Proposal: The feasibility of the end-of-outbreak under the tailored interventions

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1 Aim

Real time assessment of tailored preventive measures is important in that policy maker can decide the intensity of public health interventions. Now the measurement for the assessment is usually regarded as only effective reproduction number R_t, which means the average number of secondary cases generated by a primary case on day t. However interventions can be classified into two categories: suppression and mitigation strategies and R_t only itself does not indicate such characteristics of interventions from the both aspects of interventions: the impact of intervention on the strength and the speed of an epidemic. Indeed, R_t does not provide temporal information of the speed of an epidemic.

We aim to develop new real time measurements which quantify the impact of interventions, and estimate the probability that the epidemic would go extinct, and time to achieve zero-case by keeping the tailored interventions of the same intensity.

2 Model

2.1 Strength & speed of interventions based renewal process

Here we describe the transmission dynamics using the renewal equation which brings the expected number of new domestic cases $\mathbb{E}[i(t)]$:

$$\mathbb{E}[i(t)] = \int K(t,\tau) i(t-\tau) d\tau \tag{1}$$

where $K(t,\tau)$ and $i(t)$ denote the infection kernel and the number of incidence on an infected date t. τ denotes the time since infection, i.e., infection age. For the simplicity, we first ignore the imported cases, which reproduce new transmission tree (let me consider the issue with imported cases later). Hereafter, let us introduce the terms representing "strength" and "speed" of an epidemic intervention (got a primary idea from [1]).

First, we consider the strength of interventions. By using time from infection of a primary case to secondary transmission, i.e., the generation time, the infection kernel can be decomposed as $K(t,\tau) = R_0 g(\tau)$ (R_0 is the basic reproduction number 2.5 and $g(\cdot)$ is the probability density function of generation time estimated elsewhere [2]). Then the strength of interventions is modelled as:

$$K_{post}(t,\tau) = \frac{R_0}{\theta(t)} g(\tau) = R_{|\theta} g(\tau) \tag{2}$$

where $\theta(t)$ reflects the strength of interventions with the same scale of reproduction number.

Subsequently, let us introduce the speed of an epidemic intervention. The speed-representing-term can be given as the survival function $e^{-\phi(t)\tau}$ where $\phi(t)$ represents the constant hazard across the whole infection age. Here let us refer to $\phi(t)$ as the speed of interventions over time t. The corresponding infection kernel is, therefore, given as:

$$K_{post}(t,\tau) = K_{pre}(t,\tau) \exp(-\phi(t)\tau) \tag{3}$$

By integrating Equation (2) & (3) into Equation (1), we arrive at the total likelihood function, given that the incidence generating process follows a nonhomogeneous Poisson point process:

$$\mathbb{E}[i(t)] = \int R_{|\theta} g(\tau) i(t-\tau) \exp(-\phi(t)\tau) d\tau \tag{4}$$

$$\mathcal{L}(D|\Theta) = \prod_t \frac{\exp(-\mathbb{E}[i(t)])\mathbb{E}[i(t)]^{i(t)}}{i(t)!} \tag{5}$$

where D and Θ indicate the data, daily number of illness onset cases, and the set of parameters to be estimated, $\theta(t)$ and $\phi(t)$, respectively. Here $\theta(t)$ and $\phi(t)$ are jointly estimated in a Bayesian framework. I propose three approachs to estimate both $\theta(t)$ and $\phi(t)$.

- **Joint estimatiom**
  We perform joint estimation of both $\theta(t)$ and $\phi(t)$ with a weakly-informed normal prior: Normal$(\mu = 3, \sigma = 5)$ and a flat prior: Uniform$(0, 1)$, respectively.

- **Estimating only $\phi(t)$**
  Assuming the constant hazard θ over a short period is reasonable from many biological viewpoints. Here we assume ϕ is constant by a week and $\theta_i = 0.4, 0.8, 1.2, 1.6, 2, 2.4, 2.8, 3.2$ in week i. We estimate $\phi_i(t)$ under each value of θ_i in week i and compare eight models by widely-applicable Bayesian information criterion (WBIC). Then we can select the best fit model regarding θ_i in each week. A flat prior: Uniform$(0, 1)$ is employed.

- **Modelling $\phi(t)$ by using mobility data**
  Because many events such as the depletion of susceptibles, reduction of contact rates, etc. bring impacts on the speed of epidemics (the distribution of generation time) rather than the strength of epidemics, we model the speed of epidemic interventions $\phi(t)$ by using Google mobility data as a proxy of the measurements which influence on the daily change of $\phi(t)$. We employ softmax function, sigmoid function, and logistic function and compare their three model by WBIC.

$$\phi(t) = \tag{6}$$

$$\phi(t) = \tag{7}$$

$$\phi(t) = \tag{8}$$

We can also estimate the reproduction number using the infection kernel of post-intervention.

$$\begin{aligned} \mathcal{R}_t &= \int K_{post}(t, \tau) d\tau \\ &= \int R_{|\theta} g(\tau) \exp(-\phi(t)\tau) d\tau \\ &= R_{|\theta} M(-\phi(t)) \\ &= R_0 \frac{M(-\phi(t))}{\theta(t)} \end{aligned} \tag{9}$$

where $M(\cdot)$ is deemed as the moment generating function of $g(\cdot)$. This equation indicates that the intensities of interventions can be described as the term $\dfrac{M(-\phi(t))}{\theta(t)}$.

2.2 Extinction probability of an epidemic

The extinction probability represents the probability that an outbreak with a primary case would go extinct. To calculate the probability, we need to assume the offspring distribution, the distribution of the number of secondary cases generated by a single primary case. Though the offspring distribution is sometimes assumed to follow a Poisson distribution, some types of infectious diseases, here specifically COVID-19, are disseminated in an overdispersed manner. In the sense we usually assume negative binomial distribution (NB) as the offspring distribution of COVID-19 [3].

As for the estimation of the extinction probability, we use the branching process along with the offspring distribution. Let $h(t)$ and s be the probability density function (pdf) of the offspring distribution following a NB and the probability of extinction. Then the probability generating function $l(s)$ is written as

$$l(s) = \int_{t=0}^{\infty} h(t)s^t dt \tag{10}$$

Because of the equation $l(s) = s$, we can otain the balance equation:

$$s = \frac{1}{\left(1 + \frac{\mathcal{R}_t(1-s)}{k}\right)^k} \tag{11}$$

where $\mathcal{R}_t$ and k is denoted as the mean, i.e. reproduction number, and the dispersion parameter of the NB (offspring distribution).

We can estimate the extinction probability $s(t)$ using $\mathcal{R}_t$ and the disersion parameter k which has been estimated elsewhere [3], accounting for the uncertainty of $\mathcal{R}_t$. Besides the calculation, we can obtain the indicated relationship between the extinction probability $s(t)$ and the strength & speed of interventions $\theta(t)$, $\phi(t)$ from Equation (8) as well.

2.3 Time to zero-case of an epidemic

For understanding when we would achieve zero-case by continueing the day t's interventions of the same intensities, let us consider the issue based on the abovementioned renewal process. We consider the possibility to achieve zero-case only when $\mathcal{R}_t < 1$.

$$\mathbb{E}[i(t+\eta)] = \int_0^{t+\eta} R_{|\theta} g(\tau) i(t+\eta-\tau) \exp(-\phi(t)\tau) d\tau \tag{12}$$

$$i(t+\eta) \sim \text{Poisson}(\mathbb{E}[i(t+\eta)]) \tag{13}$$

We estimate η with its uncertainty when $i(t+\eta) \to 0$ conditional on $0.025 < \Pr[i(t+\eta)] < 0.975$. We may obtain a result similar to Figure 1.

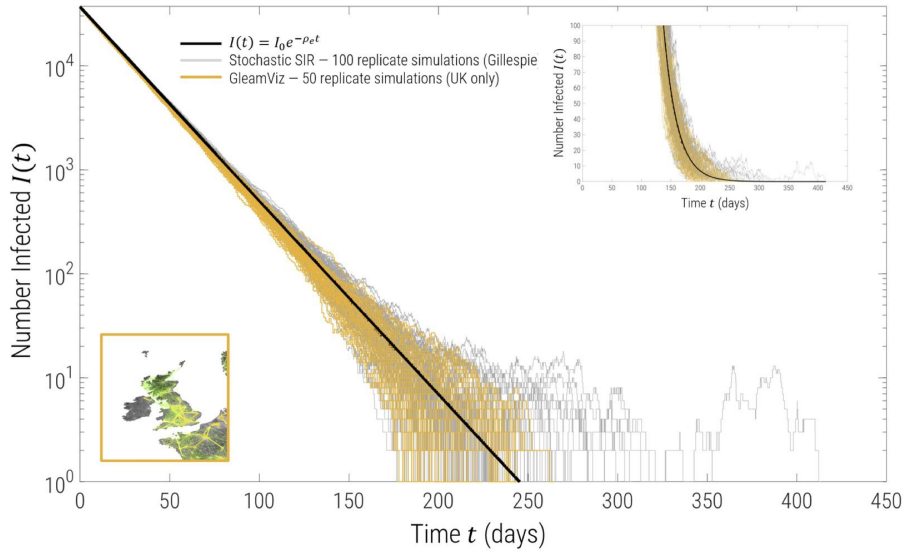

Figure 1: Stochastic extinction of epidemics: how long would it take for SARS-Cov-2 to die out without herd immunity?. Bhavin S. Khatri. medRxiv 2020.08.10.20171454; doi: https://doi.org/10.1101/2020.08.10.20171454

3 Practical model

3.1 Reconstruction of the model along with imported cases

It is not enough to infer the impact of interventions, extinction probability, and time to zero-case only in the domestic cases because the imported cases produce new transmission trees. Here we ignore the exported cases. Then Equation (4) can be reformulated as:

$$\mathbb{E}[i_{domestic}(t)] = \int R_{|\theta} g(\tau) i_{total}(t-\tau) \exp(-\phi(t)\tau) d\tau \tag{14}$$

Because of the data of imported cases, we need to use data with confirmed dates. That is, the time delay from infection to reporting should be taken into account. To account for the time delay, we employ EM algorithm based backprojection. First, we backproject the incidence on an illness onset date out of the incidence on a reported date. Subsequently we again backproject the incidence on a time of infection out of the incidence on an illness onset date. Please see the detail from [4,5]. In short, we solve the convolution (Equation(12)) to estimate $j(t)$ in backprojection.

$$\begin{aligned} \mathbb{E}[c(t)] &= \int_0^t f(t-\tau) j(\tau) d\tau \\ c(t) &\sim \text{Poisson}(\mathbb{E}[c(t)]) \end{aligned} \tag{15}$$

where, for example, $j(\cdot)$ and $f(\cdot)$ represent the number of cases on an illness onset date and the pdf of incubation period (time from infection to illness onset), respectively.

References

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[3] Endo, A., Abbott, S., Kucharski, A. J. & Funk, S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China [version 3; peer review: 2 approved] . Wellcome Open Research 5, (2020).

[4] Jung, S., Endo, A., Kinoshita, R. & Nishiura, H. Projecting a second wave of COVID-19 in Japan with variable interventions in high-risk settings. Royal Society Open Science 8, (2021).

[5] https://github.com/contactmodel/COVID19-Japan-Reff/tree/master/scripts