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Comment

Understanding apparently non-exponential outbreaks Comment on "Mathematical models to characterize early epidemic growth: A review" by Gerardo Chowell et al.

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Mechanistic mathematical modelling of the population dynamics of infectious diseases has advanced tremendously over the last few decades [1–6]. Transmission models have been applied to countless diseases of public health importance, including seasonal and pandemic influenza [7], childhood diseases such as measles [8,9] and whooping cough [10], vector transmitted diseases such as malaria [11] and dengue [12], and waterborne diseases such as cholera [13–15]. Much attention in recent years has been directed to emergent diseases such as SARS [16], new subtypes of influenza [17,18], Ebola [19,20], and Zika [21], for which an understanding of early outbreak dynamics is critical.

Early outbreak dynamics can provide clues about underlying processes that generate observed epidemic patterns. In particular, typical epidemic models predict initially exponential growth in incidence, and the assumption that such models are appropriate for studying outbreak dynamics is not usually questioned. Chowell and co-workers [22] review extensive work in the last few years that casts doubt on the common belief that initial epidemic growth should be expected to be exponential. Consequently, fitting mathematical models that generate exponential initial growth to observed epidemics—which might be growing non-exponentially—might lead to biased or meaningless parameter estimates and spurious epidemiological inferences. The two major themes of the Chowell et al. review are (i) the use of a simple, phenomenological model to investigate whether initial growth is truly exponential and (ii) transmission models with inhomogeneous contact structure that can yield initially sub-exponential epidemic growth.

In order to quantify departures from exponential growth, the approach that Chowell et al. [22] review is to fit a two-parameter generalized growth model [23] to the cumulative incidence of an observed epidemic. Writing $C(t)$ for cumulative incidence at time t, the phenomenological model is $\mathrm{d}C/\mathrm{d}t = rC^p$, which is easily solved to yield

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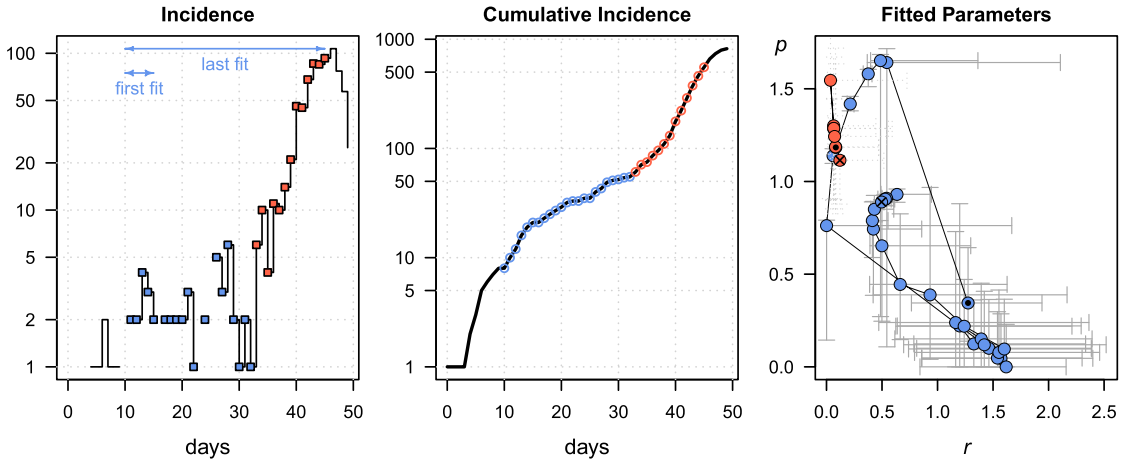

Fig. 1. *Left panel*: influenza pH1N1 incidence in Mexico from March 11th to April 29th 2009 (data sourced from [31]). Solid squares indicate data used for fitting parameters. Blue (resp. red) indicates data judged by eye to be before (resp. after) the tipping point beyond which the probability of fizzling was negligible. *Middle panel*: cumulative incidence inferred from the left panel. *Right panel*: estimates of r and p using an increasing amount of data (using parametric bootstrapping as in [23]). Solid circles are median estimates and grey segments are 95%CI. The estimates using the smallest (resp. largest) number of observations are indicated with • (resp. ×). Blue estimates correspond to fits based on data including the blue points in the left panel, so • indicates the "first fit" from day 11 to day 16 and × indicates the "last fit" from day 11 to day 45. Red estimates use only the red data in the left panel, so • indicates a fit based on days 33 to 38 and × indicates days 33 to 45. The variation of the estimates highlights their sensitivity with respect to the window of observation chosen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

$$C(t) = \begin{cases} \left(C_0^{1-p} + (1-p)rt\right)^{1/(1-p)} & p < 1, \\ C_0\, e^{rt} & p = 1, \\ \dfrac{1}{\left(C_0^{-(p-1)} - (p-1)rt\right)^{1/(p-1)}} & p > 1. \end{cases}$$

For $p = 1$, the growth is exponential at rate r. For $p < 1$ it is sub-exponential, while for $p > 1$ it is super-exponential (until the finite-time singularity at $t_{\max} = C_0^{-(p-1)}/[(p-1)r]$). Chowell et al. [22,23] assume that $p \leq 1$, and frequently find $p < 1$ when fitting the model to epidemic data.

The observation that initial epidemic growth is typically sub-exponential is important and will surely motivate much further research aiming to determine which biological mechanisms truly give rise to observed sub-exponential outbreak patterns. In addition to the issues that Chowell et al. [22] emphasize must be addressed (*e.g.*, behaviour changes, spatial structure), we suggest that the further considerations listed below deserve careful attention as this research progresses. Several of these issues are illustrated in Fig. 1, where we have applied the methodology of Chowell et al. [22,23] to the 2009 influenza pandemic in Mexico.

1. *Potential for super-exponential growth.* Imposing the constraint that $p \leq 1$ is unnecessary and potentially misleading.
2. *Sensitivity to observation window.* Defining the "initial growth period" is generally done in an *ad hoc* manner, yet estimated values of r and p can depend strongly on time range considered. Plotting how parameter estimates change as the position and length of the observation window is altered greatly increases appreciation of the limitations of parameter estimation algorithms [24].
3. *Confidence intervals may be large.* Even if they exclude $p = 1$, wide confidence intervals on r and p may preclude inferences that differ substantially from exponential growth models.
4. *Apparently non-exponential growth can be induced by demographic stochasticity (process error).* Soon after initial invasion, the probability that an outbreak will fizzle out before taking off is substantial. Until an epidemic reaches the tipping point beyond which the probability of fizzling is negligible, incidence will tend to be noisy and cumulative incidence can appear non-exponential.

5. *Apparently non-exponential growth can be induced by reporting limitations (observation error).* An exponentially growing epidemic can put strains on surveillance systems such that reporting rates decrease as incidence increases, yielding sub-exponential *reported* incidence. Depending on the disease, other systematic observation errors can be induced by changes in awareness or stigma, leading to biased reporting and growth estimates that could be non-exponential.
6. *Saturation may bias estimates of r and p.* Even in the deterministic limit, standard models yield exponential growth only instantaneously, since the growth rate is slowed by susceptible depletion. Particularly if temporal sampling of the growth phase of an epidemic is coarse (or the intrinsic growth rate is very fast), phenomenological models that incorporate saturation of growth (*e.g.*, the logistic equation) may be better for estimation of the initial exponential growth rate [24]. Exploiting the same principle might improve estimates of r and p for non-exponentially growing epidemics.

The review of Chowell et al. [22] highlights existing methodology to detect and understand sub-exponential outbreaks. Phenomenological modelling that can detect non-exponential growth in a given time series is a useful tool when investigating outbreaks precisely because it does not depend on specific biological assumptions and can be carried out quickly. Other computationally efficient tools, such as time-dependent estimation of effective reproduction numbers [25–27] or compounding decreasing reproduction numbers [28] (which implicitly provide other frameworks for assessing sub-exponentiality), can also help to narrow the focus of more demanding mechanistic modelling. Ultimately, in most infectious disease management contexts, transmission models that incorporate both process and observation error [29,30] seem likely to be unavoidable (and perhaps most informative) for understanding and controlling epidemics.

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