



## **Estimating the reproduction number of the novel influenza A virus (H1N1) in a Southern Hemisphere setting: preliminary estimate in New Zealand**

On 11 June 2009, the World Health Organization raised the influenza pandemic alert level from phase 5 to phase 6, declaring that the newly emerged influenza caused by a novel influenza A virus (H1N1) had reached pandemic levels. Although summer conditions in the Northern Hemisphere might be impeding the spread of this pandemic, in some Southern Hemisphere countries (including New Zealand) there appears to be very active and widespread transmission.

The first imported cases in New Zealand arrived on 25 April in a group of students returning from a visit to Mexico. On 30 April, this novel pandemic influenza became a notifiable and quarantinable disease in New Zealand, and widespread indigenous transmission became evident in June. By 6 July, 1059 confirmed cases had been reported, including 3 deaths (and subsequently additional deaths have occurred).

To assess the transmissibility of this pandemic influenza virus in New Zealand (i.e. the expected magnitude of an epidemic), we investigated the time-evolution of confirmed and probable cases in New Zealand up to the end of June 2009. In particular, we estimated the reproduction number,  $R$ , which is the average number of secondary cases generated by a single primary case.  $R$  is a summary measure of the transmission potential in a given epidemic setting, and has been estimated to range from 1.4–1.6 in Mexico<sup>1</sup> and 2.0–2.6 in Japan<sup>2</sup> for this current pandemic.

**Methods**—We analysed the temporal distribution of novel influenza A virus (H1N1) cases notified to medical officers of health and recorded on the national surveillance system (EpiSurv). Figure 1 shows the observed temporal distribution from 28 May to 28 June 2009, including 585 confirmed cases and 38 probable cases.<sup>3</sup>

The time-evolution is illustrated by the earliest date entered in EpiSurv, which is either date of symptom onset, hospitalisation, death, or reporting, because the date of onset has not been available for all cases (though in fact no deaths occurred in this time period).

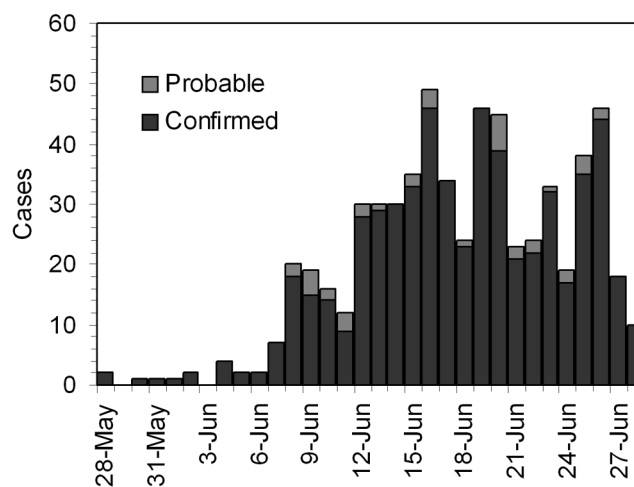
A confirmed case was defined as a person with laboratory-confirmed novel influenza A (H1N1) virus infection by means of real-time PCR, viral culture or 4-fold rise in specific neutralising antibodies. A probable case was defined as a person with an influenza-like illness (i.e. [i] history of fever, chills, and sweating or clinically documented fever greater or equal to 38°C, plus [ii] cough or sore throat) who has a strong epidemiological link to a confirmed case or defined cluster.

To estimate  $R$  we first removed 63 imported cases from the epidemic curve and assessed the growth of the remaining cases who were healthcare workers, those with known contact/s, or those with unknown contact/s. Second, we investigated the initial growth phase which was counted from 2 June when the first indigenous secondary case was reported.

The exponential growth phase was assumed to have a mean duration of 15 days (from 2–16 June) but windows in the  $15 \pm 2$  days were also used. It should be noted that the latest time points of the exponential growth phase were before 22 June, when constraints on testing began to occur due to high demand. This was also the day when health authorities switched from a containment to a “manage it” phase of pandemic control.

Assuming that the reporting delay (from onset to reporting and from onset to hospitalisation) was independent of calendar time, the growth rate of reported cases in the epidemic curve (Figure 1) mirrors the exponential growth rate of infections.<sup>4</sup>

**Figure 1. Epidemic curve of the novel influenza A virus (H1N1) infection in New Zealand**



The horizontal axis represents the earliest date entered in EpiSurv, which is either date of symptom onset, hospitalisation, death, or reporting. Imported cases from early April to early May are not shown.

Third, we estimated the intrinsic growth rate  $r$ , which is also referred to as the Malthusian growth rate. We estimated  $r$  based on a pure birth process.<sup>5,6</sup> Given our observations of the cumulative number of cases,  $C(0), C(1), C(2), \dots, C(t)$ , we have

$$\Pr(C(t) = n + m | C(t-1) = n) = \binom{n+m-1}{n-1} \exp(-rn) (1 - \exp(-r))^m \quad (1)$$

which was used to construct a likelihood function for  $r$ ,

$$L(r) \propto \exp\left(-r \sum_{i=0}^{t-1} C(i)\right) (1 - \exp(-r))^{C(t) - C(0)} \quad (2)$$

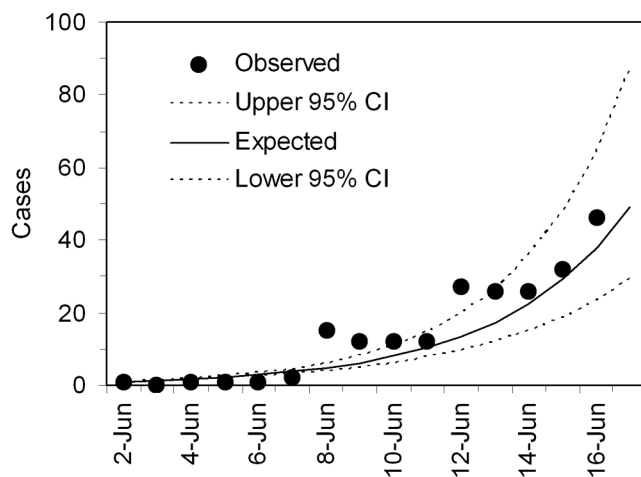
Equation (2) was used for estimating  $r$ .<sup>2,6</sup> The 95% confidence intervals (CIs) were derived from profile likelihood. Fourth, assuming that the generation time follows a gamma distribution with mean  $\mu = 2.8$  days and coefficient of variation  $k = 0.471$ , the reproduction number was estimated using the following estimator.<sup>7</sup>

$$R = (1 + \hat{r} \mu k^2)^{\frac{1}{k}} \quad (3)$$

Since the generation time of the ongoing pandemic influenza has yet to be fully clarified, we investigated the sensitivity of  $R$  to different  $\mu$  ranging from 1.6 to 4.0 days.

**Results**—Figure 2 compares the observed and predicted number of indigenous cases during the first 15 days of the pandemic in New Zealand. The maximum likelihood estimate of  $r$  was 0.26 (95% CI: 0.23–0.30) per day, and thus,  $R$  was estimated as 1.96 (95% CI: 1.80–2.15).

**Figure 2. Temporal distribution of the novel influenza A virus (H1N1) infection in New Zealand during the initial growth phase of indigenous cases**

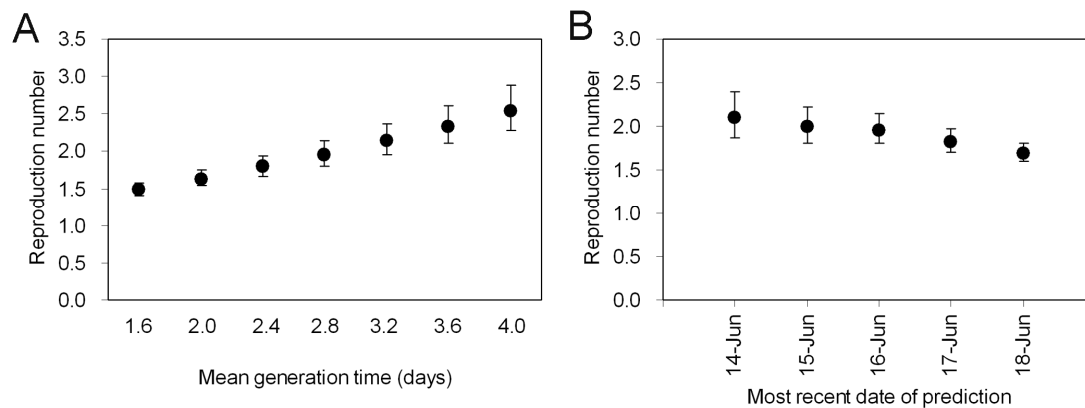


Dots, observed number of cases; Continuous line, expected number of cases; Dashed lines, uncertainty bounds of expectation based on the confidence limits of the intrinsic growth rate.

Figure 3A illustrates the sensitivity of  $R$  to variations in the mean generation time in the range of 1.6 to 4.0 days. The corresponding maximum likelihood estimates of  $R$  lie in the 1.49 to 2.55 range.<sup>7</sup> The observed pattern was consistent with our analytical understanding; the longer the mean generation time, the greater the estimate of  $R$  we will obtain.

Figure 3B shows the sensitivity of  $R$  to variations in the initial growth phase (i.e. taking 14 June to 18 June as the latest time point of reporting to observe exponential growth). The intrinsic growth rate ranged from 0.20 to 0.29 per day, and accordingly, maximum likelihood estimate of  $R$  ranged from 1.69 to 2.11.

**Figure 3. Estimates of the reproduction number of the novel influenza A virus (H1N1) infection in New Zealand.**



A) Estimated reproduction number by different mean generation times, based on the initial growth phase of the epidemic (i.e. first 15 days). B) Estimated reproduction number by different dates at the end of the initial growth phase. The mean generation time was assumed to be 2.8 days.

**Discussion**—The present study is the first to report  $R$  in a Southern Hemisphere setting for the ongoing pandemic, caused by a novel influenza A virus (H1N1). The estimates for  $R$  are generally in between the two existing estimates for Northern Hemisphere settings but were closer to the higher estimate in Japan.<sup>1,2,8</sup> It should be noted that our estimate of  $R$  is greater than published estimates for seasonal influenza in temperate countries.<sup>9</sup> Moreover, our estimate is slightly greater than that of Spanish influenza pandemic from 1918–19 in New Zealand.<sup>6</sup>

We are aware of three plausible reasons to obtain a higher estimate of  $R$  than that in Mexico:

- (i) higher virus fitness to the winter season in the Southern Hemisphere setting;
- (ii) possible large clustering of cases in certain settings (e.g. healthcare workers in hospital settings, extended families and large gatherings in Pacific People's communities); and
- (iii) possibly time-variations in the frequency of ascertaining infected individuals during the early phase of the pandemic (i.e. potential increase in the diagnostic coverage of infected individuals as a function of time).

We are actively investigating ways of improving the robustness and generalisability of  $R$  estimates for New Zealand. Addressing the impact of heterogeneous mixing on the estimate of  $R$  as well as potential under-reporting of symptomatic cases may provide more detailed insights into the transmission dynamics of pandemic influenza in this country.

Clarification of the heterogeneous patterns of transmission (e.g. age-specificity) would also permit optimising the distribution of upcoming pandemic vaccines to different age- and risk-groups. In addition, it would also be useful to explore the transmission potential using epidemic data for other outbreak-settings (to address uncertainties with respect to time, space and other risk-attributes of sub-populations).

Given that  $R$  is estimated to be 1.96 in a randomly mixing population, this would suggest that 78.6% of the population will experience infection by the end of the pandemic. Nevertheless, a smaller estimate may be more likely in a realistically-structured heterogeneously mixing population and if public health interventions around hygiene behaviours and social distancing are effective.

Thus, the transmission potential of this virus in this Southern Hemisphere setting should be regarded as relatively high. Therefore, in the context of some serious morbidity and mortality, these findings support the continuing promotion of public health interventions in this and other Southern Hemisphere countries.

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