Rapid communications

Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan

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On 16 May 2009, Japan confirmed its first three cases of new influenza A(H1N1) virus infection without a history of overseas travel, and by 1 June, 361 cases, owing to indigenous secondary transmission, have been confirmed. Of these, 287 cases (79.5%) were teenagers (i.e. between 10 and 19 years of age). The reproduction number is estimated at 2.3 (95% confidence interval: 2.0, 2.6). The average number of secondary transmissions involving minors (those under 20 years of age) traced back to infected minors is estimated at 2.8. That is, minors can sustain transmission even in the absence of adults. Estimates of the effective reproduction number R_t moved below 1 by 17 May. Active surveillance and public health interventions, including school closures most likely have contributed to keeping R_t below one.

Introduction

The reproduction number R, the average number of secondary cases generated by a single primary case, of the new influenza A(H1N1) virus, is a key quantitative measure for assessing pandemic potential [1]. In the ongoing epidemic of the new influenza A(H1N1) virus, early studies suggested that R ranged from 1.4-1.6 [2] and some estimated it to be as high as 2.2-3.1 [3]. Estimates in 1.4-1.6 range for the new influenza A(H1N1) virus are lower than estimates based on data from, for example, the fall wave of the 1918 influenza pandemic [4,5]. The present study investigates indigenous secondary transmissions of the new influenza A(H1N1) virus in Japan, not only estimating R but also exploring its age-specificity.

Methods

Epidemiological description of the epidemic

On 16 May 2009, three high school students in Kobe city, Hyogo prefecture, without a history of overseas travel, were confirmed as infected with the new influenza A(H1N1) virus. Confirmatory diagnosis in Japan requires influenza-like symptoms and a laboratory diagnosis which is made either by virus isolation, real-time PCR or a significant increase in neutralising antibody titre against the virus. Further confirmed diagnoses followed predominantly in Hyogo and Osaka prefectures. The increased number of infections among particular age groups was most evident in the data from prefectures where most secondary cases were found among high school students attending different schools.

By 1 June, the Ministry of Health, Labour and Welfare of Japan had reported 371 confirmed cases, including nine imported cases and one case traced back to a distant international airport (i.e. a worker at Tokyo-Narita airport) [6]. Figure 1 shows the geographic distribution of 361 indigenous cases. Cases outside Osaka and Hyogo prefectures had travel histories to Osaka or Hyogo before their illness onset. The index case(s) (who may have remained asymptomatic [7]), with a history of overseas travel, has (have) yet to be identified. Furthermore, there are no known cases prior to the five confirmed cases that developed the disease on 9 May in Hyogo (Figure 2A). The triggering event may be associated with Japan's two-week festive break, the "golden week", just before 9 May, when people may have travelled to and returned from Mexico, United States and Canada.

Figure 1

Spatial distribution of the epidemic of new influenza A(H1N1) virus infection in Japan. Cumulative number of confirmed indigenous cases, as of 1 June 2009 (n = 361)

Note: Cases in Tokyo, Saitama, Shiga and Kyoto had travel history to either Hyogo or Osaka prefecture before illness onset. Kobe city, where first three cases were diagnosed, is a capital city of Hyogo prefecture.

We analysed the temporal incidence distribution of confirmed cases for this epidemic (Figure 2A). The known dates of illness onset are used except for a fraction of the confirmed cases in Kobe city (45; 12.5%) whose dates of onset have yet to be fully clarified. Since the known median time from onset to diagnosis in Kobe has been estimated at 1.0 day [8], it is assumed that the dates of onset among the 45 cases in Kobe were 1 day before their date of diagnosis. We observed that by the time the first three cases had been confirmed (16 May), the epidemic curve was just about at its peak. 16-17 May fell on a weekend, and all schools in Osaka and Hyogo were officially closed for one week starting on 18 May. Figure 2B displays the age-distribution of the 361 confirmed cases, which is concentrated in the teenage population. We see the age-specific window (10-19 years of age) that includes 287 confirmed cases (79.5%; 95% confidence interval (CI): 75.3, 83.7).

Epidemiological analysis

Taking into consideration the high levels of uncertainty related to the invasion of a population by a novel influenza virus, three different methods are used to estimate the transmission potential of the new influenza A(H1N1) virus. To concentrate on the transmission potential in Japan, all nine imported cases and one case that is not associated with indigenous transmission in Hyogo and Osaka were removed from the following analyses.

Model 1 (M1)

Estimation of R using the intrinsic growth rate [3,5]. The intrinsic growth rate r, is estimated via a pure birth process [9]. The likelihood is proportional to:

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

where C(t) denotes the cumulative number of cases on day t. C(0) = 5 and t = 0 represents 9 May. The generation time (GT) is assumed to follow a gamma distribution with mean $\mu = 1.9$ days and coefficient of variation $v = 47\%$ [2]. R is subsequently estimated using the estimator [10]:

$$(1+r\mu v^2)^{\frac{1}{v^2}}$$

Given that many serial intervals reported from Spain are longer than 1.9 days [7], the uncertainties surrounding GT estimates are partially addressed through a sensitivity analysis of R to variations in the mean GT in the range from 1.3-4.0 days. The exponential growth phase is assumed to have a mean duration of 8 days but windows in the 8±2 days were also used.

Model 2 (M2)

The effective reproduction number R_t, the average number of secondary cases generated by a primary case at time t, is estimated. The daily growth rate rt is used to estimate R_t following the approach described elsewhere [11]; the distribution of GT and the estimator of R used are the same as those used in M1. The mean GT is assumed to be 1.9 days but varying in the 1.3 to 2.5 days range [2].

Time- and age-specificity of the epidemic of new influenza A(H1N1) virus infection in Japan
A) Epidemic curve of confirmed indigenous cases according to the date of illness onset, as of 1 June 2009 (n = 361)
B) Age distribution of confirmed indigenous cases, as of 1 June 2009 (n=361)
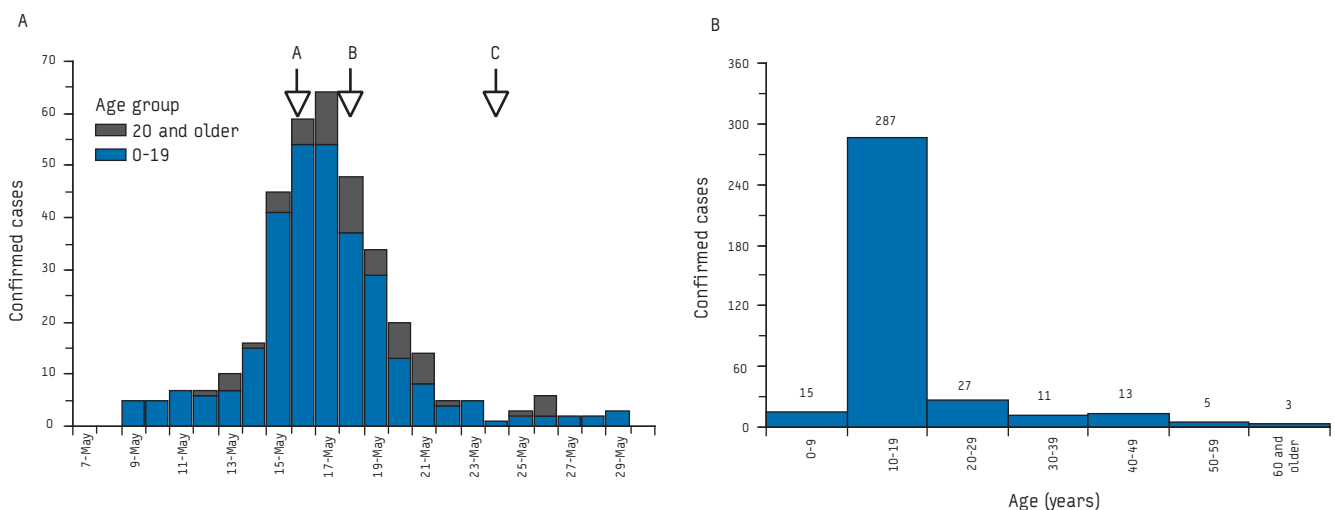
Note: None of the confirmed cases had recent history of overseas travel (except for one case in Wakayama). The nine cases, believed to have become infected abroad, and one case, arising in a worker at Tokyo-Narita airport, are excluded from these figures.
The dates of illness onset for each confirmed case are reported by prefectural governments, except for a fraction of cases in Kobe city where cases with unknown dates of onset are assumed to have developed the disease one day before the confirmatory diagnosis (based on published median estimate [8]). It should be noted that the dates of onset are based on preliminary reports and have yet to be refined.
Arrow A indicates the date on which the first three cases were diagnosed in Kobe city. All schools in Hyogo and Osaka were closed between the dates signalled by the arrows B and C.

Model 3 (M3)

The role of age-specificity in transmission is analysed using estimates of the next-generation matrix, K (Figure 3). First, we aggregate the population in two age groups, minors and adults. Second, since the mean GT is approximately 2 days [2], the daily number of cases during the exponential growth phase (i.e. first 8 days) uses as its unit of time, two-day intervals (i.e. cases, c, in days 1 & 2, 3 & 4, 5& 6 and 7 & 8 are grouped). Third, the expected value of cases in age-group i of grouped-generation τ, $E(c_i(\tau))$, is modelled by $R_{ii}c_i(\tau-1)+R_{ij}c_j(\tau-1)$ (fort = 2, 3 and 4) where Rgh is the element of K that corresponds to the average number of secondary cases in group g caused by an infected individual in group h. We estimate the entries in the matrices, assuming two different mixing patterns modelled via two unknown parameters by means of Poisson regression (Figure 3).

Results

The intrinsic growth rate r, is estimated at 0.47 (0.40, 0.56) per day. Accordingly, M1 gives an R estimate of 2.3 (95% CI: 2.0, 2.6). Figure 4A illustrates the sensitivity of R to variations in the mean GT in the range 1.3-4.0 days. The corresponding R estimates lie in the 1.8 to 4.8 range. Variations in the initial growth phase (i.e. ±2 days) do not greatly influence R; i.e. the expected values of R lie in the 1.9 to 2.3 range. The exclusion of the less documented cases in Kobe lead to an R estimate of 2.0 (95% CI: 1.7, 2.3).

Use of M2 suggests that R_t peaked on 14 May (Figure 4B). On 17 May, the day after a press release announced the first three confirmed diagnoses, R_t declined below 1. Under active surveillance efforts and school closures, R_t was kept below 1 thereafter. Consistent temporal patterns of $\hat{R}_t$ are seen using different values, except for slight increase and decrease in R_t estimates, for GT mean values in the 1.3-2.5 day-range.

F I G U R E   3

Next-generation matrix
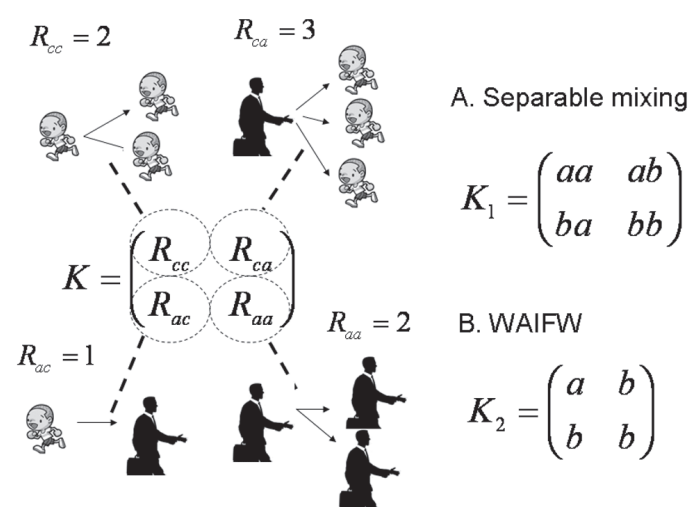
Note: Each element of the next-generation matrix, i.e., R_{cc}, R_{ca}, R_{ac} and R_{aa}, denotes the average number of secondary transmissions caused by a single primary case for child-to-child, adult-to-child, child-to-adult and adult-to-adult transmissions, respectively (note that here "child" represents "minor", aged from 0 to 19 years). The reproduction number R, for the whole population, is given by the largest eigenvalue of the next-generation matrix. By making qualitative assumptions A and B, two parameters, a and b, are estimated.

Using M3, the next-generation matrix, K_1 estimate, under the separable mixing assumption is

$$\hat{K}_1 = \begin{pmatrix} 2.82 & 0.32 \\ 0.32 & 0.04 \end{pmatrix}$$

while our K_2 estimate based on a qualitative assumption of WAIFW (who acquired infection from whom) matrix is

$$\hat{K}_2 = \begin{pmatrix} 2.82 & 0.29 \\ 0.29 & 0.29 \end{pmatrix}$$

The host-specific reproduction number [12] for minor, i.e. the average number of secondary minor cases generated by a single primary minor case was 2.8 under K_1 and K_2. Hence a population of minors can sustain the chains of secondary transmission even in the absence of adults (i.e. for this epidemic "minors" are the "core" group). Our estimate of R based on M3 is the largest eigenvalue of K, and R is estimated at 2.9 for both matrices. These estimates are slightly greater than R estimates based on M1; when the mean and variance of GT is 2.0 days and 0 days^2 (i.e. if GT is constant, following a delta function), our R estimate is 2.6.

Discussion

Two important conclusions can be drawn from our epidemiological analyses. Firstly, the reproduction number R of the new influenza A(H1N1) virus in Japan is estimated to be as high as 2.3, a value that is significantly higher than that recently reported [2]. The pandemic potential of this virus in Japan may be higher in terms of transmission potential than in other areas of the world. In particular, it should be noted that our estimate of R is greater than published estimates for seasonal influenza epidemics in temperate countries [13]. Given that our R estimate has been tested for robustness to uncertainty to mean GT, it seems plausible that high contact rates among teenagers (when compared to other populations) may be one of the main drivers of this epidemic. From a transient increase in R_t around 14 May, our high estimate of R may reflect the existence of few highly connected clusters of cases among "cliques" of high school students. There may be additional contributing factors to variations in our R estimates, including cross-protective immunity due to previous exposure to other closely related influenza viruses.

Secondly, our age-specific estimates support the view that minors can sustain transmission of the new influenza A(H1N1) virus among themselves. Available data are not enough to investigate the precise role of age-specific effects (e.g. different roles of transmission among infants, primary-school, high-school and university students) due to small case counts. Nevertheless, we believe that the population of minors could play a key role as a "reservoir" for sustained chains of secondary transmission, despite the fact that cases in this group include those infected in some atypical school clusters. Should further data confirm these results then the value of public health interventions targeting minors (closing schools and further contact restrictions between minors) could be effective in controlling further outbreaks in Japan and other countries.

Our estimates of R_t provide a quantitative measure of the time-evolution of the "force" of the epidemic. Although the dates of onset have yet to be refined and, thus, the precision of R_t estimate may have been influenced by possible delay in diagnosis and reporting, R_t declined below 1 one day after the news of the first

three confirmed diagnoses. Thereafter, the implementation of active surveillance programmes, including contact tracing, combined with school closures, most likely have contributed to keeping R_t below 1.

R is useful for assessing transmission potential, and it is one of the ways of assessing pandemic potential. This study puts emphasis on quantifying the impact of contact patterns on the transmission potential, factors that vary across space and time. Thus, further analyses of R for the new influenza A(H1N1) virus in different settings are needed to better quantify the role of uncertainty and heterogeneous patterns of transmission in these estimates. Validation of our quantitative understanding of the role of age-specific transmission should lead to improved effectiveness of age-specific control measures.

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FIGURE 4

Estimates of the reproduction number for the epidemic of new influenza A(H1N1) virus infection in Japan
A) Estimated reproduction number R, based on the initial growth phase of the epidemic (i.e. first eight days)
B) Effective reproduction number R_t, as a function of time
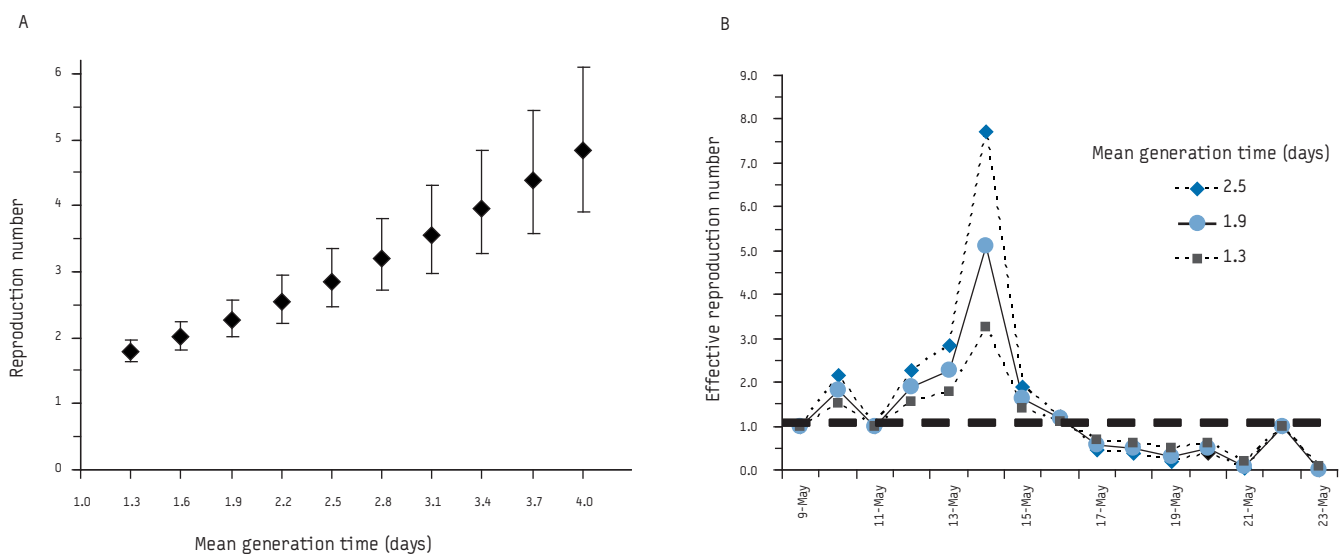
Note:
A) Mean and variance of the generation time were 1.9 days and 0.8 days^2 (given a coefficient of variation of 47%), and the sensitivity of R to different mean generation times is examined. Coefficient of variation is kept constant when the mean generation time is varied.
B) $R_t > 1$ indicates growth of cases at a given point of time, while $R_t < 1$ indicates that the epidemic is in declining trend and may be under control. The horizontal dashed line represents the threshold value, $R_t = 1$. It should be noted that the dates of onset in Japan have yet to be refined, and the precision of R_t estimate may have been influenced by possible delay in diagnosis and reporting