

Evaluation of strategies for control and prevention of pandemic influenza (H1N1pdm) in Japanese children attending school in a rural town

Simulation using mathematical models

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Objectives In 2009, epidemics of influenza (H1N1pdm) occurred worldwide. We evaluated 4 strategies for control and prevention of influenza (treatment with antiviral drugs, preventive actions, cancellation of large events, and school closures) by surveying the H1N1pdm epidemic in a geographically isolated rural town in Japan, and applying the epidemic to mathematical models.

Methods Subjects were 291 children attending nursery, primary, and junior high schools in Kounu town. The 4 strategies were evaluated by 3 types of mathematical models with varying parameters.

Results The total number of infected cases, as reported in questionnaires, was 120. In the best-fitting model, treatment with antiviral drugs shortened the epidemic period from 31 to 23 days. Event cancellation reduced the total number of infected cases from 127.1 to 87.6 and the maximum number of cases from 63.7 to 41.7. In this simulation, 56 people were affected by the intervention. Immediate school closure reduced the total and maximum numbers of infected cases to 62.6 and 23.1, respectively.

Conclusion Statistical analysis confirmed that event cancellation and school closure are effective strategies for control of an influenza epidemic. The effective contact rate varied, which reflects a localized and rapidly spreading epidemic in a subpopulation.

Key words : influenza, mathematical modeling, prevention, health policy, influenza vaccines

INTRODUCTION

Influenza viruses have high infectivity. In the global epidemic of 2009, young people were infected with the pandemic influenza strain H1N1 (H1N1pdm)¹⁾ because of its novel genetic characteristics, although it was very similar to the 1918 strain A/H1N1. Although there is a commonly held view that antiviral drug treatment, wearing a mask, vaccination, event cancellation, and school closures are effective in preventing and controlling influenza, it is important to evaluate these strategies on the basis of actual survey data to determine which strategy is most effective.

In Japan, the use of antiviral drugs and preventive actions, such as vaccination, are encouraged and widespread among the general population. National

guidelines recommended school closure during the H1N1pdm epidemic in 2009, but this action was not always implemented appropriately. Moreover, during the epidemic, the cancellation of events was left to the discretion of organizers rather than being mandated by law.

Therefore, in this study, we aimed to evaluate and compare the effectiveness of the primary strategies used for H1N1pdm control and prevention, i.e., treatment with antiviral drugs, preventive actions such as wearing a mask or vaccination, event cancellation, and school closures. Evaluation was performed using mathematical modeling based on survey data taken from a discrete area.

A survey of children was possible in Kounu town, Hiroshima, Japan because of its geographic features (it is separated from other towns by mountains). The total registered school-going population in Kounu town was 291 as of April 1, 2010. All children who had influenza were prevented from attending school during the infectious period by the School Health Law. Therefore, it was possible to conduct an almost complete survey of schoolchildren aged 1 to 15 years during the period.

An SIR model describes the reciprocal relationship among the groups²⁾, but it is believed that this model

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cannot be applied to many epidemics because it is based on the assumption that the infection rate is the same throughout the population³⁾. Consequently, various extended models of SIR have been suggested. One of them, the multitype epidemic model³⁾, divides a population into subpopulations with different effective contact rates, and describes the reciprocal relationship of SIR. In this study, a multitype epidemic model was further developed to be fit for the characteristics of Kounu town by dividing the subpopulations into various groups. As a result, this model can be applied to more epidemics than SIR. Moreover, the effects of the different strategies for controlling and preventing influenza can be simulated by changing the parameters in the model, because the parameters of this model show effective contact rates for each subpopulation. The details are described in the Methods section.

The primary strategies for H1N1pdm control and prevention are treatment with antiviral drugs, preventive actions such as wearing a mask or vaccination, event cancellation, and school closures. To evaluate these mathematically, these strategies were substituted in the models as follows: treatment with an antiviral drug was replaced with decreasing the duration of virus shedding by 1 day; preventive actions was replaced with decreasing the effective contact rate by 30% of the total population; event cancellation was replaced with decreasing the effective contact rate by 50% in the area in which most infected cases occurred; school closure was replaced with an infectivity of 10% for the subpopulation of the school on a weekday. The epidemic was analyzed from these 4 aspects.

In this study, by conducting a survey of schoolchildren in Kounu town aged 1–15 years during the H1N1pdm epidemic of 2009 and applying the data to an SIR model and multitype epidemic models, we aimed to evaluate and compare the effectiveness of the strategies for H1N1pdm control and prevention; that is, treatment with antiviral drugs, preventive actions, event cancellation, and school closures.

METHODS

The subjects were schoolchildren in Kounu town under 15 years of age. The questionnaires answered by their parents provided data on their school, area, and condition (Susceptible, Infected, or Removed). Three mathematical models were adopted, and the best-fitting one was selected for the actual epidemic dynamics. By changing the parameters of the selected model and running 5 simulations on strategies for control and prevention, the total number of infected subjects and the basic reproduction numbers were compared.

Subjects

The subjects were 291 children registered as attending nursery, primary, or junior high school in Kounu town as of April 1, 2010. No subject received vaccination during the epidemic. The subjects were classified

according to schools and areas (Table 1).

Data acquisition

Anonymous questionnaires were distributed by schools to parents between December 14 and 21, 2009. Schools reported infected cases according to the dates of absence due to influenza, grade, and living area. We received 120 responses to questionnaires and schools reported 129 cases of influenza infection. The response rate among infected cases was 93.0%. We used the questionnaire data, which included age, address, date of infection, duration of symptoms, and information about whether the subject received treatment with an antiviral drug, and the average duration of symptoms was calculated. All children with influenza were prevented from attending school during the infectious period by the School Health Law. Therefore, the number of undetected cases can be expected to be relatively small in Japan compared to in other countries. The study design conformed to the principles of the 1975 Declaration of Helsinki, and was approved by the Ethics Committee of Epidemiological Research of Hiroshima University, Hiroshima, Japan (Epi-351, Hiroshima University).

Models

Three discrete stochastic models with varying coefficients to approximate the observed epidemic curve were adopted. We assumed that the logarithmic-transformed varying coefficients are quadratic polynomial of the reciprocal of the day after the epidemic started.

Model 1 (an SIR model with varying coefficients): Assuming that Kounu town had a uniform time-dependent infection rate, the epidemic can be simulated in the SIR model. The model is described as

$$\begin{aligned} S_{n+1} &= -\beta_n S_n I_n, \\ I_{n+1} &= \beta_n S_n I_n - \gamma_n I_n, \\ R_{n+1} &= \gamma_n I_n, \end{aligned}$$

where S_n , I_n , and R_n denote the number of susceptible, infected, and removed individuals at day n after the epidemic started. Parameters β_n and γ_n denote the infection rate and recovery rate at day n .

We estimated parameters using the likelihood esti-

Table 1 Subjects' background data (N=291)

School	Area						Total
	HN	KjF	Km	U	S		
K nursery school	24	21	4	9	19	77	
K primary school	56	37	8	0	0	101	
U primary school	0	0	0	11	0	11	
S primary school	0	0	0	0	29	29	
K junior high school	21	15	8	6	23	73	

Subjects' background data

Subjects were students at 1 of 5 schools in Kounu town. Each subject lived in 1 of the 5 areas.

mation method based on the corresponding stochastic model:

$$\begin{aligned} \Delta N_{n+1} | N_n &\sim \text{Poisson}(\beta_n S_n I_n), \\ \Delta R_{n+1} | R_n &\sim \text{Poisson}(\gamma_n I_n), \end{aligned}$$

where $\Delta N_{n+1} = N_{n+1} - N_n$, $N_n = (N_1, N_2, \dots, N_n)$, $\Delta R_{n+1} = R_{n+1} - R_n$ and $R_n = (R_1, R_2, \dots, R_n)$.

Models 2 and 3 (Multitype epidemic models with varying coefficients): If the infection rate was not constant, however, an epidemic curve formed by an SIR model would not be able to approximate the observed epidemic curve. Multitype epidemic models divide a population into subpopulations according to infection. In Model 2, the subjects were divided into 5 subpopulations according to the schools they attended. In Model 3, the subjects were divided into subpopulations according to schools (into 5 groups) and were further divided into 5 groups according to the area in which they lived. The subpopulations were labeled $i = 1, 2, \dots, 5$; in all there were 25 subpopulations. Mathematical explanations of the dynamical model and the corresponding stochastic model are

$$\begin{aligned} S_{i,n+1} &= -\beta_{i,n} S_{i,n} I_{i,n}, \\ I_{i,n+1} &= \beta_{i,n} S_{i,n} I_{i,n} - \gamma_n I_{i,n}, \\ R_{i,n+1} &= \gamma_n I_{i,n}, \end{aligned}$$

and

$$\begin{aligned} \Delta N_{i,n+1} | N_{i,n} &\sim \text{Poisson}(\beta_{i,n} S_{i,n} I_{i,n}), \\ \Delta R_{i,n+1} | R_{i,n} &\sim \text{Poisson}(\gamma_n I_{i,n}), \end{aligned}$$

where $I_n = \sum_i I_{i,n}$, $\Delta N_{i,n+1} = N_{i,n+1} - N_{i,n}$, $N_{i,n} = (N_{i,1}, N_{i,2}, \dots, N_{i,n})$, $\Delta R_{i,n+1} = R_{i,n+1} - R_{i,n}$ and $R_{i,n} = (R_{i,1}, R_{i,2}, \dots, R_{i,n})$.

Simulations

The best-fitting model for the observed epidemic was selected. Assuming 4 strategies for influenza control and prevention, epidemic dynamics were simulated by changing the parameters as follows.

Simulation 1: It was assumed that sufficient antiviral drugs were provided in hospitals. According to the results of a randomized controlled trial on the effect of oseltamivir in Japan^{4,5)}, oseltamivir-treated patients recover 1 day earlier than untreated patients. A similar trend is observed for other antiviral drugs^{6~8)}. Therefore, γ^{-1} was replaced with $\gamma^{-1} - 1$.

Simulation 2: It was assumed that preventive actions such as vaccination were practiced. Influenza vaccination decreases susceptibility by 30%^{9,10)}. Therefore, the effective contact rate β was replaced with $0.7 \times \beta$.
Simulation 3: It was assumed that large events were cancelled. This inhibits the spread of infection in an especially high infectivity area. Therefore, the effective contact rate of a high infectivity area was replaced with $0.5 \times \beta_i$.

Simulations 4 and 5: It was assumed that school closure was carried out. School closure is considered to reduce contact between schoolchildren. Because contact with members of family or the community cannot be ignored, the effective contact rate for children at-

tending school was replaced with $0.1 \times \beta_i$, and not 0, on weekdays. School closure can only be carried out on a weekday after the epidemic has started. We assumed that school closure was carried out in K primary school from 6 days after the epidemic started in Simulation 4, and 1 day after the epidemic started in Simulation 5.

RESULTS

Epidemic in Kounu town

The epidemic started with an infected 15-year-old female subject on October 29 (day 1). The maximum number of infected subjects was 68 on November 8 (day 11), and the epidemic ended on November 25 (day 28). The total number of infected subjects was 120/291 (34/77 in K nursery school, 55/101 in K primary school, 2/11 in U primary school, 10/29 in S primary school, and 19/73 in K junior high school). School closures were executed at K primary school (from Nov 5 to 6; day 8 to 9), K junior high school (from Nov 5 to 6; day 8 to 9), and K nursery school (Nov 9; day 12). We used day 8 data for the error sum of squares turn and day 9 data for the penalties turn (Fig. 1). The epidemic for each school and each area is shown in Table 2 and Figures 2 and 3.

Models

We reproduced epidemic curves and estimated effective contact rate (Fig 4). The sum of squares was 0.870 in Model 1, 0.696 in Model 2, and 0.883 in Model 3. Furthermore, considering the total number of infected cases, the maximum number of infected cases, and the epidemic duration, we found that the epidemic curve in Model 3 was the best-fitting of the 3 models, and we used this model for the simulations. According to Model 3, the effective contact rates for each subpopulation ranged from 0.00009 to 0.00534 (Table 3); the total and maximum numbers of infect-

Figure 1. The observed epidemic curve and intervention by school closure in Kounu town. Students in Kounu town were divided into 3 groups: Susceptible, Infected, and Removed. Figure 1 shows the transitional curve for each group. Note that 3 schools had been closed during the period (indicated by arrows).

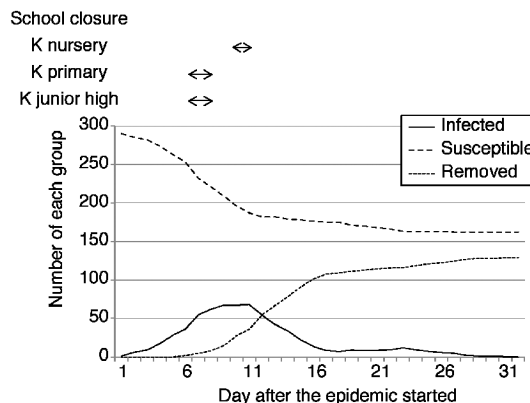


Table 2 Infected cases in each subpopulation

School \ Area	HN	KjF	Km	U	S	Total
K nursery school	10 (41.7%)	8 (38.1%)	1 (25.0%)	3 (33.3%)	12 (63.2%)	34 (44.2%)
K primary school	30 (53.6%)	20 (54.1%)	5 (62.5%)	—	—	55 (54.5%)
U primary school	—	—	—	2 (18.2%)	—	2 (18.2%)
S primary school	—	—	—	—	10 (34.5%)	10 (34.5%)
K junior high school	9 (42.9%)	3 (20.0%)	1 (12.5%)	1 (16.7%)	5 (21.7%)	19 (26.0%)

The number of infected cases

Infected cases from 5 schools in Kounu town divided into 5 areas.

Data are expressed as number of students (percentage of those at each school).

Figure 2. The observed epidemic curve of each school. Figure 2 shows infected numbers in each school.

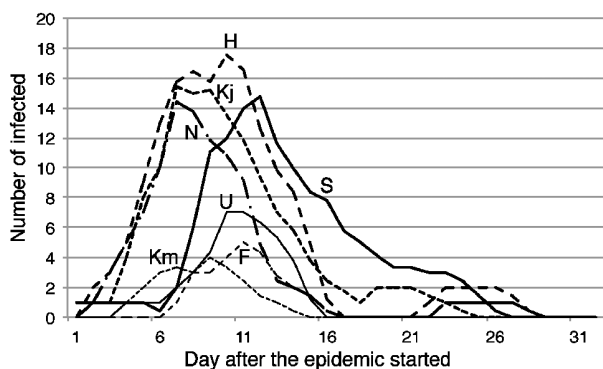


Figure 3. The observed epidemic curve of each area. Figure 3 shows infected numbers in each area.

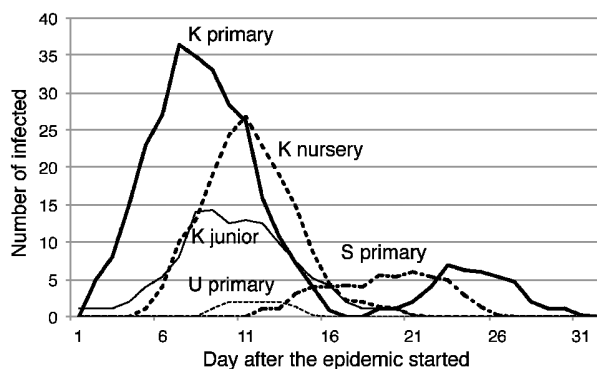


Figure 4. Comparisons between the 3 epidemic curves. The observed epidemic curve and 3 epidemic curves simulated by mathematical modeling are shown. Model 1 was an SIR model, while Models 2 and 3 were multi-type epidemic models with varying coefficients.

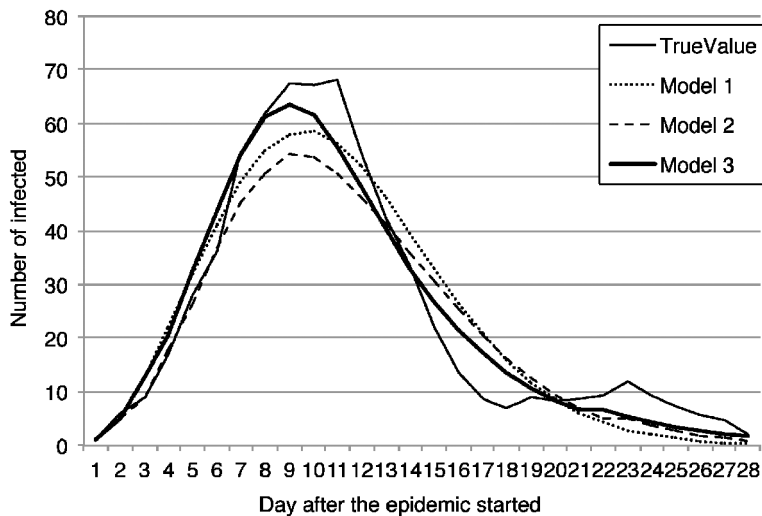


Table 3 Effective contact rate in each subpopulation

School \ Area	HN	KjF	Km	U	S
K nursery school	0.000265	0.000595	0.000174	0.000284	0.001264
K primary school	0.003301	0.001931	0.005336	—	—
U primary school	—	—	—	0.000199	—
S primary school	—	—	—	—	0.002883
K junior high school	0.004544	0.000316	0.000093	0.000116	0.000227

The effective contact rate in each area represents the probability that a member of the susceptible population becomes newly infected when they contact a member of the infective population.

Infected cases of 5 schools in Kounu town divided into 5 areas are shown.

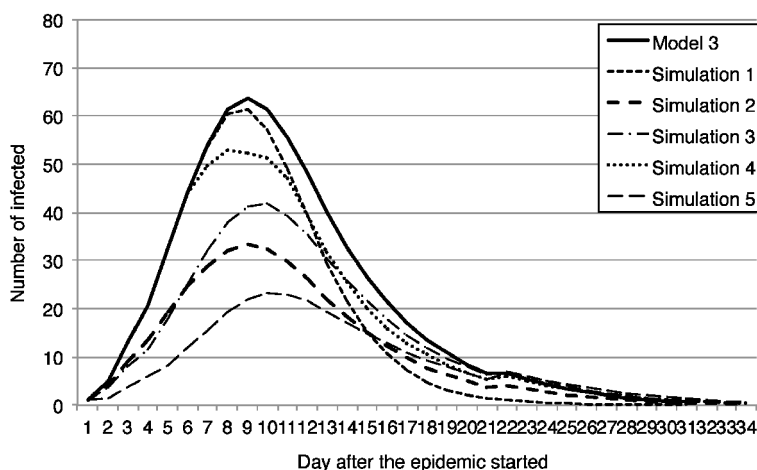
Table 4 Comparison between the models

	Actual epidemic	Model 1	Model 2	Model 3
Coefficient of determination R^2	—	0.870	0.696	0.883
Period of epidemic (days)	28	26	28	31
Maximum number of infected cases (persons)	68	58.5	54.2	63.7
Total number of infected cases (persons)	120	123.7	120.1	127.1

Comparison between the models

Coefficient of determination and some parameters of each model are shown.

Figure 5. Comparison of policies for prevention. This figure shows the comparison epidemic curves with/without intervention by policies for prevention. Simulations 1, 2, 3, 4, and 5 assume sufficient antiviral stockpiles, preventive behavior such as wearing a mask or vaccination, event cancellation, normal school closure, and theoretical school closure, respectively.



ed cases were 127 and 63.7, respectively, and the epidemic duration was 31 days (Table 4).

Simulation

The simulation results are shown in Figure 5 and Table 5.

In Simulation 1, in which virus shedding was shortened by 1 day, the epidemic was shortened from 31 days to 23 days. The total number of infected cases reduced from 127.1 to 113.2, and the maximum num-

ber of infected cases reduced from 63.7 to 61.6. In Simulation 2, in which the effective contact rate was decreased by 30 percent, the total and maximum numbers of infected cases were reduced to 51.2 and 33.3, respectively, and the epidemic was shortened to 29 days. In Simulation 3, in which the effective contact rate of the high infectivity area was replaced with $0.5 \times \beta_i$, the total and maximum numbers of infected cases were reduced to 87.6 and 41.7, respectively. However,

Table 5 Comparison between policies for prevention

	Model 3	Simulation 1	Simulation 2	Simulation 3	Simulation 4	Simulation 5
Period of epidemic (days)	31	23	29	32	31	33
Total number of infected cases (persons)	127.1	113.2	51.2	87.6	85.5	62.6
Maximum number of infected cases (persons)	63.7	61.6	33.3	41.7	53.1	23.1
The number of persons affected by the intervention	—	291	291	56	101	101

Comparison between policies for prevention
Some parameters for each situation are shown.

the epidemic was not shortened. In Simulation 4, in which the effective contact rate of the schoolchildren was replaced with $0.1 \times \beta_i$ on weekdays, the total and maximum numbers of infected cases were reduced to 85.5 to 53.1, respectively, and the epidemic was not shortened. This pattern was similar to that observed for Simulation 3.

In Simulation 5, in which school closure was carried out immediately at Kounu primary school, the total and maximum numbers of infected cases were reduced to 62.6 and 23.1, respectively. The epidemic was not shortened.

DISCUSSION

In this study, the actual epidemic dynamics were duplicated using mathematical models. Moreover, by changing the parameters of the effective contact rates, the epidemic dynamics were simulated in order to evaluate the relative effectiveness of 4 strategies for influenza control and prevention.

Previous studies have used 2 standard approaches for evaluating epidemics using mathematical models. The first approach is to evaluate epidemics in large areas using survey estimates of the numbers of patients who were hospitalized or died because of influenza. The other is to simulate a hypothetical epidemic in a city. Generally, the distribution of a population and its activity, which influence effective contact rates in each subpopulation, vary in different towns. In small towns, as compared to large towns, each subpopulation has greater influence over other subpopulations. The 2 standard approaches cannot evaluate an epidemic in a small, discrete area where the effective contact rates are different in each subpopulation. Therefore, we created a new epidemic model based on survey data for schoolchildren in Kounu town, and we simulated 4 strategies used to control and prevent epidemics of influenza in small, discrete areas.

Model 3 compared infectivity in terms of effective contact rate. High infectivity was identified in Km, HN, KjF, and S areas of the primary school and in the HN area of K junior high school. High infectivity is a result of several factors: the presence of immunocom-

promised hosts, a population's high activity, high population density, and so on. When a few members of a minor subpopulation contract influenza, infectivity can increase; this was the case in the Km area of K primary school. The high activity level typical of primary schoolchildren may have been the cause of the high effective contact rates in the Km, HN, KjF, and S area of the primary school. We found that the HN area of not only the primary school but also the junior high school had high effective contact rates. This suggests that another factor was operating in this area. In fact, in the HN area, K primary school students often gathered in close proximity to prepare for the community festival. This is likely to have been the cause of the rapid spread of infection. We changed the parameters in Model 3 to evaluate the effectiveness of the 4 strategies in an area with a high-infectivity subpopulation. Antiviral drugs can alleviate and shorten the symptoms of influenza, but their effects on an epidemic are not known. We found that antiviral drugs can shorten an epidemic's duration and reduce the total and maximum numbers of infected individuals.

In Simulation 3, the infectivity of the HN area of the K primary school was reduced to half of that observed during the festival preparation period. During this period of 4 days, 56 persons were affected by the intervention. School closure is an appropriate intervention for a high-infectivity population that attends school, and is effective for the prevention of epidemics. The Japanese pandemic influenza guidelines strongly recommend school closure on the day on which a single individual is found to be infected. The school-closure simulation conducted according to the guidelines led to a marked reduction in the total and maximum numbers of infected persons. However, during the actual epidemic, school closure was carried out after the infection had spread. As Simulation 4 shows, school closure after an infection has spread has little effect.

Although the other strategies also had an effect, event cancellation was effective and is considered to be the minimum intervention required to reduce the total and maximum numbers of infected individuals.

Moreover, event cancellation is particularly useful because it can be carried out immediately if appropriate guidelines are available. In this simulation, we assumed that event cancellation would reduce the infectivity of the highest infectivity area to that of the average of other areas. The simulation can also be applied to other situations, such as factories, gymnasiums, and so on. Intervention is necessary only in areas of high infectivity and susceptibility. Therefore, targeted intervention upon identification of an event or area with high infectivity and susceptibility may be effective.

Although the durations of the epidemics in Simulations 3–5 were not shorter than that of Model 3 without a strategy, it is unnecessary to increase the quantity of antiviral drugs because the total number of infected individuals is decreased. Moreover, the duration of the epidemic can be expected to be shorter than that estimated, due to the combined use of antiviral drugs in Simulation 1. A decrease in the maximum number of infected individuals will no doubt reduce hospital workloads.

It is difficult to compare actual epidemics with those in which interventions were applied. Event cancellation in the United States^{11–13}) in 1918 and school closure in Israel^{14,15}) in 2000 reduced the number of infected individuals. Although some studies suggest that school closure is not effective, others — including those using mathematical models — have reported its effectiveness^{16–22}).

Two peaks in the epidemic in the K primary school were identified; these were not simulated by any of the models. If no preventative actions, such as antiviral treatment, mask wearing, or school closure, had been taken, then a higher second peak may have occurred.

In this study, it was assumed that the effective contact rate and removal ratio can change every day during an epidemic. However, in actual epidemics, both the susceptibility and infectivity change according to individuals' behavior. For example, susceptible individuals will undertake preventive actions, while infected subjects will remain at home. These factors could have affected the accuracy of our simulated epidemic curves, although our model described the actual epidemic in a small, discrete area very well. Our model may not be applicable to a large city in which the population is mobile.

In this study, the non-epidemic effects of the 4 strategies were not evaluated. For example, the cancellation of a festival may have mental health consequences. Negative economic and educational effects may result from uninfected children being unable to attend school, such as their parents not being able to go to work.

Although event cancellation may have social, economic, and political consequences^{23–25}), our findings demonstrate its effectiveness in a small discrete area

during an epidemic.

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