Jpn. J. Infect. Dis., 65, 132-137, 2012

Original Article

Case-Based Surveillance of Pandemic (H1N1) 2009 in Maebashi City, Japan

Satoshi Tsukui*

Maebashi Public Health Center, Gunma 371-0014, Japan

(Received March 24, 2011. Accepted December 14, 2011)

SUMMARY: After national case-based surveillance for pandemic influenza A (H1N1) ceased on July 23, 2009, a daily case-based surveillance system was implemented in Maebashi City, Japan. All medical facilities in the city reported all patients who had positive rapid antigen tests for influenza A. When the epidemic exploded in late October, case-based surveillance for influenza-like illness (ILI) was implemented from November 3, 2009 until the end of the epidemic. A total of 7,781 influenza cases were reported between July 25 and November 2, 2009, with a cumulative incidence rate of 22.5 per 1,000 population. Nearly 70% of the patients were under 15 years old. Between November 3, 2009 and the end of March 2010, a total of 16,394 ILI cases were reported, with a cumulative incidence rate of 47.4 per 1,000 population. Of the ILI cases reported, 63% were in patients younger than 15 years old. Only one death with laboratory confirmation of the H1N1 2009 virus was reported during the epidemic. The age-specific reproduction number among children under 15 years of age was almost 1.40, whereas between children and adults (15 years of age and above) it was considerably less than 1.0. The reproduction number derived from the next-generation matrix using data from September 30 to October 14 was estimated to be 1.48 (95% confidence interval, 1.41–1.56). Among individuals under 15 years of age, the infection rate calculated using the final size equation under the assumption of no mitigation measures was nearly twice the rate reported during the epidemic. These findings indicate that the majority of the transmission of influenza A (H1N1) 2009 in the city occurred among children.

INTRODUCTION

In response to the influenza pandemic phase 4 alert declared by the World Health Organization on April 27, 2009 (1), the Ministry of Health, Labour and Welfare of Japan implemented a case-based surveillance system for H1N1 influenza beginning April 28 (2,3). On May 16, the first domestic case of influenza A (H1N1) 2009 was confirmed in Japan in a high school student with no history of travel to endemic countries (4). By late July, more than 5,000 cases had been reported in Japan (2) and the disease had spread throughout the country. Consequently, national case-based surveillance was discontinued on July 23 and integrated into routine sentinel surveillance (2).

Maebashi City, the capital of Gunma Prefecture, is located about 100 km northwest of Tokyo, and had a population of approximately 345,000 in 2009. The first case of influenza A (H1N1) 2009 in Maebashi City in a patient without a history of traveling abroad was confirmed by means of real-time polymerase chain reaction (PCR) on July 3. By July 23, 3 more cases were confirmed. After the national case-based surveillance system was discontinued, the Maebashi Public Health Center launched a new surveillance system for counting the daily number of cases of influenza reported in the city.

The reproduction number R, defined as the expected number of secondary cases generated by a single primary case, is a key quantitative measure in mathematical transmission models (5,6). In the early stage of new infectious disease epidemics, the estimate of R will be close to the basic reproduction number (R_0) in a fully susceptible population. Since the majority of H1N1 2009 cases occurred in children and youths in Japan (7) and other countries (8–12), we estimated transmissibility of the disease using the age-specific reproduction number (13,14). This report presents a description of the influenza (H1N1) 2009 epidemic wave based on case-based surveillance in Maebashi City, Japan.

*Corresponding author: Present address: Takasaki City Health Center, Takamatsu-cho 5-28, Takasaki, Gunma 371-0829, Japan. Tel: +81-27-381-6112, Fax: +81-27-381-6125, E-mail: tsukui6568@city.takasaki.gunma.jp

MATERIALS AND METHODS

Case data in the present study were collected during the epidemic in Maebashi City. During the early epidemic phase (July 25 to November 2), daily reports on cases of influenza were received from all the medical facilities (340 clinics and 21 hospitals) in the city. Patients with sudden onset of fever $\geq$38°C, one or more respiratory symptoms (e.g., rhinorrhea, cough, or sore throat), and a positive rapid antigen test for influenza A were reported.

Simultaneously, under the framework of the National Epidemiological Surveillance of Infectious Diseases (NESID), routine sentinel survei11ance data from 15 designated sentinel clinics/hospitals of the city were available during the epidemic. The sentinel surveillance was based on weekly reports of patients who had acute onset of symptoms, fever $\geq$38°C, upper respiratory symptoms, and general discomfort, as well as patients suspected of having the disease who had a positive rapid antigen test.

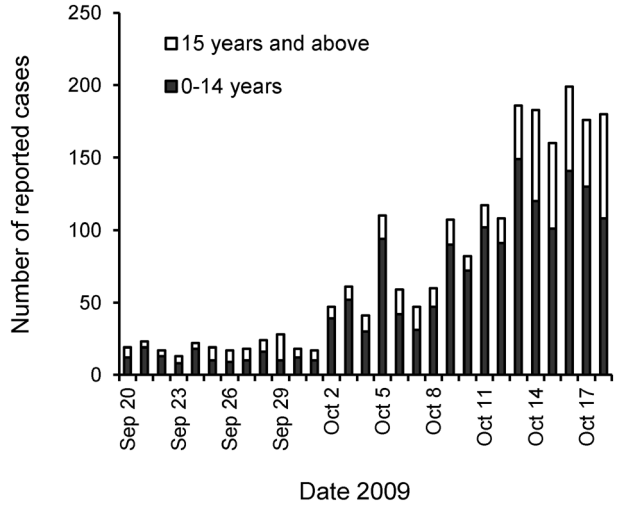

Fig. 1. Number of reported cases based on the date of initial visit from case-based influenza surveillance during the exponential growth phase, Maebashi City, Japan.

In October, the rate of reported cases accelerated. When the number of cases per sentinel reached 26 on week 43 (October 19–25), rapid antigen testing for all suspected patients was determined to be impracticable. On November 3, the reporting form was changed and the surveillance recorded daily counts of cases with influenza-like illness (ILI), defined as fever with cough and/or sore throat in the absence of a known cause other than influenza. The ILI case-counting surveillance continued until the end of March 2010 for all the medical facilities in the city. Since the dates of symptom onset were not available, the date of initial visit was used for the analyses in this study. Rates were calculated using 2009 mid-year population estimates. We assumed that the number of cases reported by doctors in Maebashi City during the epidemic for patients who lived outside the city was equal to the number of cases among city residents who consulted a doctor outside the city.

The other assumptions are the exponential growth of the epidemic and the generation time. Based on the epidemic curve (Fig. 1), we considered that the initiation phase, during which small clusters of the disease occurred but spread was localized, continued up to the end of September. Thus, September 30 was assumed to be the starting point of exponential growth. We also assumed that the exponential growth phase continued until October 14. For the period between September 30 and October 14, we divided the population into children (under 15 years of age) and adults (15 years of age and above). The periods between September 27 and October 11, September 28 and October 12, and September 29 and October 13 were also examined.

The age-specific reproduction number R_{ij}, defined as the average number of secondary cases in age group i caused by a single primary case in age group j, was entered into the next-generation matrix (K) (11,13). Using the incidence $C_i(t)$ of age group i and R_{ij}, the renewal equation used by Nishiura et al. (11) has the form:

$$C_i(t) = \sum_i R_{ij} \int_0^\infty C_j(t - s)g(s)ds$$

where $g(s)$ is the generation time distribution of length s. In this study, two different fixed-lengths of the generation time were used to simplify the model. The mean generation time was assumed to be 3 days for 5 generations because the mean generation time or serial interval of influenza A (H1N1) 2009 from several previous studies was found to be 3.0 days (95% confidence interval [CI], 2.4–3.6) (15). We also adopted a generation time of 2 days for 7 generations to examine the sensitivity of the reproduction number. $C_i(\tau)$ is the number of observed cases in age group i during generation τ. The expected number of group i (child/adult) in generation τ is calculated from

$$E(C_c(\tau)) = R_{cc}C_c(\tau - 1) + R_{ca}C_a(\tau - 1)$$
$$E(C_a(\tau)) = R_{ac}C_c(\tau - 1) + R_{aa}C_a(\tau - 1)$$

where R_{cc} is the child-to-child, R_{ca} is the adult-to-child, R_{ac} is the child-to-adult, and Raa is the adult-to-adult age-specific reproduction number. Assuming two different mixing patterns (13), the entries of the 2×2 matrix using parameters a and b are estimated by means of Poisson regression. The matrix under the separable mixing assumption is given by

$$K_1 = \begin{pmatrix} aa & ab \\ ba & bb \end{pmatrix}$$

The matrix K_1 assumes that the contact between the age groups is separable. Another assumption is based on the WAIFW (who acquired infection from whom) matrix (16), given by

$$K_2 = \begin{pmatrix} a & b \\ b & b \end{pmatrix}$$

The matrix K_2 assumes a higher transmission rate between children and children than those of other types of contact. The estimate of R is given by the dominant eigenvalue of K, as proposed by Diekmann et al. (5). The 95% CIs are estimated using the parametric bootstrap method.

The effect of asymptomatic infection on estimates of the age-specific reproduction number was also examined. Since detailed data on asymptomatic infections during the epidemic were not available, we assumed a rate of asymptomatic infection of 30% based on a previous report (17). We compared 3 conditions using computer-generated data sets from observed daily symptomatic cases between September 30 and October 14; assuming that (i) 30% of child infections were asymptomatic, (ii) 30% of adult infections were asymptomatic, and (iii) 30% of both child and adult infections were asymptomatic. For each condition, 2,000 simulations were performed, and results are presented as the median estimate and the 95% percentile interval.

An estimate of the number of people who are expected to develop infection by the end of an epidemic can be derived from the transmission model in heterogeneously mixing populations, given by the following equation (18):

$$z_i = 1 - \exp\left(-\sum_j R_{ij}z_j\right)$$

where z_i is the proportion infected among age group i by the end of the epidemic. This assumes an entire population with no prior immunity, and no effective mitigation measures.

RESULTS

Between July 25 and November 2, 2009, a total of 7,781 cases were reported, with a cumulative incidence rate of 22.5 per 1,000 population. The age of the patients ranged from <1 year to 87 years, with a median age of 12 years. Of the cases reported, 69.7% were in patients under 15 years old, 29.5% were in patients between 15 and 64 years of age, and 0.5% was in patients 65 years old and above.

After the change of the surveillance strategy on November 3, a total of 16,394 ILI cases were reported. From the beginning of November 2009 to the end of March 2010, the cumulative incidence rate of ILI was 47.4 per 1,000 population. The ages of the ILI patients ranged from <1 year to 96 years, with a median age of 11 years. Of the ILI patients reported, 62.8% were under 14 years of age, 35.7% were between 15 and 64 years of age, and 0.6% were 65 years of age and above. Visit dates in the ILI surveillance were available for 6,309 cases (38%) and report dates were used for the remaining cases.

As shown in Fig. 2, the shape and duration of the epidemic curves from the influenza surveillance and ILI surveillance are similar to those from the sentinel surveillance under NESID. The cases of 186 hospitalized patients during the epidemic were analyzed. Of these, 85% were children under 15 years of age. In November, one death occurred in a patient aged >80 years who had a positive PCR for the pandemic A (H1N1) 2009 virus (A(H1N1)pdm09).

Table 1 gives estimates of the age-specific reproduction number from the entries of the next-generation matrices K_1 (separable mixing) and K_2 (WAIFW). The estimated children-to-children reproduction number was 1.39 for K_1 and 1.40 for K_2, while the other estimated reproduction numbers were considerably less than 1. The dominant eigenvalue of K under each assumption gave us an estimated R of 1.48 (95% CI: 1.41–1.56) using an assumed generation time of 3 days. The different periods between September 27 and October 11, between September 28 and October 12, and between September 29 and October 13 led to similar R values of 1.45–1.55. When we used 2 days as the mean generation time, the estimate of R was reduced to 1.34 (95% CI, 1.29–1.39) for K_1 and to 1.34 (95% CI, 1.28–1.40) for K_2.

Figure 3 shows the effect of asymptomatic infection on estimates of the age-specific reproduction number. The results appear to be consistent in both matrices. If asymptomatic infection occurred evenly across children and adults, both age-specific estimates were likely to be unbiased. If it occurred among children, the adult-to-adult reproduction number was underestimated. If it occurred among adults, the child-to-child reproduction number was slightly underestimated and the adult-to-adult reproduction number was overestimated.

A serological study indicated that Japanese residents born after 1920 had few antibodies against the A(HINI)pdm09 before the epidemic (19). We applied the age-specific reproduction numbers derived from K_1 or K_2 to the final size equation, assuming that the infected population was negligible in the initial exploration phase. The estimate of the final proportion of the infected population among children was 59%, and the es-

Table 1. Estimates of age-specific reproduction number for pandemic influenza 2009, Maebashi City, Japan

	Matrix K_1 (separable mixing)	Matrix K_2 (WAIFW[1)])
Child to child[2)]	1.39	1.40
Adult to child[2)]	0.37	0.31
Child to adult[2)]	0.37	0.31
Adult to adult[2)]	0.10	0.31

[1)]: Who acquired infection from whom.
[2)]: Number of secondary children (under 15 years of age)/adults (15 years of age and above) caused by a single primary child/adult.

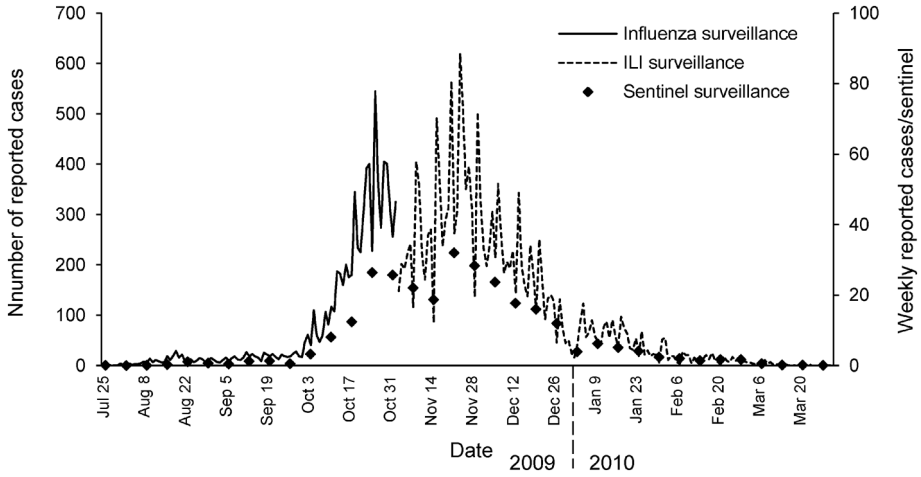

Fig. 2. Daily number of cases reported during influenza surveillance between July 25 and November 2, 2009; daily number of cases reported during influenza-like illness (ILI) surveillance between November 3, 2009 and the end of March 2010; and weekly cases reported per sentinel based on the time of diagnosis from sentinel surveillance during the epidemic in Maebashi City, Japan.

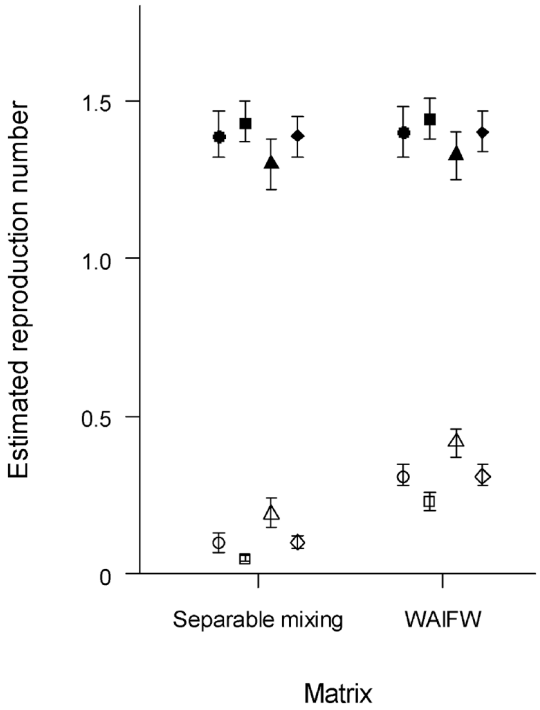

Fig. 3. Effect of asymptomatic infection on estimates of age-specific reproduction number. The symbol indicates the median estimate and the whisker shows the 95% percentile interval from the simulations. Closed and open symbols indicate the child-to-child and adult-to-adult reproduction numbers, respectively. Circles, no asymptomatic infection; squares, asymptomatic infection among children; triangles, asymptomatic infection among adults; diamonds, asymptomatic infection among children and adults.

timate among adults was 22%, whereas the rate of cases reported by the influenza surveillance and ILI surveillance was 34% among children and 3% among adults.

DISCUSSION

Our surveillance system has limitations. First, until November 2, 2009, case ascertainment was based on the presence of influenza-like symptoms with a positive rapid antigen test. Although real-time PCR is highly sensitive for A(H1N1)pdm09, it was not feasible to perform PCR in all suspected cases in a variety of clinical settings. The usefulness of rapid antigen test kits for the detection of the A(H1N1)pdm09 remains unclear. Previous studies (20,21) have demonstrated specificities of nearly 100% with relatively low sensitivities as compared with the PCR assay. These results suggest the possibility that the number of cases detected in the surveillance prior to the end of October was underestimated. We believe, however, that diagnosis using a rapid antigen test should be more reliable than that based on symptoms alone. Moreover, the Infectious Disease Surveillance Center of Japan reported that 98% of the influenza virus detected in 2009/2010 season was the A(H1N1)pdm09 (3). Second, this study used initial visit dates. Use of transmission data based on visit dates involves potential errors associated with the delay from symptom onset to visit. However, a short lag period between onset date and visit date may not affect the overall estimation of disease transmission. Third, from November 2009 to March 2010, cases reported as ILI may have included patients with influenza as well as those with acute respiratory infections caused by other viruses in the community such as rhinoviruses and coronaviruses. This could potentially lead to an overestimation of epidemic influenza activity during this period.

According to the Infectious Agents Surveillance Report (3), the epidemic in Japan started in week 33 (August 10–16) of 2009, peaked in week 48 (November 23–29) of 2009, and lasted for as long as 29 weeks, until week 8 (February 22–28) of 2010. From the sentinel surveillance of Maebashi City, the number of cases per sentinel exceeded 1.0 in week 40 (September 28 to October 4) of 2009 and peaked at 32.0 in week 47 (November 16–22) of 2009. The beginning of the epidemic in Maebashi City was late compared with that in the rest of Japan, and the peak of the epidemic in the city was slightly lower than that of the nationwide epidemic (39.6 in week 48). The epidemic in the city lasted until week 8 (February 22–28) of 2010.

We observed an overall incidence of 7.0% (95% CI, 6.9–7.1) by case-based influenza surveillance and ILI surveillance during the epidemic. This rate is higher than the ILI rate of 1.7% estimated in Portugal (8), lower than that of 9.7% in Italy (10), and consistent with that of 5.7–11% in Singapore (9). We identified a large proportion of cases in children under 15 years of age, while there were few cases in adults aged 65 years and above. Similar age distribution was reported in other regions and countries (8–12).

The transmission model in the present study has some limitations. First, we used fixed lengths of generation time to simplify the model. Accordingly, aggregation of daily cases according to the mean generation time suffers some overlapping of the cases in successive generations. Hence, this approach may affect estimates of R. Although we have not yet assessed the performance of the model, our estimates seem reliable because of the data from case-based surveillance. It should be noted that estimates of R are sensitive to the generation time; namely, higher values for the generation time tend to yield higher estimates of R (22). Certainly, our estimate of R decreased with the generation time. Second, we estimated the age-specific reproduction number from daily reported data. However, unequal rates of asymptomatic infection between children and adults could bias estimates of the age-specific reproduction number. Further work is needed to investigate suitable models for age-dependent transmission.

The exponential growth assumption for R was arbitrarily decided upon visual inspection of the epidemic curve. Indeed, estimates of R in this study fluctuated with different adopted periods corresponding to the early exponential growth. Nevertheless, our R estimates seem to be consistent with previous estimates ranging from 1.4–1.6 in Mexico (23) and 1.2–1.7 in Peru (24). However, earlier studies from Japan (13), New Zealand (25), and Mexico (26) reported higher estimates of R at 2.3, 1.96, and 2.2–3.1, respectively. One of the reasons is that our estimation of R was based on data from the general population. Usually, estimates of R tend to be higher when measured in household or close-contact studies, but lower in community-based studies. In fact,

later studies from Japan (11) and New Zealand (12) reassessed the transmissibility under community-based conditions and gave estimates as low as ours.

Age-specific analysis showed that transmission among children (under 15 years of age) was initially sufficient to be self-sustaining, whereas transmission between children and adults was minimal. Similar age-specific transmission was demonstrated in previous studies from Japan (13) and Australia (14), but the estimated values of age-specific reproduction numbers among children were higher than those in our study.

Among individuals under 15 years of age, we found that the infection rate estimated using the final size equation under the assumption of no mitigation measures was nearly twice as high as the incidence rate reported during the epidemic. This difference may be partly explained by the presence of asymptomatic infected individuals, although serological surveys (27,28) have reported various rates of asymptomatic infection for the A(H1N1)pdm09. The analysis using the final size equation may also indicate the effectiveness of mitigation measures. One of the school health care regulations for the prevention of influenza in Japan is temporary school closing. Japanese children with ILI are not permitted to go to school and are advised to consult a doctor. Nearly 45% of the schoolchildren in Maebashi City consulted a doctor during the epidemic. Most of them were probably given antiviral medication because the Japanese Association for Infectious Diseases recommended early use of neuraminidase inhibitors for patients with influenza as of mid-September 2009 (29). Moreover, pandemic influenza vaccination for children began in December 2009 in Maebashi City, and the vaccination coverage until the end of March 2010 for residents aged between 1 year and 18 years was estimated to be only 22%.

In conclusion, the wave of H1N1 influenza pandemic in Maebashi City, Japan during the 2009/2010 season was observed by case-based influenza surveillance and ILI surveillance. Despite their limitations, these surveillance systems provided valuable information for understanding the epidemiology of the disease. Our results suggest that the majority of transmission of the virus occurred among children. Further studies are needed to evaluate the impact of mitigation measures, such as school closures, antiviral medication, and vaccination, on the epidemic.

Conflict of interest None to declare.

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