Jpn. J. Infect. Dis., 70, 333-339, 2017

Epidemiological Reports

Prospective Epidemiological Evaluation of Seasonal Influenza in All Elementary Schoolchildren in Matsumoto City, Japan, in 2014/2015

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SUMMARY: Seasonal influenza is known to spread within and among educational organizations. Detailed understanding of the pattern of infection requires comprehensive prospective epidemiological studies, involving all schools within a community. This prospective survey evaluated 13,217 schoolchildren attending all of the 29 public elementary schools in Matsumoto City, Japan, in 2014/2015. Questionnaires were distributed to school nurses to obtain information about onset date and suspected route of transmission of influenza for all schoolchildren diagnosed with influenza virus at medical institutions. Responses were obtained for 2,548 infected schoolchildren, representing 96% of reported cases. Epidemic curves were plotted for each school by calculating the numbers of incident cases. Distance between schools was not associated with influenza spread over time. However, modeling showed that the occurrence of initial infection at each school and its spread over time could be fitted with a logistic curve. The transmission route for most children initially infected at each school was through a household member, whereas for most remaining schoolchildren it was through the school. These findings indicated that seasonal influenza was initially transmitted to schoolchildren by household members and then spread throughout the schools, with the initially infected child at each school fitting logistic curves over time.

INTRODUCTION

Seasonal influenza is a common communicable disease worldwide, with a significant impact in developing countries, in particular (1). In Japan, approximately 5,000 medical institutions track influenza epidemics, reporting patients diagnosed with influenza to the nearest public health center (2). The development of surveillance systems has allowed detailed analysis of several recent epidemics (3–5). These data have increased the understanding of epidemics and have enabled the design of preventive measures in real time. However, these surveillance systems do not assess individual patient characteristics.

Detailed epidemiological research, that includes information on individual patients, is required to determine the development and transmission of influenza. Several community-based observational and intervention studies have attempted to evaluate the transmission and control of seasonal influenza, assessing both pharmaceutical and non-pharmaceutical interventions (6–9). Despite the understanding gained from these studies, additional longitudinal epidemiological studies are required to assess the spread of influenza virus (10). As epidemics of seasonal influenza mainly spread throughout school systems, many studies have investigated routes of transmission and susceptibility factors among schoolchildren (11–16). However, as the majority of these studies were limited to study subjects visiting a medical center or schoolchildren at selected schools within a community, the results may not be representative of epidemics within specific communities. Influenza epidemics differ among schools and are thought to spread between schools. Therefore, the lack of information may hamper infection control measures throughout school systems.

To better understand the spread of influenza epidemics, all schools within a community should be assessed. This may allow mapping of the spread of infection across geographic locations and over time and may establish why epidemics differ between schools. Although infection control measures are usually uniform, findings from a community-wide survey may be useful to design infection control measures tailored to the characteristics of individual schools. Therefore, this prospective epidemiological study assessed seasonal influenza infection among children attending all public elementary schools

Received January 25, 2016. Accepted July 11, 2016.
J-STAGE Advance Publication August 31, 2016.
DOI: 10.7883/yoken.JJID.2016.037
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in Matsumoto City, Japan. The survey identified the routes of influenza transmission within and between schools, as well as the features of influenza spread through the community.

SUBJECTS AND METHODS

Study subjects: This study was conducted in Matsumoto City, Nagano prefecture, Japan, during the 2014/2015 school year. Matsumoto City is located in the middle of Japan and occupies an area of approximately 978 km^2. The altitude of the city is 600 m. In December, January, and February of 2014/2015, the average temperatures were 2.3°C, −0.4°C, and 0.2°C, respectively, and the average relative humidity was 69%, 67%, and 66%, respectively. The total population of the city was approximately 240,000 people, and the number of elementary schoolchildren aged 7–12 years was 13,582 (17). The city has 29 public elementary schools and, in 2014/2015, 13,217 (97.3%) children aged 7–12 years were enrolled in these schools. There is also one private elementary school in Matsumoto City, which was not included in this study. However, the school is located on the border with an adjacent city and is therefore, geographically separate from the public elementary schools. The study protocol was reviewed and approved by the Committee for Medical Ethics of Shinshu University (approval number 2715).

Questionnaire survey: Before distributing the survey, the study design and aims were explained to the board of education, medical association, and public health center of Matsumoto City, as well as to the parents and teachers at all 29 elementary schools in Matsumoto City. All approved the contents of the survey.

This study used a prospective observational epidemiological study design. In Japan, when the parents or guardians of schoolchildren diagnosed with influenza at a medical institution call the school to inform them that their child is absent from school with influenza, a report form is handed by the school nurse to a sibling or neighbor of each sick child. The parents or guardians must submit the completed report form, which includes a record of medical examinations and diagnosis, to the school. The school nurse was asked to submit our anonymous questionnaire along with the report form; therefore, only schoolchildren infected with influenza were included in the survey. Responses were collected by the school nurse via a collection box. After excluding questionnaires involving children diagnosed with other types of infection, there were 2,548 responses regarding schoolchildren diagnosed with influenza at a medical institution. During the same time period, the school nurses received report forms for 2,651 schoolchildren diagnosed with influenza; the questionnaire response rate was therefore, 96.1%.

The questionnaire included sociodemographic and clinical factors, as follows: child's grade and class; calendar date of symptom onset; diagnosis of influenza at a medical institution (yes or no); diagnostic result (type A, type B, or unknown type of influenza); and suspected influenza transmission route (including school, after school care provider, park, friend's house, tutoring school, site of after school music or exercise classes, household, transport links including bus or train, and shopping). Data input was performed by researchers or trained operators and integrated into a database.

Calculation of reproduction numbers in schools: A reproduction number (R) was used to evaluate influenza spread at each school. Generally, a basic reproduction number (R_0) is used to express the dynamics or calculate the infectiousness of influenza when the numbers of infected individuals increase at the beginning of an epidemic in a specific population. In addition, if a specific infection control measure is implemented at time t, an effective reproduction number (Rt) is used to express the change in the basic reproduction number. However, in this study, because vaccination and other infection control measures were implemented by individuals intermittently and asymptomatic children could not be identified, the basic reproduction number may be underestimated. Therefore, the basic and effective reproduction numbers, calculated according to standardized techniques, could not be used. However, estimates of the magnitude of an epidemic or of infectiousness, based on epidemiologically reported data, are required at the school and community level. Therefore, R was expressed taking into account the effects of individual infection control measures and asymptomatic individuals. We hypothesized that the children in Matsumoto City were well mixed and homogeneous and a Susceptible, Infected, Recovered (SIR) model was applied to each school independently. R was calculated on the basis of the number of symptomatic children in each school, using a rate of final size p (18).

$$R = \frac{-\ln(1-p)}{p}$$

The association between R calculated for each school and school factor was evaluated.

Influenza spread among schools: To determine influenza spread among schools in a specific community, mathematical modeling was employed, using the date of infection of the first infected child at each school (19). If influenza breaks out in one school, it may be transmitted within that school over time. We therefore hypothesized that the SIR model was applicable to each school independently. We also hypothesized that, following initial infection, influenza would be transmitted over time within that school, whereas infection of children in other schools would only result from infection of the first child in these schools, with subsequent spread within these schools. Because this type of transmission among school units differs from a general SIR model, a recovery group, which is usually used in SIR models, was omitted from this model of interschool transmission. It was postulated that influenza spread among schools in this study would fit a logistic model. Influenza was hypothesized to spread to a total of N schools on day $t = 0$, with $x\ (t)$ defined as the number of schools with an infected child on day t. In this study, carrying capacity data were used for 27 schools. Because influenza had already occurred in the first 2 schools separately, transmission among schools was thought to have occurred in the remaining 27 schools. The number of schools Δx to which influenza had spread within time Δt was hypothesized to be proportional to both $x\ (t)$, representing the number of already infected schools, and $N - x(t)$, representing the number of not yet infected schools. Therefore, Δx was expressed as $\Delta x = ax(N - x)\Delta t$, in which a was a positive coefficient.

Using this formula and setting $\Delta t = 0$ resulted in a differential equation:

$$\frac{dx}{dt} = ax\ (\ N - x\ )$$

This logistic equation can be used to solve for x, using the equation:

$$x = \frac{Nexp\ (\ aNt\ )}{(\ N - 1 + \exp\ (aNt))}$$

A maximum log likelihood method was used to estimate the modeling parameters from observational data.

Statistical analysis: Correlation was determined using Spearman's rank correlation coefficient because the distribution was not normal. Categorical data were analyzed using the Chi-square test, with $P < 0.05$ regarded as statistically significant. Interval estimation was expressed as 95% confidence intervals. All analyses were performed using SPSS ver.22 (Chicago, IL, USA).

RESULTS

Descriptive epidemiology: The location of each public elementary school and the areas of Matsumoto City covered by each school are shown in Fig. 1. Enrolment in public schools is based on place of residence of the student, therefore, the spread of an epidemic through a community can be evaluated by analyzing the spread of influenza within each school. The geographic area covered by schools in the city center was smaller than that covered by schools in the surrounding areas.

The influenza epidemic first occurred at the end of November 2014, decreasing at the end of December, due to the winter recess, and peaking between January and February 2015, after the schools reopened (Fig. 2). Although epidemic curves could be plotted for most schools, a few curves could not be plotted clearly because few children in those schools were infected (data

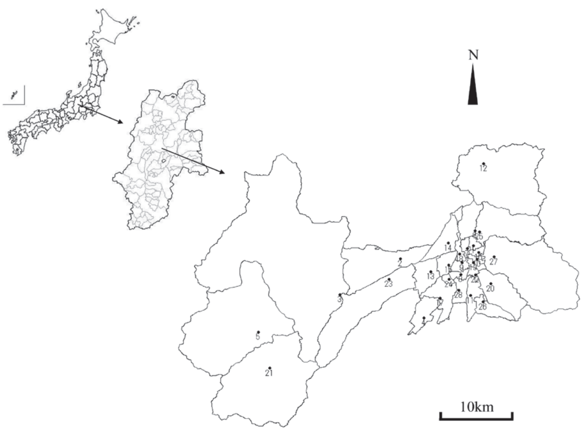

Fig. 1. Geographic location of all public elementary schools in Matsumoto City. Schools in the center of the city are concentrated but are more dispersed in the surrounding area.

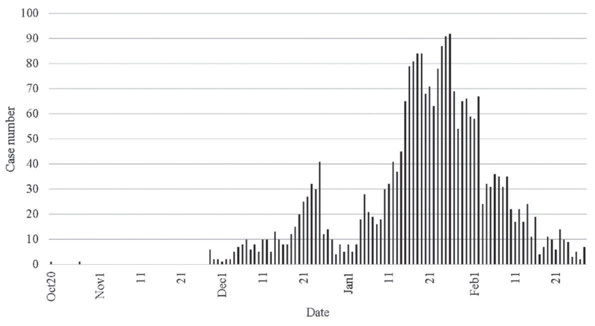

Fig. 2. Epidemic curve of the study population. The influenza epidemic among elementary schoolchildren in Matsumoto City began at the end of November 2014, decreased at the end of December because of winter recess, and peaked in January to February 2015 after the schools reopened.

Table 1. Proportion of influenza cases and R of each school

School number	Number of schoolchildren	Case	(%)	R
1	382	30	7.9	1.04
2	931	107	11.5	1.06
3	37	6	16.2	1.09
4	167	56	33.5	1.22
5	14	7	50.0	1.39
6	410	86	21.0	1.12
7	662	98	14.8	1.08
8	791	187	23.6	1.14
9	890	173	19.4	1.11
10	305	48	15.7	1.09
11	904	91	10.1	1.05
12	154	57	37.0	1.25
13	453	61	13.5	1.07
14	663	106	16.0	1.09
15	338	54	16.0	1.09
16	602	139	23.1	1.14
17	650	120	18.5	1.11
18	259	55	21.2	1.12
19	423	53	12.5	1.07
20	127	51	40.2	1.28
21	30	0	0.0	NA
22	352	29	8.2	1.04
23	889	259	29.1	1.18
24	335	91	27.2	1.17
25	364	46	12.6	1.07
26	438	134	30.6	1.19
27	508	100	19.7	1.11
28	703	210	29.9	1.19
29	436	94	21.6	1.13
Total (average)	13,217	2,548	(19.3)	(1.13)

NA, not applicable.

not shown). Of the 29 schools, one had no cases of influenza. Classes were closed when the absence rate was ≥10% and the school doctor and educational board decided to close that class. The incidence of influenza tended to decrease when classes were closed, but the effect could not be expressed by *Rt* because contact tracing was not performed in this study.

The proportion of children at each school infected with influenza ranged from 0.0% to 50.0%, with an average of 19.3% (Table 1). Similarly, *R* ranged from 1.04 to 1.39 and averaged 1.13. Of the children infected with influenza, 95.0% were diagnosed with type A influenza, with almost all diagnoses made using rapid diagnostic kits at medical institutions. Children who did not yield positive results using the kits were diagnosed by physicians, based on the presence of symptoms of an influenza-like illness. In addition, because all children were diagnosed at clinics or hospitals, none required laboratory confirmation.

Evaluation of influenza spread among schools: The first child infected at each school and the date of influenza onset in that child were determined. There was a gap in time after the first 2 schools, although continuity was observed beginning with the third school. Moreover, one school had no infected children. The correlation between school distance (km) and time lag (day) from the third school (Fig. 3) was analyzed for the remaining 26 schools. Spearman's test showed no significant correlation (ρ = 0.329, *P* = 0.101). Gradual spread was not observed in the schools in the city center, with a longer time tending to be required for schools in more distant areas.

The time course of accumulation of the first infected child at each school was modeled (Fig. 4). Beginning with the third school, the logistic curve was fitted to all remaining schools. The number *a* was calculated as 0.006349, with influenza spreading to all schools within 50 days.

Suspected transmission routes were evaluated (Table 2). Assessments of the first infected children in each school showed that spread within the household was the most frequent (32.1%) route of transmission. Sub-

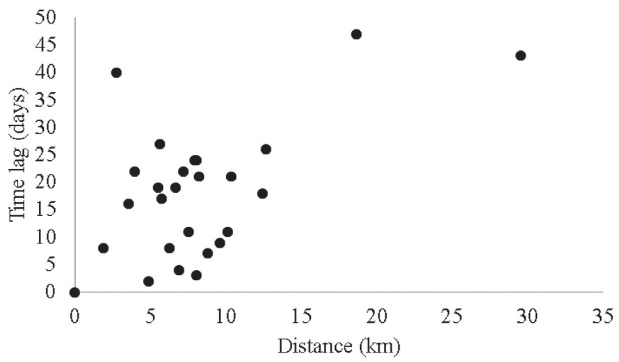

Fig. 3. Association between distance between schools and the time of detection of initially infected students at each school. The onset date of the first infected student at each school was determined. The first 2 schools were excluded from the analysis because continuity was not shown. The association between distance (km) and time lag (day) from the third school was evaluated with Spearman's test, but the association was not statistically significant (ρ = 0.329, *P* = 0.101)

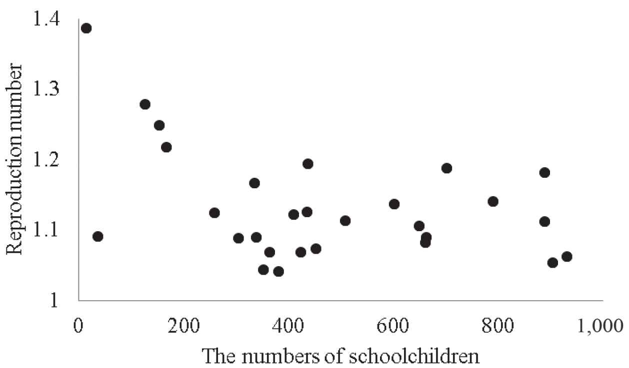

Fig. 5. Association between *R* and the number of schoolchildren at each school. Association was evaluated with Spearman's test. Although a negative tendency was observed, the association was not significant (ρ = − 0.293, *P* = 0.130).

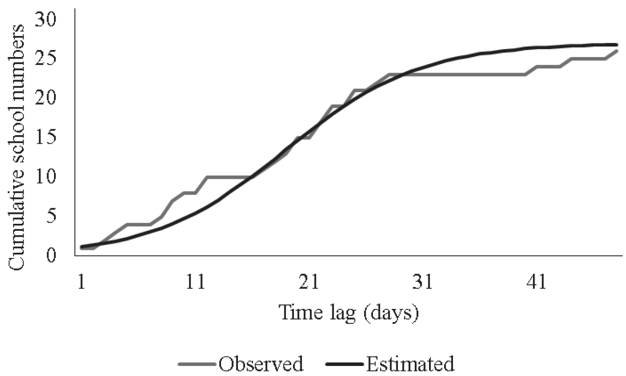

Fig. 4. Time course accumulation of initially infected children at all schools. A logistic curve was fitted to the time course accumulation by modeling. Influenza had spread to all schools within 50 days.

Table 2. Suspected transmission route of initial case of each school and all cases

Suspected transmission route	Initial case	(%)	All cases	(%)
Household	9	32.1	369	14.5
Shopping	5	17.9	119	4.7
Exercise practice after school	3	10.7	92	3.6
School	2	7.1	1,561	61.3
Friend's house	1	3.6	33	1.3
Cram school	1	3.6	13	0.5
Care place after school	0	0.0	38	1.5
Bus or train	0	0.0	18	0.7
Park	0	0.0	4	0.2
Music practice after school	0	0.0	2	0.1
Other	4	14.3	119	4.7
Unknown	3	10.7	180	7.1

sequently, however, spread was most frequent within schools (61.3%).

R was calculated for each school (Table 1), a negative correlation was observed between *R* and the total number of schoolchildren at each school, although this was not significant ($\rho = -0.293$, $P = 0.130$) (Fig. 5).

DISCUSSION

This prospective epidemiological study evaluated the spread of seasonal influenza among schoolchildren attending all 29 public elementary schools in Matsumoto City, Japan, in 2014/2015. The magnitude of the epidemic differed among schools. Seasonal influenza first occurred in Matsumoto City at the end of December 2014 and peaked in January 2015, similar to the epidemic observed across Japan (20). The main influenza subtype during 2014/2015 reported by the National Institute of Infectious Diseases was AH3 (21). Similarly, we found that 95% of affected schoolchildren were infected with type A influenza. Thus, both the timing and influenza subtype in Matsumoto City were comparable to those throughout Japan, suggesting that our evaluation of the influenza epidemic in Matsumoto City in 2014/2015 may reflect the general epidemic in Japan.

Analysis of whether influenza transmission among schools was dependent on distance showed no significant association. However, influenza transmission is affected by distance and by a complicated network based on interpersonal interactions (22). Stronger interactions are anticipated in more densely populated areas. A greater influenza transmission has been reported among communities than among schools (6). Moreover, seasonal influenza spreads geographically among prefectures across Japan (20), suggesting that the geographic spread of influenza may occur on both large and small scales.

This study found that most of the schoolchildren infected first in each school acquired influenza from a member of their household, consistent with previous research results (23,24). Transmission between a household and a community has also been reported (25), as has influenza spread from a household to a school, particularly during pandemic influenza outbreaks (26). It is postulated that influenza spread among schools is affected more by household transmission than by direct transmission between schools. Moreover, throughout the study period, over 60% of individuals infected at a later stage were thought to have acquired influenza through their schools. Epidemic curves could be plotted for many schools, showing small epidemics in each school. Therefore, it is postulated that influenza epidemics among schoolchildren within a specific community follow a 2-step transmission. First, influenza is transmitted between members of households including schoolchildren, who will later trigger epidemics in schools. Second, influenza is spread from infected schoolchildren to members of their households. Household members will then transmit influenza to other households, including children attending other schools. These transmission cycles may result in the spread of an epidemic within a community. Although our prospective epidemiological survey indicates the likelihood of this 2-step process, further studies are required to determine the specific details of influenza spread patterns among schools.

The time dependent spread of the first infected children at each school showed a logistic curve-like accumulation. A slow reduction of accumulation at the end of the period may have been affected by the distance to outlying schools, although influenza spread among schools was similar to the general epidemic time course of an infected population. The spread curve can be used to calculate the spread of seasonal influenza epidemics among schools. Moreover, yearly accumulation of this information may result in more precise modeling.

We were unable to detect a significant correlation between the number of schoolchildren at each school and *R*. Although *R* tended to be smaller in schools containing large numbers of schoolchildren, this tendency was less clear among schools containing smaller numbers of schoolchildren. A negative correlation was found between state population and the proportion of individuals infected (27). This inconsistency may be due to the insufficient sample size in this study, as only 29 schools were included. Further sampling may strengthen the association. There is also a need to evaluate the association between *R* and the proportion of individuals at each school subject to infection control measures, such as vaccination, wearing masks or washing hands. These factors were not evaluated in this study, but may have differed among schools or affected herd immunity.

This study has several limitations. First, because it was based on questionnaire results, biochemical data were not evaluated. Therefore, data on infections, including laboratory confirmation, could not be evaluated. Only data on symptoms reported by the patients were examined. Although some of these patients may have been false-positives, we relied on their diagnoses by medical institutions. However, some individuals infected with seasonal influenza may have been asymptomatic (28), resulting in a difference between infected and symptomatic patients. This may have resulted in an underestimation of the infected population and *R*, thus affecting the interpretation of the study results. As epidemiological studies of influenza often assess symptoms (29,30), our results meet the aims of this study. Second, this study only evaluated the geographic and temporal spread of influenza among schools. Because we did not consider infection control measures, the differences in individual factors between patients and non-patients could not be determined. We hypothesized, however, that the study population was well mixed and homogeneous, with regard to infection control measures. Third, because the study population included only elementary schoolchildren, children in kindergarten and junior high school were not evaluated. Fourth, influenza epidemics, even during the same season, differ among countries, suggesting that geography usually affects influenza epidemics during large-scale evaluations (31,32). Influenza epidemics are also affected by weather-associated factors, including humidity (33). However, because this study was conducted in a city, large-scale effects of geography and humidity were regarded as negligible.

This prospective epidemiological study evaluated the spread of influenza among all elementary schoolchildren in Matsumoto City, Japan. The route of transmission for most of the children initially infected at each school was through a household member, while the route for the majority of the remaining schoolchildren was through the school. These findings indicated that seasonal influenza was initially transmitted to schoolchildren by household members, later spreading throughout the schools. Although the geographic spread of influenza could not be clearly determined, a logistic curve could show the time course of the first infected patients at each school. This study may be useful in understanding how influenza spreads among schoolchildren.

Acknowledgments We thank all of the school nurses at each elementary school and the parents/guardians of all schoolchildren. We also thank Nozomi Ohashi of the board of education of Matsumoto City; Kazuo Maezumi of the Matsumoto Health Center; and Kenji Furihata, Dr. Takashi Matsuoka, and Dr. Muneo Minoshima of the Medical Institution of Matsumoto City. We also thank Tomoko Fujimura, Hiroko Hayashi, Naomi Yuzawa, Kiyomi Tanaka, Yoko Watanabe, Kazuki Nagai, Kyoko Inuura, and Yoshinobu Shinkai of the Center for Health, Safety and Environmental Management and all other organization members for their assistance in the collection and analysis of data. This work was supported by a Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (study number: 26860413) and a Health Labour Sciences Research Grant from The Ministry of Health, Labour and Welfare, Japan (study number: 201447016A).

Conflict of interest None to declare.

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