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 pandemic influenza A (H1N1) 2009 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 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.

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 ≥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 surveillance 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 ≥38°C, upper respiratory symptoms, and general discomfort, as well as patients suspected of having the disease who had a positive rapid antigen test.
The age-specific reproduction number \( R_{ij} \), defined as the average number of secondary cases in age group \( j \) caused by a single primary case in age group \( i \), was entered into the next-generation matrix \( K \) (11,13). Using the incidence \( C(t) \) of age group \( i \) and \( R_{ij} \), the renewal equation used by Nishiura et al. (11) has the form:

\[
C(t) = \sum_{j} R_{ij} \int_{0}^{\infty} C(t-s) g(s) ds
\]

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. \( C(t) \) is the number of observed cases in age group \( i \) during generation \( t \). The expected number of group \( i \) (child/adult) in generation \( t \) is calculated from

\[
E(C_i(t)) = R_{cc} C_i(t-1) + R_{ca} C_a(t-1) + R_{ac} C_a(t-1) + R_{aa} C_a(t-1)
\]

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

\[
K_1 = \begin{pmatrix} a & a \\ b & b \end{pmatrix}
\]

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):

\[
z_t = 1 - \exp\left(-\sum_{i} R_{ij} z_i\right)
\]
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 \( \geq 80 \) 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(H1N1)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 est-
of nearly 100

Recent studies (20,21) have demonstrated specificities for the detection of the A(H1N1)pdm09 remains unclear. The usefulness of rapid antigen test kits for the form PCR in all suspected cases in a variety of clinical settings. The usefulness of rapid antigen test. Although real-time PCR is highly sensitive for A(H1N1)pdm09, it was not feasible to per-

rapid antigen test. Although real-time PCR is highly sensitive for A(H1N1)pdm09, it was not feasible to per-

pared with the PCR assay. These results suggest the presence of influenza-like symptoms with a positive

symptom onset to visit. However, a short lag period between onset date and visit date may not affect the over-

all 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 overes-

timation of epidemic influenza activity during this period.

Fig. 3. Effect of asymptomatic infection on estimates of age-
specific reproduction number. The symbol indicates the med-
ian 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, re-

spectively. Circles, no asymptomatic infection; squares,

asymptomatic infection among children; triangles, asympto-
matic infection among adults; diamonds, asymptomatic infection among children and adults.

estimated among adults was 22%, whereas the rate of cases reported by the influenza surveillance and ILI surveil-

lance 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 per-

form 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 com-

pared with the PCR assay. These results suggest the pos-

sibility that the number of cases detected in the surveil-

lance prior to the end of October was underestimated.

We believe, however, that diagnosis using a rapid anti-
gen test should be more reliable than that based on symp-
toms alone. Moreover, the Infectious Disease Surveil-

lance 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 in-

volves potential errors associated with the delay from symptom onset to visit. However, a short lag period be-

tween onset date and visit date may not affect the over-

all estimation of disease transmission. Third, from

0

1.0

1.5

Separable mixing WAIFW

Matrix

Estimated reproduction number

Fig. 3. Effect of asymptomatic infection on estimates of age-
specific reproduction number. The symbol indicates the med-
ian 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, re-

spectively. Circles, no asymptomatic infection; squares,

asymptomatic infection among children; triangles, asympto-
matic infection among adults; diamonds, asymptomatic infection among children and adults.

We observed an overall incidence of 7.0% (95% CI, 6.9–7.1) by case-based influenza surveillance and ILI surveil-

lance 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 perfor-

mance 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 esti-

mate 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 ar-

bitrarily decided upon visual inspection of the epidemic curve. Indeed, estimates of R in this study fluctuated with different adopted periods corresponding to the ear-

ly 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 transmission may also indicate the effectiveness of mitigation measures.

A 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 andILI 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.

REFERENCES
