

MEASURES AGAINST TRANSMISSION OF PANDEMIC H1N1 INFLUENZA IN JAPAN IN 2009: SIMULATION MODEL

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The first outbreak of pandemic H1N1 influenza in Japan was contained in the Kansai region in May 2009 by social distancing measures. Modelling methods are needed to estimate the validity of these measures before their implementation on a large scale. We estimated the transmission coefficient from outbreaks of pandemic H1N1 influenza among school children in Japan in summer 2009; using this transmission coefficient, we simulated the spread of pandemic H1N1 influenza in a virtual community called the virtual Chuo Line which models an area to the west of metropolitan Tokyo. Measures evaluated in our simulation included: isolation at home, school closure, post-exposure prophylaxis and mass vaccinations of school children. We showed that post-exposure prophylaxis combined with isolation at home and school closure significantly decreases the total number of cases in the community and can mitigate the spread of pandemic H1N1 influenza, even when there is a delay in the availability of vaccine.

Introduction

Cases of pandemic H1N1 influenza were first reported in Mexico in April 2009 [1]. Subsequently, the virus spread rapidly across the United States and Canada, and then became a global concern [2]. Initial countermeasures, including rigorous fever screening at ports of entry, were introduced by the Japanese government in response to the elevated pandemic alert level of the World Health Organization [3].

In May 2009, an outbreak of pandemic H1N1 influenza occurred in the Kansai region of Japan in Hyogo and Osaka prefectures and was contained by the end of the month [4]. After early July, the virus emerged again and spread throughout Japan [5].

Urgent implementation of measures against pandemic H1N1 influenza is required.

Vaccination against pandemic H1N1 influenza was started in Japan on 19 October 2009, targeting first the healthcare workers. As there may not be enough vaccines to cover all needs, and it is already November, the effectiveness of other measures, such as the use of antiviral drugs and social distancing, must also be considered.

To implement these measures effectively in order to contain the spread of the disease and decrease the associated costs to society, we must first estimate the impact of these measures.

Simulation is a useful method for this purpose. We have developed an individual-based Monte Carlo simulation code by constructing a virtual regional community called the virtual Chuo Line, based on the real Chuo Line area west of Tokyo [6].

In the present study, we use the virtual Chuo Line model for the simulation of pandemic H1N1 influenza and propose measures to be implemented. To estimate the impact of these measures in Japan, we decided to base the parameters on the simulation of Japanese pandemic H1N1 influenza cases.

Methods

Simulation of the spread of pandemic H1N1 influenza in virtual communities

We have developed a Monte Carlo simulation code using an individual-based model [6]. We constructed a virtual regional community called the virtual Chuo Line, based on statistical data of the real Chuo Line area west of Tokyo. In the virtual Chuo Line scenario, the total number of people involved was 8,800, including 2,000 in Hachioji City, 2,600 in Tachikawa City, 2,800 in the Kichijoji area of Musashino City next to Suginami ward in Tokyo metropolitan area, and the rest were in Shinjuku and Tokyo. In our model 8,800 people were sufficient for Monte Carlo simulation in the preliminary estimation. These people were connected to many different types of families: singles, couples, fathers, mothers, and children. We also constructed "compartments" consisting of 4,040 homes, 60 schools, 658 companies, and 117 shops. The size of the families ranged from single to eight persons. The proportion of different size families was determined by Japanese census data. For schools we modelled using local government statistics one class or two classes per school; the numbers of students were 30-40 or 70-100 per school. The size of workplace was from 3 to 30 persons and the various size workplaces were determined using local government statistics. We operated trains that moved between stations in the cities according to a virtual railroad timetable. Twelve percent of the people in the model commuted to Tokyo. We gave people event histories, consisting of movement from one compartment to another. Event histories were constructed using statistical data of the daily life of about 30,000 Japanese people. In these compartments, people contacted each other stochastically and were occasionally infected. When measures, such as school closure or prohibition of traffic, were implemented, students or commuters were assumed to stay in their households. The results

of simulations were obtained by an average of 100 runs. We showed other two numbers in parentheses, one is the sum of the lower values of 95% CI and the other is the sum of the upper values of 95% CI.

Real data in public health centres

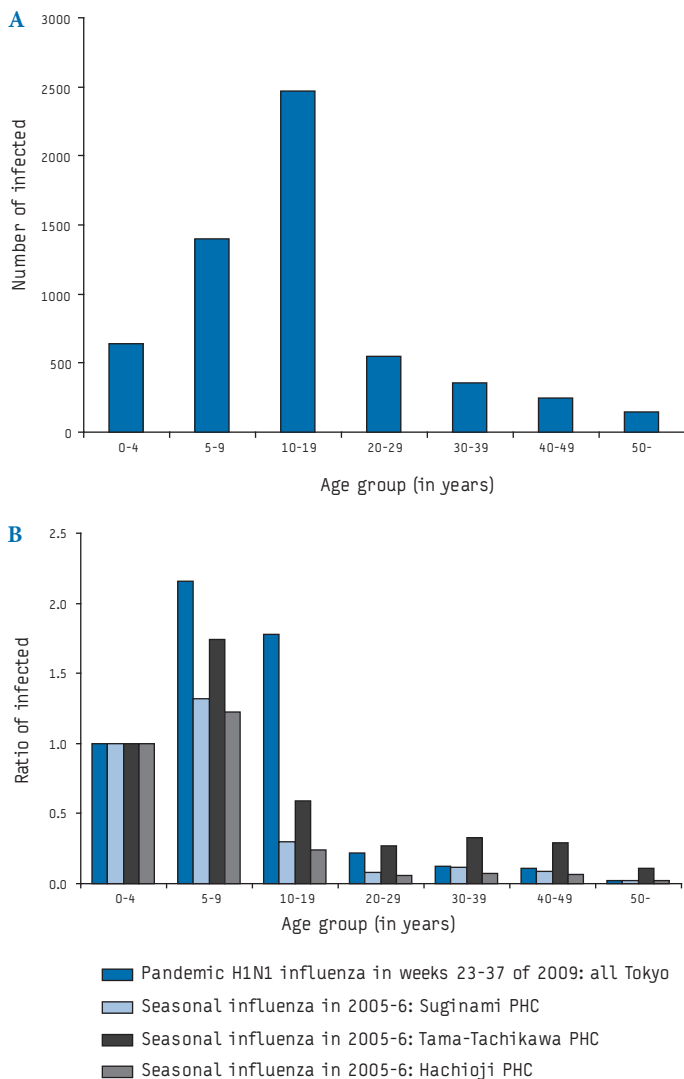
The spread of pandemic H1N1 influenza was reported to be prominent among young people. In order to confirm this, we compared the data on age distribution of cases of pandemic H1N1 influenza in Tokyo in the summer 2009 [7] with the data on cases of seasonal influenza in 2005-6 in three public health centres

FIGURE 1

Real data on reported numbers of cases of pandemic H1N1 influenza in Tokyo in 2009 and of seasonal influenza in three public health centres (PHCs) along a real railway, the JR Chuo Line in Tokyo in 2005-6:

A. Age distribution of reported cases of pandemic H1N1 influenza in greater Tokyo from week 28 to week 37 of 2009;

B. Ratio of persons infected by seasonal influenza per unit population normalised by the age group of zero to four, Tokyo and three PHCs along the Chuo Line, 2005-6.



(PHC): Hachioji, Tama-Tachikawa and Suginami which are in the Chuo Line area [6]. We used surveillance data of infectious diseases including influenza collected by the National Institute of Infectious Diseases (NIID) to which every PHC reports the number of newly infected persons every week. The data reported to PHCs come from 3,000 paediatricians and 2,000 general practitioners. With the permission of NIID, we analysed the number of notifications in the winter of 2005-6 from the Hachioji, Tama-Tachikawa and Suginami PHCs [6]. As for the data of summer 2009, the number and age of patients in the greater Tokyo was published weekly by the Tokyo Metropolitan Institute of Public Health through the notifications from PHCs in the greater Tokyo [7]. The influenza data reported after July 2009 were considered to be mostly the pandemic influenza data, because seasonal influenza is rare in summer in Japan. We also estimated the transmission coefficient of pandemic H1N1 influenza among school children using data on outbreaks among small groups of students during summer vacation 2009.

Results

Age distribution of cases of pandemic H1N1 influenza

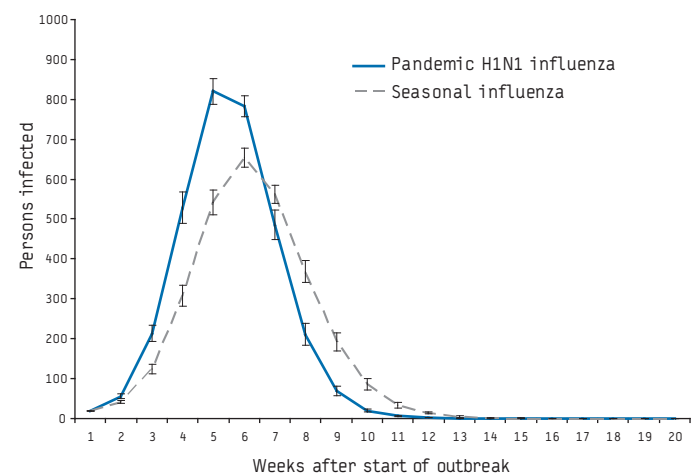
Data on age of persons infected with pandemic H1N1 influenza from week 28 to week 37 (6 July to 13 September) 2009 in Tokyo was obtained from the PHC reports [7] (Figure 1A). We calculated the ratio of the number of persons infected divided by the population of each age group in Tokyo from the Japanese census data and normalised it by age group from 0 to 4 years (Figure 1B). As shown in Figure 1B, the number of cases among school children, especially among teenagers, was significantly higher in comparison to seasonal influenza in the three PHCs in Tokyo: Kichioji PHC, Tama-Tachikawa PHC, and Hachioji PHC in the Chuo Line area during the 2005-6 season [6].

Transmission coefficient

We searched the national newspapers for information on outbreaks of influenza among children during the summer vacation 2009. During the summer holidays, outbreaks of seasonal influenza are rare in Japan therefore we assumed these outbreaks had been due to the pandemic. We analysed the cases if the size of the group was specified. After 24 July, the policy of the Japanese government

FIGURE 2

Simulation model results for the number of persons infected with pandemic H1N1 influenza and seasonal influenza



has changed from testing all suspected cases to sample testing by PCR. If H1N1 is confirmed by sampling, we assume all cases to be infected with H1N1. After 25 August, no laboratory testing by PCR has been required to confirm an outbreak of H1N1 in a school setting.

The following outbreaks were identified:

Outbreak 1: Health recovery camp for asthmatic children, 29-31 July 2009. Approximately 70 people attended the camp: 43 children and 27 staff members. Of these, 22 children and four staff members showed symptoms, and one child was confirmed to have H1N1.

Outbreak 2: A university tennis club, 30-31 July 2009. Approximately 100 persons attended. The university announced that 12 were infected with H1N1.

Outbreak 3: Residential high school training camp, 1-4 August 2009. Enrolment was 47 people: 38 students, two teachers and seven former students. Of these, 26 were shown by a simple test to be infected with influenza A, and one was confirmed with the pandemic H1N1 influenza.

Outbreak 4: Regional basketball camp on 6 August 2009. Approximately 150 attended, including elementary and junior high school students and coaches. Simple test indicated nine junior high school students were infected with influenza A, and three of them were confirmed with the pandemic H1N1 influenza by PCR.

We estimated the transmission coefficient β by $\beta = \ln(I(T))/(S_0 * T)$, $I(T)$: the number of persons infected; S_0 : the size of the group; T : the period of the event. To derive the formula, we integrated the following equation from time 0 to T , assuming the number of the initially infected children to be one:

$$\frac{dI(t)}{dt} = \beta S_0 I(t), I(0) = 1.$$

The pandemic H1N1 influenza did not prevail during summer vacation in Japan and seasonal influenza is rare in summer, therefore we could assume that susceptible children who attended the event were not exposed to other sources of infection except at the event. Then, $I(T)$ is the number of children infected during the event. The estimated values per day are 0.016, 0.011, 0.017 and 0.012. The settings where the above outbreaks occurred were different from schools. However, from the point of view of the behaviour of a group of children, there are many similarities regarding the contacts among children during class room or physical activities. It is therefore expected that the transmission coefficients calculated from the above outbreaks can be applied to school outbreaks as well.

For probability of infection by seasonal influenza, we used $P = 0.005$ per hour for homes, $P = 0.0016$ for schools, $P = 0.0125$ for trains, and $P = 0.00001$ for companies and shops. For the probability of becoming infected on the train, we assumed passengers are densely crowded, as during the rush hour peak. The probability of infection by pandemic H1N1 influenza is within the range of seasonal influenza, except for school children. We used the probabilities of seasonal influenza, except for schools. We estimated the probability of infection among school children to be $P = 0.0023$, assuming 5-8 hours of activity per day in these cases. The medical conditions of simulation were specified by scenario of infection. We specified the latent time to be two days and the period of infection five days.

Simulation in model cities along the virtual Chuo Line

The average number of infected people in 100 simulation runs is shown in Figure 2. No social distancing measures were implemented in the runs. The peak of pandemic H1N1 influenza was higher than that of seasonal influenza and occurred one week earlier. The total number of persons infected with pandemic H1N1 influenza was 3,211 (range: 3,001-3,421), whereas the total number of people with seasonal influenza was 2,945 (2,756-3,152).

Home isolation of school children (HIS)

When one in three adults and 70%, 80%, 90%, or 100% of children stayed home 48 hours after the appearance of symptoms, the total number of persons infected in the community was 2,729 (2,443-3,015), 2,561 (2,298-2,824), 2,425 (2,167-2,683) and 2,121 (1,853-2,389), respectively. When all of the children and 0%, 66% and 100% of adults stayed home 48 hours after the appearance of symptoms, the total number of persons infected was 2,288 (2,089-2,487), 2,001 (1,760-2,242) and 1,779 (1,514-2,044). Figure 3A (simulation with no SC) illustrates a situation where all of the children and one-third of the adults stayed home 48 hours after the appearance of symptoms

School closure (SC)

We implemented SC in a situation where all students/pupils and one-third of adults stayed home 48 hours after onset of symptoms. We simulated seven-day SC for one and two weeks after the outbreak (Figure 3A), and then compared the results with the option without SC. The total number of persons infected was 1,812 (1,532-2,092), 1,766 (1,461-2,071) and 2,121 (1,853-2,389), respectively. Next, we simulated SC for four, five and six days, one week after the outbreak (Figure 3B). The total number of persons infected was 2,136 (1,845-2,427), 1,997 (1,714-2,280) and 1,927 (1,662-2,192), respectively. The spread lasted approximately 20 weeks, averaging the results of 100 runs. However, in some cases, the spread ended before 10 weeks. Four of 100 runs in situations without SC ended before 10 weeks. Three, nine, 12 and 17 runs ended before 10 weeks in case of four-, five-, six- and seven-day SC.

Post-exposure prophylaxis with antiviral drugs (MED)

We assumed antiviral drugs were used only for household contacts of cases. When all children and one-third of adults stayed home 48 hours after symptoms appeared, we simulated the situations where all families used MED but the proportion of family members who were administered the antiviral drugs at any time within 48 hours after appearance of symptoms was 20%, 40%, 60%, 80%, and 100%. Then, the total number of persons infected was 1,903 (1,682-2,124), 1,654 (1,397-1,911), 1,412 (1,180-1,644), 1,082 (889-1,275) and 883 (666-1,000), respectively (Figure 3C). In these runs, we assumed the efficiency of antiviral drugs to be 80%, i.e. to prevent infection in eight out of ten contacts of the infected persons.

In the situation where 40% of families were administered the drug with an efficiency of drugs 60%, 70%, and 90%, the total number of persons infected was 1,815 (1,560-2,070), 1,761 (1,519-2,003), and 1,574 (1,336-1,812), respectively.

Mass vaccination of school children (VSC)

Children were assumed to be vaccinated and become immune before the influenza season. When the efficiency of vaccine is $X\%$, X persons in 100 were assumed to become immune. We also

FIGURE 3

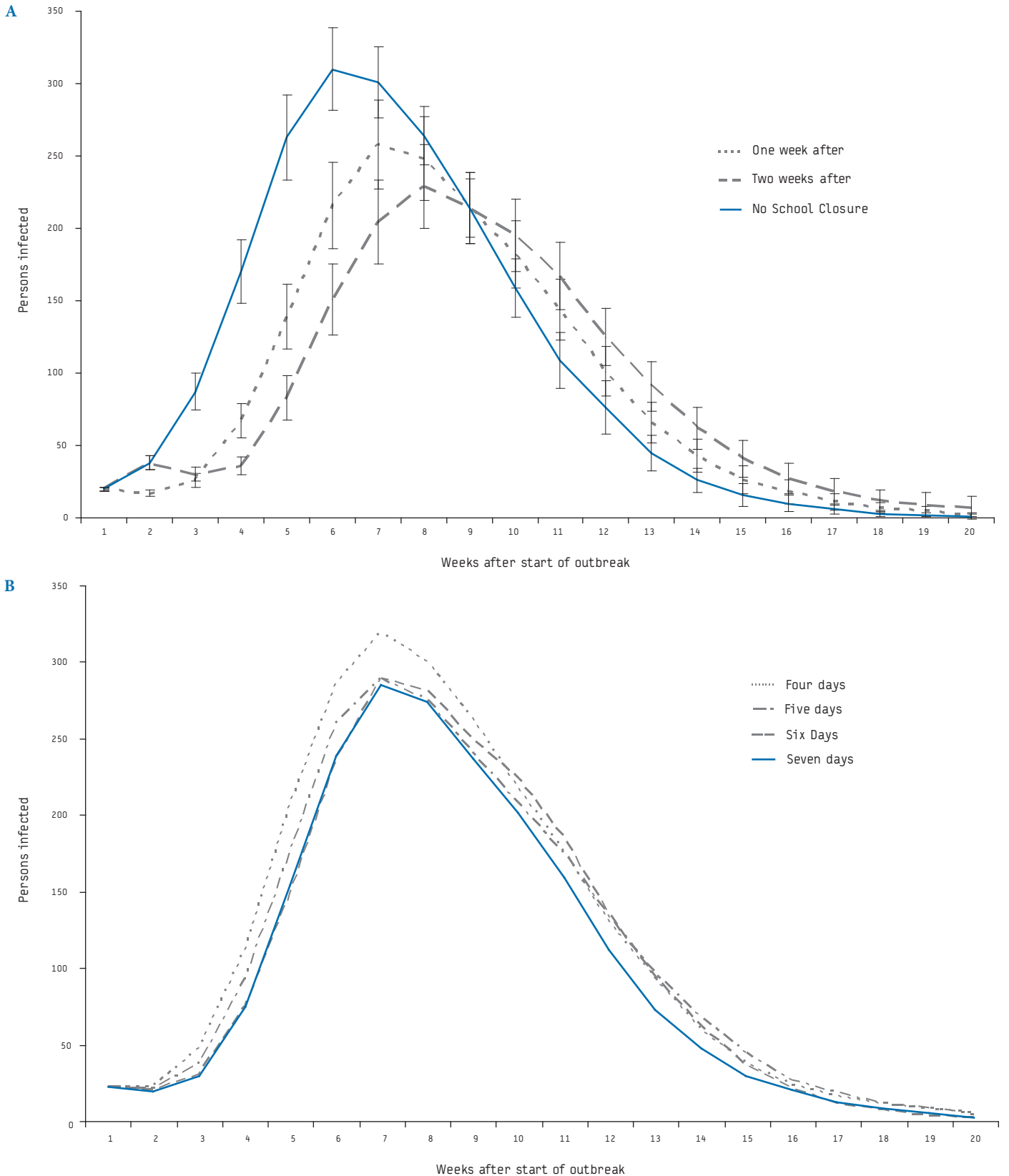
The number of persons infected with pandemic H1N1 influenza, simulation model results for different scenarios:

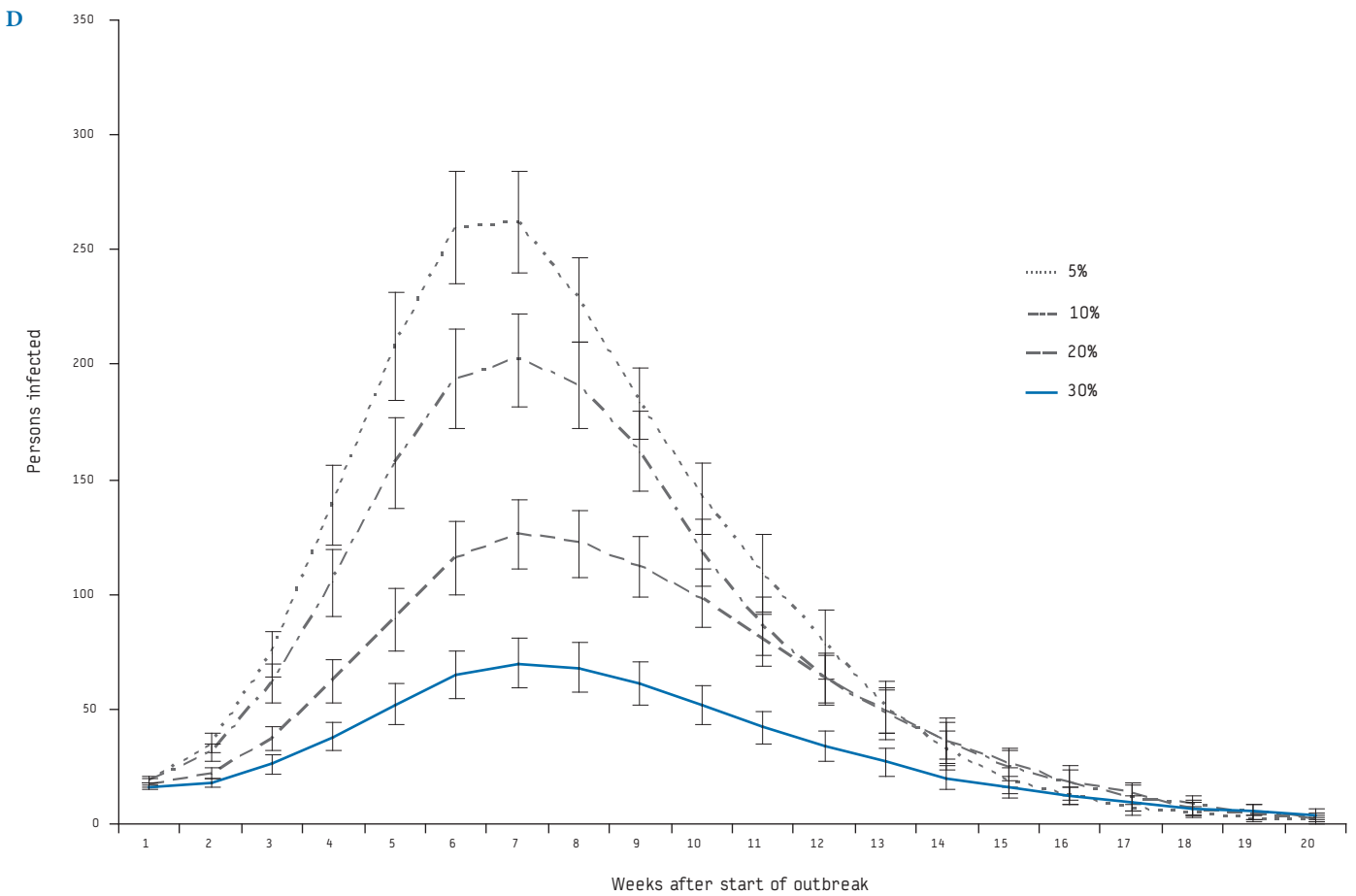
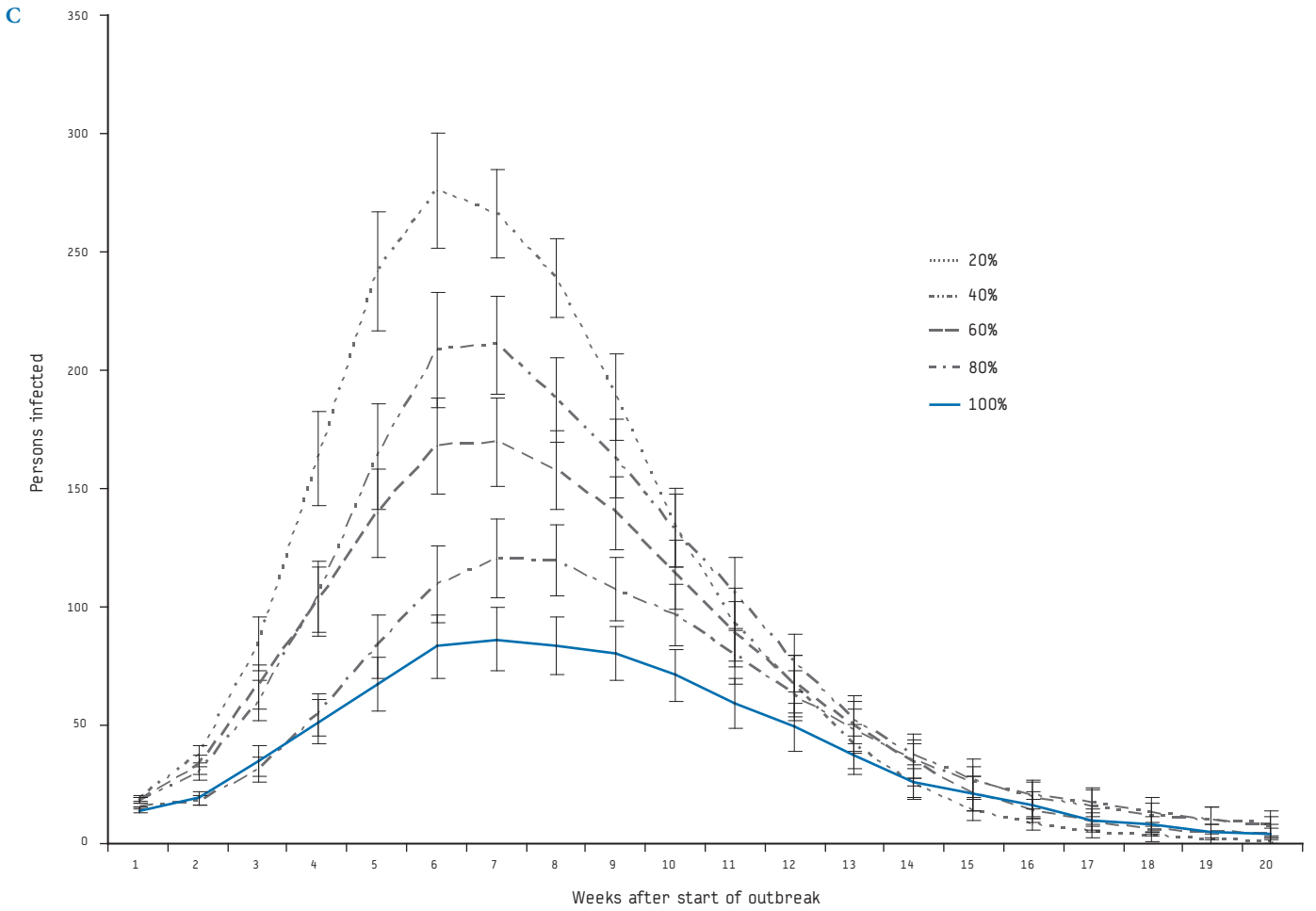
A. Seven-day school closure one or two weeks after the outbreak and no school closure;

B. School closure for four, five, six and seven days one week after the outbreak;

C. Post-exposure prophylaxis with antiviral drugs administered to 20%, 40%, 60%, 80%, and 100% of the family members;

D. Mass vaccination of school children, assuming the efficiency of vaccinating children was 5%, 10%, 20%, and 30%.





assumed all children and one-third of adults stayed home 48 hours after symptoms appeared. The total number of persons infected in the community was 1,879 (1,624-2,134), 1,546 (1,324-1,768), 1,094 (932-1,270) and 645 (528-780) when the efficiency of the vaccine to children was 5%, 10%, 20%, and 30%, respectively (Figure 3D). The number of infected children was 975 (838-1,112), 793 (676-910), 538 (451-625) and 291 (229-353), respectively. When the vaccine was delayed, children became immune 1, 2, or 3 weeks after the spread of pandemic H1N1 influenza, and the total number of persons infected was 762 (628-896), 881 (744-1,018) and 1,011 (872-1,150) in case of 30% efficiency.

Combination of measures

We performed a simulation of measures according to the following possible scenario: all children and one of three adults were isolated 48 hours after the appearance of symptoms. Four-day SC one week after the outbreak was implemented. Thirty percent of children became immune by vaccination only eight weeks after the outbreak. Forty percent of families of persons infected were administered the antiviral drugs with efficiency 80%. It is shown that the number of persons infected, indicating the major venues where they became infected, was 1027(860-1194) (Figure 4), strongly suggesting measures to mitigate the spread of pandemic H1N1 influenza even if the vaccine is delayed.

Discussion

In the present study, it was shown that the spread of pandemic H1N1 influenza in Japan is more severe among school children than seasonal influenza. Nishiura et al. [8] estimated the average number of secondary cases in children generated by a single primary child case in Japan to be 2.8. Meanwhile, transmission among other age groups is comparable to that of seasonal influenza. It was thus confirmed that children play an especially important role in the spread of pandemic H1N1 influenza [4].

Home isolation

School principals have the authority to suspend children infected by influenza according to Japanese school health laws. Our

simulation shows the total number of persons infected decreased to approximately two-thirds when all children and one-third of adults were isolated at home compared with the scenario of no measures taken. When all children and two-thirds of adults were isolated at home the additional decrease was not so significant, indicating that the impact of HIS is mainly through preventing infection in schools. Children in the household could infect their family members. However the family members were fewer than their classmates.

School closure

In May 2009, an outbreak of pandemic H1N1 influenza, the first in Japan, occurred in Hyogo and Osaka prefectures. In the beginning of the outbreak, primarily high school students were infected. After peaking on 17 May 2009, the outbreak decreased [4]. All junior high and high schools in Osaka prefecture were closed for 1-2 weeks after 16 May, and elementary schools and kindergartens in the cities where cases occurred were closed. Schools were also closed in Kobe city [4].

SC was implemented in our present simulation in addition to HIS, resulting in a lower peak and a decrease of the total number of infected persons in comparison to the scenario without SC. SC without HIS slows only the transmission of spread; peak becomes lower, but the decrease of the total number of persons infected is small [6]. SC mainly slows down the spread and HIS decreases the number of persons infected by pandemic H1N1 influenza in the present simulation.

For the scenario of SC implemented one week later, our simulation shows that SC for four days was not sufficient, although it did delay the peak. The total number of infected decreased with longer SC. However, infected children may be expected to recover at home during SC for four days due to its latency for two days. In large infected families (i.e. 5-8 members) children would be infected newly during SC.

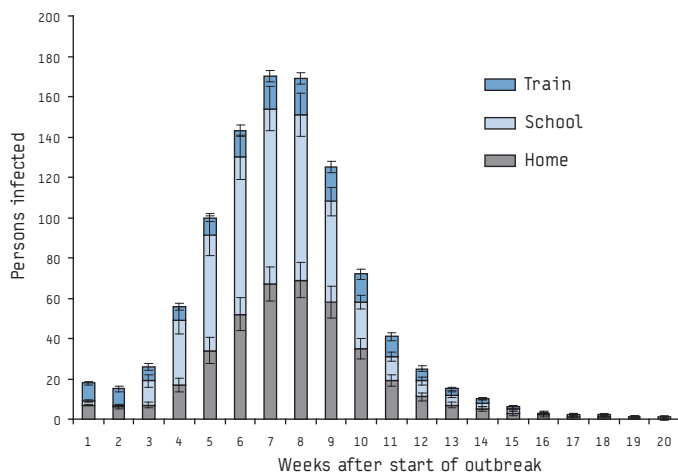
Our simulation shows it is not easy to affect outbreaks using SC in the commuter towns of Tokyo after an epidemic. Although in some cases the spread of disease in three cities ended soon after implementation of SC, in other cases, commuters mitigated the effect of SC. For example, in Hachioji and Tachikawa, the spread ended, but in Kichijoji, it persisted. Influenza was introduced into the cities and began to spread again by commuters in Hachioji and Tachikawa, who were infected in trains or businesses. If we prohibited traffic between cities in the case of seven-day SC, 83 of 100 runs ended before 10 weeks. Indeed, the first outbreak for a short period in Osaka spread among high school students, not adult commuters.

Post-exposure prophylaxis

Post-exposure prophylaxis by administration of antiviral drugs is not officially permitted in Japan. However, antiviral drugs, for example oseltamivir, are the first prescription of choice in cases of seasonal influenza. The use of neuraminidase inhibitors has been reported to decrease the incidence of influenza by 68-89% [9]. Our results show the total number of persons infected in the community decreased significantly when the number of families who received antiviral drugs increased. Hence MED is an effective method that blocks infections in households.

FIGURE 4

The number of persons infected with pandemic H1N1 influenza in a scenario with combination of measures: traffic prohibition, school closure, and isolation at home



Vaccination of school children

The supply of vaccine for pandemic H1N1 influenza in Japan is estimated to be insufficient and therefore priority of vaccination will have to be scheduled, but to date no decision has been taken as to whether children, except those in the lower grade of elementary school, would be included among the priority groups. Even if the vaccine is closely matched, we cannot expect high efficiency. However, simulations show that vaccines are highly effective in protecting communities; this also holds true for seasonal influenza [6].

We considered mass vaccination of school children, because systematic vaccination of adults seems difficult due to lifestyle differences. In Japan, children were mass-vaccinated by law against seasonal influenza from 1962 to 1987. In 1987, the law was relaxed and then repealed in 1994, but the effectiveness of VSC against seasonal influenza is still under discussion. A study on deaths from pneumonia and influenza from the 1950s to the 1990s demonstrated mortality of the elderly decreased when school children were vaccinated [10].

When children were mass-vaccinated against seasonal influenza, not only did the number of infected children decrease, but also that of infected adults [6]. Mass vaccination of children is therefore effective in protecting the whole community. However, our simulations showed that when children did not become immune due to the delay of vaccine the number of persons infected increased. Our simulation strongly suggests vaccination is effective; however, delay of distribution of vaccine mitigates the effectiveness. After the end of October 2009, the effectiveness of vaccine in preventing the spread of disease is questionable.

Combination of measures

In the present study, the spread of influenza is decreased, even when the delivery of the vaccine is delayed. The mechanism of spread also shows that infected commuters introduce influenza into cities, then infections occur in the homes, children spread influenza in the schools and, in turn, infected children infect their families in the households, similar to seasonal influenza [6].

Conclusions

Home isolation of infected children greatly decreases the number of persons infected. In Osaka in May 2009, SC slowed down the outbreak. However, our simulation shows it is not easy for the commuter towns of Tokyo to slow down outbreaks after the beginning of an epidemic, even if long SC with HIS is implemented. Post-exposure prophylaxis combined with HIS greatly decreases the total number of infected people in the community. Also mass vaccination of school children combined with HIS greatly decreases the total number of persons infected, even if the efficiency is low. However, the delay of VSC decreases the efficiency. Our simulation shows that a combination of measures can mitigate the spread of pandemic H1N1 influenza, even when vaccines are delayed.

Acknowledgements

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