Estimation of the reproduction number for 2009 pandemic influenza A(H1N1) in the presence of imported cases

H Nishiura (h.nishiura@uu.nl)[1,2], M G Roberts[3]
1. PRESTO, Japan Science and Technology Agency, Saitama, Japan
2. Theoretical Epidemiology, University of Utrecht, Utrecht, the Netherlands
3. Institute of Information and Mathematical Sciences and New Zealand Institute for Advanced Study, Massey University, Auckland, New Zealand

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To the editor: Paine *et al.* recently reported an estimate of the reproduction number (R) for 2009 pandemic influenza A(H1N1) in New Zealand [1]. Given that early epidemiological assessments of pandemic potential (i.e. transmission potential and severity of the disease) were limited in accuracy and precision, identifying technical pitfalls in relevant past studies is of the utmost importance. While we enjoyed reading Paine *et al.*'s contribution [1], we believe more emphasis on the estimation framework and relevant data needs is essential for improving future studies. Namely, constructing an epidemic model involving imported cases requires particular attention to the estimation of the number of secondary cases generated by a single imported case relative to the time since immigration (i.e. arrival of the imported case into the country).

Compared with an earlier study estimating R of the pandemic influenza in New Zealand [2], a new aspect of Paine *et al.*'s study [1] is the method used to account for imported cases. It should be noted, however, that an earlier study in Japan, cited in [1], did not involve any imported cases and thus did not ignore this aspect [3]. Despite the improvement reported in [1], the estimate of R obtained should not be regarded as correct or as a revised estimate, as compared with [2], for the reasons given below.

To demonstrate our concerns, we have used a renewal equation (which captures the birth process of infected individuals) to describe the time dependent increase in incidence $j(t)$ (i.e. the number of new local infections) at calendar time t. With generalisation, the modelling approach taken by Paine *et al.* [1] is identical to a classical branching process model with immigration [4], i.e.

$$j(t) = R\int_0^\infty \left[j(t-\tau) + i(t-\tau) \right] g(\tau) d\tau \qquad \text{(Equation 1)}$$

where R is the reproduction number, $i(t)$ is the number of new imported cases (incidence of imported cases) at time t and $g(\tau)$ is the probability density function of the generation time of length τ. Of course, the corresponding estimator of R is given by

$$\hat{R} = \frac{j(t)}{\int_0^\infty \left[j(t-\tau) + i(t-\tau) \right] g(\tau) d\tau} \qquad \text{(Equation 2)}$$

Direct application of Equation 2 to the epidemiology of influenza results in an underestimation of R for three reasons. Here we propose a more appropriate equation than Equation 1 to describe the observed epidemiological dynamics:

$$j(t) = R\left(\int_0^\infty j(t-\tau) g_1(\tau) d\tau + \alpha \int_0^\infty i(t-\tau) g_2(\tau) d\tau \right) \qquad \text{(Equation 3)}$$

where α is the relative contribution of imported cases to secondary transmission (as compared with local cases), $g_1(\tau)$ is the probability density function of the generation time (i.e. identical to $g(\tau)$ in Equation 1), and $g_2(\tau)$ is a truncation of the generation time distribution, i.e.

$$g_2(\tau) = \begin{cases} 0 & \text{for } \tau < \tau_0 \\ g_1(\tau) & \text{for } \tau \geq \tau_0 \end{cases} \qquad \text{(Equation 4)}$$

where τ_0 represents the time elapsed from infection of imported cases to their entry into New Zealand.

The first of our concerns is that the relative infectiousness, α, not only rescales $g_2(\tau)$ but also reflects both the intrinsic and extrinsic dynamics of imported cases (e.g. international travellers may have a smaller number of contacts than local cases and, moreover, may have been more likely to be tested than local febrile cases), which would have changed the estimate obtained in [1]. Given that the early epidemic period of interest corresponds to the containment phase, it is natural to assume that α was smaller than one. This was the case in Japan, where α = 0.15 was estimated, ignoring the difference between g_1 and g_2 [5]. If α were

zero, employing Equation 3 would have the same effect as removing imported cases from the analysis, as in [2]. Second, failing to account for Equation 4 led to an underestimation of R in [1], although an explicit estimation of $g_2(\tau)$ would require substantial epidemiological and statistical effort. Third, Paine *et al.* [1] adopted an exponential distribution for $g(\tau)$ in Equation 1, which is known to yield a smaller estimate of R compared with that from a more realistic distribution with an identical mean [6]. Although Paine *et al.* [1] emphasised the importance of imported cases and obtained a smaller R compared with the earlier study [2], none of the three key issues mentioned above were discussed. Without addressing these, the modelling approach of Paine et al. [1] could be interpreted as arbitrarily scaling down the magnitude of R.

Although we agree that the early estimate of $R = 1.96$ in New Zealand is now regarded as an overestimate, due to the observed final size of the epidemic (i.e. the proportion infected in a population by the end of first epidemic wave) and when compared with estimates of R in other countries, we believe that the underlying reasons for the overestimation have not been clarified by Paine *et al.* [1], leading to concerns about the modelling method. An important implication that can be drawn from this letter is that an explicit modelling approach to immigration requires us to know at least the times of infection and arrival of imported cases. In addition, understanding the frequency of contacts of travellers (in comparison with non-travellers) and empirically observing the number of secondary cases arising from imported cases would add great value when attempting to obtain a precise estimate of R. Critical assessment of early naive studies of pandemic potential must be based on a firm analytical understanding.

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