\mathbf{v}$. Equation (E2) can be decomposed as follows:

$$\mathbf{I}(t) = \underbrace{\mathbf{R} \int_0^{t_p} ds \zeta(t-s)\mathbf{G}_p(s)\mathbf{v}}_{\mathbf{h}(t)} + \mathbf{R} \int_{t_p}^t ds \zeta(t-s)\mathbf{I}(s), \quad (\text{E3})$$

where we replaced $\mathbf{I}(s)$ in the first integral with the solution at $t \leq t_p$. Now, this first integral $[\mathbf{h}(t)]$ no longer contains the unknown and acts as a source term. We define the shifted variables $\tilde{t} = t - t_p$, $\tilde{\mathbf{I}}(\tilde{t}) = \mathbf{I}(t)$, and $\tilde{\mathbf{h}}(\tilde{t}) = \mathbf{h}(t)$ and rewrite:

$$\tilde{\mathbf{I}}(\tilde{t}) = \tilde{\mathbf{h}}(\tilde{t}) + \mathbf{R} \int_0^{\tilde{t}} ds \zeta(\tilde{t}-s)\tilde{\mathbf{I}}(s), \quad (\text{E4})$$

whose solution for $\tilde{t} > 0$ is

$$\tilde{\mathbf{I}}(\tilde{t}) = \int_0^{\tilde{t}} ds \tilde{\mathbf{G}}(\tilde{t}-s)\tilde{\mathbf{h}}(s). \quad (\text{E5})$$

We perform the Laplace transform of this last equation noting that the time shifting generates e^{at_p} terms:

$$\hat{\mathbf{I}}(a) = e^{at_p} \hat{\mathbf{G}}(a) \hat{\mathbf{h}}(a). \quad (\text{E6})$$

Performing the Laplace transform of $\mathbf{h}$, one gets Eq. (23).

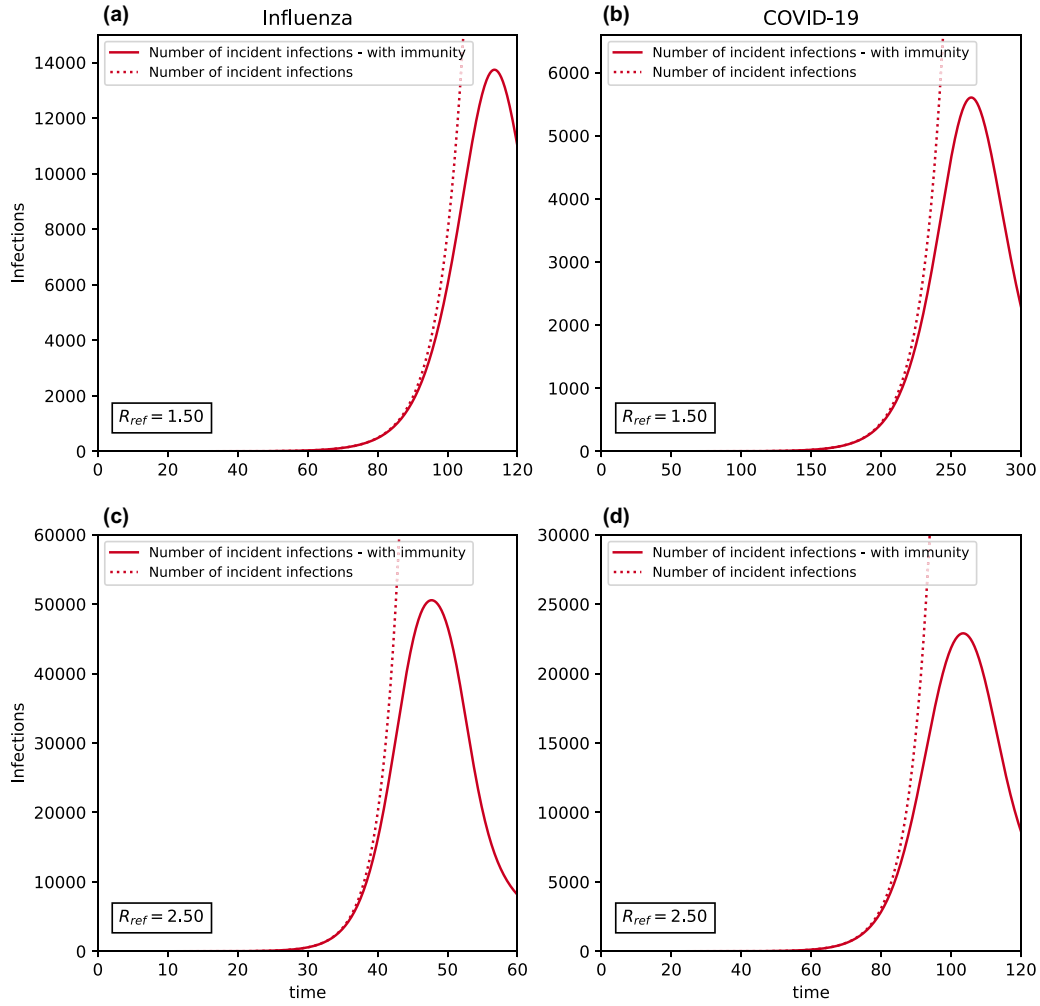


FIG. 8. Evolution of the number of incident infections $I_{\text{tot}}(t)$ as a function of time, according to four scenarios combining different values of R_{ref} [1.5 for panels (a) and (b) and 2.5 for panels (c) and (d)] and different diseases [Influenza H1N1 for panels (a) and (c) and COVID-19 (historical strain) for panels (b) and (d)]. The solid line represents the full epidemic evolution [with time-varying susceptibles as Eq. (G1)], the dotted line the linear approximation.

APPENDIX F: SHORT-TIME EXPANSION OF THE PERTURBATION

To compute the short-term expansion in the time domain, we compute the asymptotic (large a) expansion in the Laplace domain:

$$\hat{\zeta}(a) = 1 + \left(\frac{k}{\tau a}\right)^k + \mathcal{O}\left(\frac{1}{a^{k+1}}\right), \quad (\text{F1})$$

which leads to, for each term in the Green's function [see Eq. (5)],

$$\frac{1}{1 - \Lambda_{p,\beta} \hat{\zeta}(a)} = 1 + \Lambda_{p,\beta} \left(\frac{k}{\tau a}\right)^k + \mathcal{O}\left(\frac{1}{a^{k+1}}\right), \quad (\text{F2})$$

$$\begin{aligned} \rightarrow \delta(t) + \Lambda_{p,\beta} \left(\frac{k}{\tau}\right)^k \frac{t^{k-1}}{(k-1)!} \\ + \mathcal{O}(t^k). \end{aligned} \quad (\text{F3})$$

This last term appears in the integral

$$\begin{aligned} \int_0^{t_p} ds \, e^{\Gamma_{\beta}(t_p-s)} \left[\delta(s) + \Lambda_{p,\beta} \left(\frac{k}{\tau}\right)^k \frac{s^{k-1}}{(k-1)!} + \mathcal{O}(s^k) \right] \\ = e^{\Gamma_{\beta} t_p} \left[1 + \Lambda_{\beta} \left(\frac{t_p}{\tau}\right)^k \frac{k^{k-1}}{(k-1)!} + \mathcal{O}(t^{k+1}) \right]. \end{aligned} \quad (\text{F4})$$

We note that, for k large enough,

$$\frac{k^{k-1}}{(k-1)!} \approx \frac{e^k}{k^{3/2}}. \quad (\text{F5})$$

APPENDIX G: ADDITIONAL SUPPORTING ANALYSES

This Appendix contains supporting analyses.

Figure 6 shows the temporal evolution of R_{corr} from Eq. (9) under the assumption that importation and exportation of infections are ignored. We used Spanish data and imposed a constant inflow of infections proportional to the resident population, $J_i(t) \propto N_i$, where N_i is the population of province i .

We then assumed that importations are disregarded: $J_{\text{corr}}(t) = \delta(t)$, v_i^* , corresponding to an initial introduction in community $\bar{i}$ (we chose Madrid, which has the largest population).

Figure 7 presents the time of convergence of R_{estim} to R_{ref} as a function of the shape parameter k .

Figure 8 examines the scope of the validity of the assumption of constant $\mathbf{R}$ when describing epidemic evolution. Specifically, we compared epidemic evolution while assuming constant $\mathbf{R}$ [Eq. (D1)] and with a time-changing reproduction operator that accounts for the fact that past infection confers immunity. Specifically, we updated the number of susceptible in community i at time t as

$$S_i(t) = N_i - \int_0^t ds I_i(s), \quad (\text{G1})$$

and then updated the reproduction operator accordingly: $R_{ij}(t) = R_{ij} S_i(t)/N_i$. We examined four scenarios, combining two diseases (COVID-19 and H1N1 influenza, each with its observed generation time distribution) and two reference values of R_{ref} (1.5 and 2.5). For $R_{\text{ref}} = 1.5$, nonlinearity becomes noticeable only after roughly 100 days for influenza and 225 days for COVID-19. This indicates that the framework remains valid for a substantial period after the onset of the epidemic, longer than the interval over which one typically assumes the contact rate matrix to be unaffected by exogenous effects (e.g., seasonality). For $R_{\text{ref}} = 2.5$, nonlinear effects obviously emerge earlier, but the underlying assumption remains valid for the scope of our study.

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