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A generalized-growth model to characterize the early ascending phase of infectious disease outbreaks

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ABSTRACT

Background: A better characterization of the early growth dynamics of an epidemic is needed to dissect the important drivers of disease transmission, refine existing transmission models, and improve disease forecasts.
Materials and methods: We introduce a 2-parameter generalized-growth model to characterize the ascending phase of an outbreak and capture epidemic profiles ranging from sub-exponential to exponential growth. We test the model against empirical outbreak data representing a variety of viral pathogens in historic and contemporary populations, and provide simulations highlighting the importance of sub-exponential growth for forecasting purposes.
Results: We applied the generalized-growth model to 20 infectious disease outbreaks representing a range of transmission routes. We uncovered epidemic profiles ranging from very slow growth ($p = 0.14$ for the Ebola outbreak in Bomi, Liberia (2014)) to near exponential ($p > 0.9$ for the smallpox outbreak in Khulna (1972), and the 1918 pandemic influenza in San Francisco). The foot-and-mouth disease outbreak in Uruguay displayed a profile of slower growth while the growth pattern of the HIV/AIDS epidemic in Japan was approximately linear. The West African Ebola epidemic provided a unique opportunity to explore how growth profiles vary by geography; analysis of the largest district-level outbreaks revealed substantial growth variations (mean $p = 0.59$, range: 0.14–0.97). The districts of Margibi in Liberia and Bombali and Bo in Sierra Leone had near-exponential growth, while the districts of Bomi in Liberia and Kenema in Sierra Leone displayed near constant incidences.
Conclusions: Our findings reveal significant variation in epidemic growth patterns across different infectious disease outbreaks and highlights that sub-exponential growth is a common phenomenon, especially for pathogens that are not airborne. Sub-exponential growth profiles may result from heterogeneity in contact structures or risk groups, reactive behavior changes, or the early onset of interventions strategies, and consideration of "deceleration parameters" may be useful to refine existing mathematical transmission models and improve disease forecasts.

1. Introduction

Identifying signature features of the growth kinetics of an outbreak can be useful to design reliable models of disease spread and understand important details of the transmission dynamics of an infectious disease (Chowell et al., 2015). However, ideal data are typically not available; rather there will be an absence of high-resolution epidemiological datasets needed to characterize transmission pathways in key settings, e.g., transmission trees in hospitals, schools, households (Cleaton et al., 2015; Faye et al., 2015). The force of infection in mathematical transmission models is typically estimated using time-series data that describe epidemic growth as a function of time (e.g., (Lipsitch et al., 2003; Chowell et al., 2003; Nishiura et al., 1922; Chowell et al., 2004; Riley and Ferguson, 2006; Dietz, 2009)). In fact, during the 2003 SARS (Severe Acute Respiratory Syndrome) threat, the 2009 A/H1N1 influenza pandemic, and the 2013–2015 Ebola epidemic in West Africa, aggregated case series at the national or district level were the primary sources of data available for model calibration (e.g.,

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Riley et al., 2003; Pandey et al., 2014; Ferguson et al., 2006; Halloran et al., 2002). A better understanding of observed epidemic growth patterns across different pathogens and across temporal and social contexts could prove useful to improve our ability to design disease transmission models, including the important task of forecasting the likely final size of the epidemic (morbidity, mortality impact), as well as to assess the effects of control interventions.

Classical compartmental transmission models assume exponential growth during the early phase of a well-mixed population (Anderson and May, 1991). In a recent article (Chowell et al., 2015) we reported that the initial apparently exponential spread of the 2013–2015 Ebola epidemic in West Africa was in fact a composition of local asynchronous outbreaks at the district or county level that each displayed sub-exponential growth patterns during at least 3 consecutive disease generations (Chowell et al., 2015). In semi-logarithmic scale, exponential growth is evident if a straight line fits well several consecutive disease generations of the epidemic curve, whereas a strong downward curvature in semi-logarithmic scale is indicative of sub-exponential growth. Here, we introduce a generalized model with a "deceleration" parameter that modulates growth and helps quantify departure from exponential theory, allowing for behaviors ranging from constant to exponentially-growing incidences (Tolle, 2003). Our simple quantitative framework is useful for public health decision-making as it provides a time-varying assessment of growth rates and informs the likely "signature feature" of the threat as well as the type and intensity of interventions required for effective mitigation. We illustrate our method using a diverse set of historic and contemporary outbreaks of acute viral and bacterial pathogens, including the recent West African Ebola virus epidemic, focusing on local outbreaks. Our results underscore the high sensitivity of epidemic size to small variations in the "deceleration" parameter.

2. Materials and methods

2.1. Data sources

We characterized the initial epidemic growth patterns in various infectious disease incidence time series including pandemic influenza, measles, smallpox, bubonic plague, foot-and-mouth disease (FMD), HIV/AIDS, and Ebola (Table 1). The temporal resolution of the datasets varied from daily, weekly, to annual. These selected outbreak data represent a convenience sample encompassing a range of pathogens, geographic contexts, and time periods. For each outbreak, the onset week corresponds to the first observation associated with a monotonic increase in incident cases, up to the peak incidence.

2.2. Generalized epidemic growth model

The growth pattern of infectious disease outbreaks has been extensively studied using models that assume exponential growth dynamics in the absence of control interventions (e.g., classical compartmental models (Anderson and May, 1991; Kermack and McKendrick, 1937)). Hence, the cumulative number of cases, $C(t)$, grows according to the equation: $C(t) = C(0)e^{rt}$ where, r is the growth rate per unit of time, t denotes time, and $C(0)$ is the number of cases at the start of the outbreak. Here the growth rate "r" is related to R_0 as derived from classic SIR-type compartmental transmission models, e.g., for the simple SIR (susceptible-infected-removed) model, $R_0 = 1 + r/\gamma$ where, $1/\gamma$ is the mean infectious period (Anderson and May, 1991). However, slower-than-exponential epidemic growth is expected in settings that involve highly constrained population contact structures with infectious diseases that spread via close contacts (e.g., sexually-transmitted infectious diseases, smallpox, and Ebola) (Chowell et al., 2015). To relax the assumption of exponential growth, we use a simple generalized model (Tolle, 2003) from the field of demography (e.g., Reppell et al., 2014), following:

$$\frac{\mathrm{d}C(t)}{\mathrm{d}t} = C'(t) = rC(t)^p$$

where, $C'(t)$ describes the incidence curve over time t, the solution $C(t)$ describes the cumulative number of cases at time t, r is a positive parameter denoting the growth rate (1/time), and $p \in [0, 1]$ is a "deceleration of growth" parameter. If $p = 0$, this equation describes constant incidence over time and the cumulative number of cases grows linearly while $p = 1$ models exponential growth dynamics (i.e., Malthus equation). Intermediate values of p between 0 and 1 describe sub-exponential (e.g., polynomial) growth patterns. For example, if $p = 1/2$ incidence grows linearly while the cumulative number of cases follows a quadratic polynomial. If $p = 2/3$ incidence grows quadratically while the cumulative number of cases fits a cubic polynomial. For sub-exponential growth (i.e., $0 < p < 1$) the solution of this equation is given by the following polynomial of degree m (Tolle, 2003):

$$C(t) = \left(\frac{r}{m}t + A\right)^m$$

where, m is a positive integer, and the "deceleration of growth" parameter is given by $p = 1 - 1/m$. (Tolle, 2003) A is a constant that depends on the initial condition, $C(0)$. Specifically, $A = \sqrt[m]{C(0)}$. Furthermore, for sub-exponential growth dynamics, the relative growth rate, $[\mathrm{d}C(t)/\mathrm{d}t]/C(t) \propto m/t$, decreases inversely with time while the doubling time $T_{\mathrm{d}} \propto t(\ln 2)/m$ increases proportionally with time (Fig. 1) (Chowell et al., 2015). This differs from the constant doubling time that characterizes exponential growth. Here, we do not consider faster than exponential growth (i.e., super-exponential growth), for which p exceeds 1.0 (Tolle, 2003).

2.3. Parameter estimation

Parameters r and p can be jointly estimated through nonlinear least-square curve fitting to the case incidence curve modeled by equation $C'(t)$, in the first few generations of disease spread. For this purpose, we used the Levenberg–Marquardt algorithm implemented in MATLAB (The Mathworks, Inc.) as in prior studies (e.g., Chowell et al., 2007). The initial number of cases $C(0)$ was fixed according to the first observation. We estimate r and p during the initial epidemic growth phase comprising approximately 3–5 generations of disease transmission when the proportion of susceptible individuals in the population approximates its initial value. The mean generation interval has been estimated at ∼3–5 days for influenza (Carrat et al., 2008), about two weeks for measles (Fine, 2003), smallpox (Halloran et al., 2002), and Ebola (Team WHOE.R., 2014), about one week for pneumonic plague (Gani and Leach, 2004), ∼3–7 days for foot-and-mouth disease (Burrows, 1968) and has been estimated at ∼4 years for HIV/AIDS (Nishiura, 2010).

2.4. Confidence intervals

Confidence intervals for the model parameter estimates were constructed by simulating 200 realizations of the best-fit curve $C'(t)$ using parametric bootstrap with a Poisson error structure, as in prior studies (Chowell et al., 2007; Chowell et al., 2006a). Parameters r and p were then estimated from each of the 200 simulated epidemic curves to derive nominal 95% confidence intervals.