Introduction

Given the potentially devastating features of pandemic influenza [1], it is of outstanding importance to construct detailed control plans. Several industrialized countries have developed their own original plans of action, partly using mathematical and/or simulation methods [2-9]. For example, the original plans in the United States were published on November 3, 2005. These plans consider area quarantine as one of the possible control measures [10]. The World Health Organization (WHO) has also emphasized the potential effectiveness of area quarantine as one of their choices [11]. Among various studies on this issue to date [2-9], area quarantine was included in two seminal papers [2, 4]. These studies modeled potential pandemics in a community consisting of 500,000 and 85,000,000 individuals, respectively, the models of which realistically permitted them to go to schools, workplaces and so on. It is possible for these models to depict detailed features of the spread of disease since they are constructed on an explicitly structured realistic field that is often referred to as an individual based model (ibm) [12]. Consequently, it has been suggested that area quarantine within 5 km could contain pandemic influenza in rural areas at a very early stage. In a more recent study, a similar model was proposed to simulate the detailed contact patterns of the epidemic both at long and short distances, exploring the potential roles of facility closure, area quarantine and travel ban.

This study further facilitates our understanding of the effectiveness of preventive measures that are directed at reducing the (spatial) spread of disease. Specifically, we attempt to assess and compare the effectiveness of freezing human movement (e.g., shutting down trains, area quarantine and facility closure). This is motivated by several characteristic features of the spread of influenza in urban settings (e.g., the spread of Asian flu through urban train networks [13]). Since both the pandemic plans for the US and the Tokyo Metropolitan Government state that instituting partial shutdowns of public transportation is likely, we feel that it is crucial to clarify the impact this will have on an epidemic. Thus, our study is aimed at examining two unclear points: (1) "Is it possible to contain the pandemic at an early stage in an urban area?" and (2) "what would be the most optimal conditions for area closure to contain outbreaks in urban areas?" For this purpose, the household structures (i.e., family members), spatial distribution of households and detailed transportation system used in our simulation model explicitly reflect those of Japan [14].

Method

We construct a model city using the ibm. It consists of 20 by 20 districts. One district includes 900 households. Since there are 400 districts in this city, it has 360,000 households. The width of each district is assumed to be 1km.

Each household consists of 1-6 agents. Each agent is classified into five types: two types of adults (A1, A2), two types of children (C1, C2), and the elderly (E). A1 commutes to work, A2 goes to a shopping mall, C1 goes to a school, C2 goes to a kindergarten, and E goes to a daycare facility.

This distribution of family structure is based on the actual family structure reported in the 2000 Population Census in Japan [14]. There are five types of households, i.e. "couple only", "couple and children", "couple, children, and grandparents", "couple, children, and a grandparent", and "single".

On average, one household has about 2.49 agents. Since there are 360,000 households in the city, the population of the city is about 896,400.

A workplace is located in every district and A1 commutes to it. A1 is assigned to a workplace following a distribution of distances traveled to work. This is based on the distribution of commute time from the 2000 Population Census in Japan [14]. For the distribution of the distance traveled we assume that A1 can advance 5km in 30 minutes.

A part of A1's commute is by a crowded train. A1 rides in the train from the closest station to the home toward the workplace. The agent comes in contact with all other agents on the train. The railroad system is composed of 20 blocks, and is the length of 20 districts and width of 1 district. We set 20 stations, one in the center of each block. The closest station to a home or a workplace is set as the one in the same block as that home or workplace. We assume a straight railroad which connects all 20 stations. Trains run on this railway once per day. Passengers who are going in the same direction are assumed to ride on the same train. A1 commutes by the train if the distance from the home to the workplace is longer than the sum of the distance "from the home to the closest station" and "from the workplace to the closest station". A1 commutes on foot otherwise.

A shopping mall, a school, a kindergarten, and a daycare facility exist in every district and it is assumed that agents go to the nearest facility.

Basically, we apply similar intrinsic dynamics to those which were assumed in previous studies [3, 15]. We set transmission probabilities in this model based on the contact rate in a previous study [15]. We suppose that withdrawal means absence from work, school, etc. to visit a doctor. Thus withdrawal indicates clinical cases. Initially all agents are assumed to be susceptible and no vaccines are available.

We assume that agents contact each other in the following social groups: home, neighborhood, community, workplace, train, shopping mall, school, kindergarten, and daycare facility.

In a social group, an agent contacts all other agents in a unit time. The transmission probability in this study is defined as the probability that one susceptible agent becomes infected when it comes in contact with one infectious agent.

Since the transmission probability in the train is not very well known, we examined the sensitivity of epidemic trajectories with three probabilities, i.e. no transmission, moderate transmission, and high transmission. These cases seem to represent approximately non-crowded, moderately crowded, and highly crowded trains, respectively.

We suppose three counter measures for pandemic influenza, i.e. facility closure, shutdown of trains, and area quarantine. These three interventions were simulated as follows:

(1) The first measure is facility closure. It means that when the absentee rate of a facility exceeds a set criterion, we close the workplace, school, kindergarten, or daycare facility for three days. If the absentee rate is less than the set criterion for three days, the facility reopens. Facility closure means that there is no contact in the closed

facilities, and A1 who commutes to a closed workplace will have no contact in the train as well. We examined three criteria, i.e. no closure, closing at 5%, and closing at 1%.

(2) The second measure is the shutdown of trains when the clinical rate of the city exceeds a set criterion. If the clinical rate is less than the set criterion for three days, the shutdown is terminated. This policy means no contact on trains, and A1 who commutes by train cannot go to the workplace.

(3) The third measure is area quarantine. Since we did not model the entire nation, but only one city, our model could not exactly realize area quarantine as in a previous study [2]. Instead of that, we measure the maximum radius where the infected agents are located when the number of infected clinical cases reaches 20. This is the same timing of area quarantine in the previous research. This radius represents the necessary distance for area quarantine in order to contain an outbreak.

As an initial case, we released one A1 on the first day of the incubation period into the center of the city. As state transitions are decided stochastically, we examined the behavior for 360 days, repeated the simulation 50 times, and took an average of the outbreak cases from these 50 simulations.

Results

During 50 simulation runs, there were 38 runs in which the disease declined to extinction and there was no transmission on the train. Thus, in the following, the extinct runs were excluded.

Figure 1 shows the epidemic curve without facility closure and transmission on the train. The number of new clinical cases reaches the maximum number on the 117th day and about 16% of the population is clinically diagnosed (refer to Figure 2).

Figure 2 shows the impact of facility closure and shutdown of trains. When facility closure is not assumed, moderate transmission in the train hastens the peak by 30 days and high transmission hastens it by 79 days. Closing facilities at 1% criterion delays the peak of the epidemic by 42 days when transmission in the train is not assumed. However, no counter measure delays the peak in the case of high transmission.

When transmission in the train is assumed to be moderate, closing facilities at 1% criterion reduces the cumulative attack rate by about 4.8% and shutting down trains reduces it by about 0.4%. The combination of closing facilities at 1% criterion and shutting down trains at 1% criterion has about the same effectiveness as facility closure alone.

Figure 3 shows the diffusion of infections. Moderate transmission in the train decreases the probability of successfully containing the epidemic within 10km by about 80% and with high transmission containment fails within 10km.

The effectiveness of facility closure and the shutdown of trains is shown in Table 2. Facility closure at 1% criterion appears to be about 25% effective regardless of transmission in the train. Shutdown of trains at 1% criterion appears to be about 2% effective, which is less effective than facility closure.

Discussion

This paper evaluated the risks for a megacity where we assumed transmission in the train. If the transmission probability in the train was high, the shutdown of the transportation system was 2.16% effective in reducing the clinical attack rate. However, if facilities were closed with a 1% criterion, most effects caused by the shutdown of trains seemed to disappear. It is important to note that facility closure is more effective here than the shutdown of trains. So far, in previous research the possibility of transmission on a commuter train or bus has been ignored. This may be appropriate in the US or UK where cars are the main mode of transportation, but it seems inappropriate for megacities in Asia such as Tokyo, Seoul, or Shanghai.

Transmission probabilities and natural history were mainly based on previous studies [3, 15]. The previous study by Germann et al. [6] suggests that the illness attack rate is 43.5% with no intervention and 29.3% with school closure for R_0=1.9. Therefore, the effectiveness of school closure is (43.5-29.3)/43.5*100=32.6%. This effectiveness is roughly the same as the effectiveness in our study even though we could not make a simple comparison because of the difference in closure criterion. The initial seeding is one individual in our study. However, the number of initial seeding seems to affect only the frequency of outbreaks. The necessary distance for containment at a probability of 90% in our model city is 11km without transmission in the train and 13km-14km with transmission in the train. However, the previous study by Ferguson et al. [2] indicates that a 5km ring policy can contain a pandemic in Thailand.

Our findings suggest that school or workplace closure at a very early stage can mitigate the transmission, but late closure may not affect transmission at all. At the very least, schools and workplaces should be closed at 1% criterion. On the other hand, the effectiveness of the shutdown of trains may be limited. The simultaneous use of both mitigation policies, especially when started at a very early stage, is strongly suggested for preparation planning for pandemic flu. Conversely, area quarantine seems to be impossible to perform in Japan.

The most important limitation in this research is reality. Even though this paper models a hypothetical city based on the actual distribution of family structure, commuting time and so on, it is not real. Individual based models, including this paper and the previous research thus far use only distribution, and have no base in actual data of movement and location at the individual level. Therefore, these models cannot evaluate the risks for specific areas or policies; they can only suggest the general propensity of diffusion or efficacy of a policy. On the other hand, we know of research which uses actual data of movement and location at the individual level [16], so the next step is to move towards a hybrid of the ibm and this actual data.

Acknowledgments

We used the Information Technology Center at the University of Tokyo for computer simulations.

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Table 1: Actual distribution of household types

	Household	Proportion [%]
Couple only	8,835,119	22.0
Couple and children	14,919,185	37.1
Couple, children, and grandparents	1,441,698	3.6
Couple, children, and a grandparent	2,083,801	5.2
Single	12,911,318	32.1

Table 2: Effectiveness of facility closure and shutdown of trains - Percentage reduction in the cumulative clinical attack rate by counter measure comparison to baseline. For each transmission in the train, the baseline measure is assumed to be no facility closure and no shutdown of trains. 95% CI for the mean effectiveness is shown in parentheses.

	No transmission in the train	Moderate transmission		High transmission	
		No shutdown	Shutting down at 1%	No shutdown	Shutting down at 1%
No closure	Baseline	Baseline	1.85 [1.36, 2.27]	Baseline	2.16 [1.81, 2.84]
Closing at 5%	7.20 [6.24, 8.41]	6.74 [5.98, 7.22]	7.52 [6.60, 8.09]	5.76 [5.20, 6.14]	7.28 [6.77, 7.93]
Closing at 1%	27.1 [25.9, 28.2]	25.0 [24.3, 26.0]	25.0 [24.3, 26.0]	25.6 [25.1, 26.5]	24.7 [24.1, 25.4]

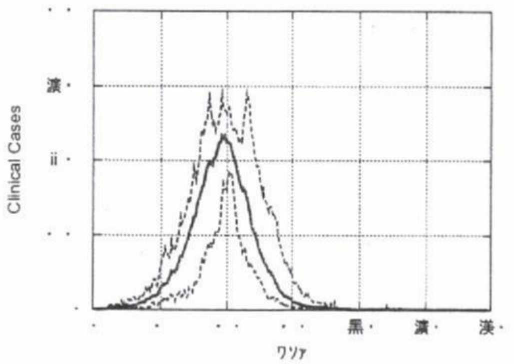

Figure 1: Epidemic curve - Transition of new clinical cases without facility closure and transmission in the train. Solid lines represent the mean of clinical cases in the simulations. Dashed lines represent the 95% confidence interval (CI) for clinical cases.

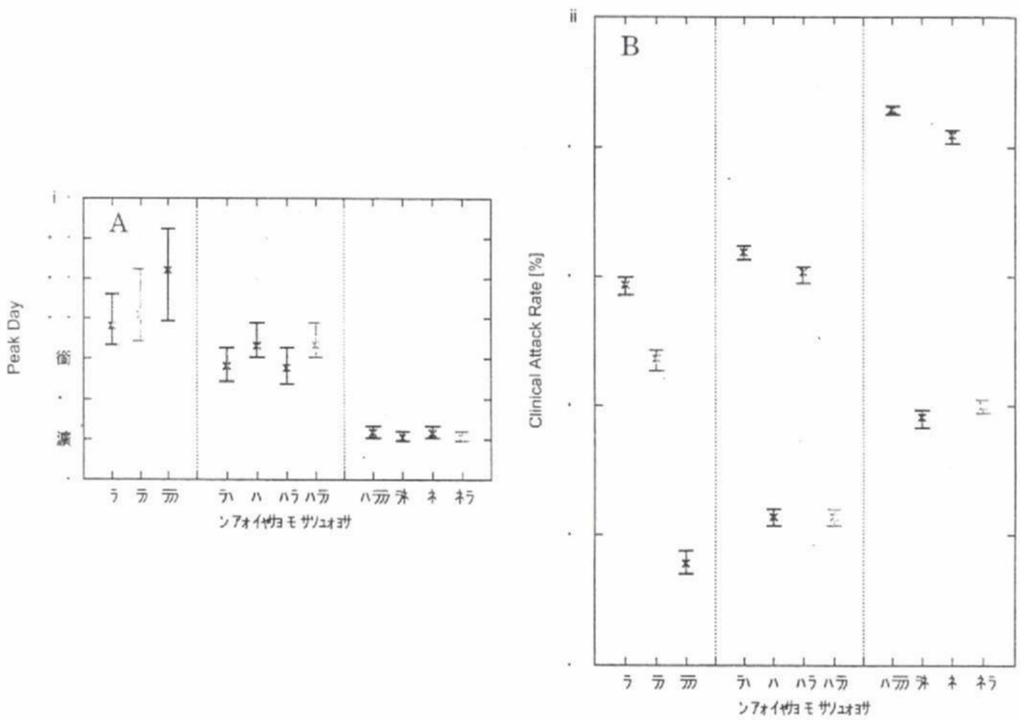

Figure 2: Impact of facility closure and the shutdown of trains - A: The peak of the epidemic with no transmission in the train (left three lines: I-III), moderate transmission (middle four lines: IV-VII), and high (right four lines: VIII-XI). Counter measures are assumed to be no facility closure (red), closing facilities at 5% criterion (green), closing at 1% (dark blue), shutting down trains at 1% criterion (purple), and both closing facilities and shutting down trains at 1% (light blue). Multiplication signs represent the mean of peak days and intervals represent the 95% CI for peak days. B: The same as A, but the cumulative clinical attack rate for the various counter measures.

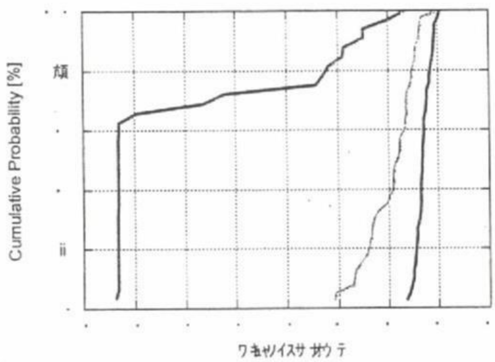

Figure 3: Diffusion of infections – The distance from the farthest clinical case to the initial case when the number of clinical cases exceeds 20. Transmission probabilities in the train are assumed to be none (red), moderate (green), and high (dark blue). For example, the probability that we can contain an epidemic within 10km is about 85% on the red line.

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ORIGINAL ARTICLE

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Effect of facility closure in the SEIR epidemic model

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Abstract H5N1, a highly pathogenic avian influenza virus subtype, has been causing outbreaks among poultry in Southeast Asia. This virus is highly virulent in humans, who are infected directly from birds. However, the virus still has not acquired human-to-human transmission capability. If a new strain of the virus capable of sustaining human-to-human transmission emerges, it could cause an influenza pandemic. We propose the use of the SEIR epidemic model of influenza transmission to assess the influence of facility closure as a containment strategy for such an epidemic. If the fraction of infected individuals exceeds a set threshold, we apply the facility-closure countermeasures for a set period. If the basic reproduction number R_0 is assumed to be 2.0, our model suggests that long-term facility closure is usually a desirable nonpharmaceutical measure, but it may not necessarily reduce the prevalence.

Key words Influenza · Pandemic · Mathematical model · Facility closure

Introduction

The threat of an influenza pandemic has been increasing for decades.[1] H5N1, a highly pathogenic avian influenza virus subtype, has been causing outbreaks among poultry in Southeast Asia. The transmission from birds to humans has been sporadic. The virus has not yet acquired the capability to sustain human-to-human transmission. However, if the virus does further mutate, the novel variant may be capable of sustaining human-to-human transmission. In addition, an influenza pandemic could cause a public health crisis because most people would be immunologically naive to the new virus.[1] Although vaccines may offer protection against infection, production delays would limit their availability during the initial periods of the pandemic outbreak.[2]

Influenza prevention and containment strategies can be broadly categorized into antiviral, vaccine, and nonpharmaceutical measures. In this study, we focus on nonpharmaceutical measures, especially facility closure. For example, schools are known to be a primary context of influenza transmission.[3] However, few data or analyses exist for proposing illness thresholds or rates of change that would lead to considering closing or reopening schools.[4]

The purpose of this study was to clarify the impact of facility closure as a containment strategy by changing the threshold or the duration of closure. We constructed a simple epidemic model of influenza transmission with deterministic differential equations. Mathematical models are useful tools for building theories, assessing conjectures, answering questions, and determining sensitivities to parameter values.[5] We can use mathematical models to compare, plan, implement, and evaluate various detection, prevention, and control programs.[5]

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SEIR model

We used a mathematical model referred to as the susceptible-exposed-infective-recovered (SEIR) epidemic model, which is represented as follows:

$$\frac{dS}{dt} = -\beta SI \tag{1}$$

$$\frac{dE}{dt} = \beta SI - \sigma E \tag{2}$$

$$\frac{dI}{dt} = \sigma E - \gamma I \tag{3}$$

$$\frac{dR}{dt} = \gamma I \tag{4}$$

Here, $S(t)$, $E(t)$, $I(t)$, and $R(t)$ are the number of susceptible, exposed, infective, and recovered individuals, respectively. This model is based on the Kermack–McKendrick model.[6]

The transitions of the SEIR model are as follows[5]: The susceptible class S comprises individuals who are at the risk of being infected. When a susceptible individual comes in contact with an infected person and transmission happens, the individual enters the exposed class E for a latency period. An exposed individual is infected but noncontagious. After the latency period, the individual enters the infective class I for an infection period. An infective individual is contagious, i.e., capable of transmitting the infection. After the infection period, the individual enters the recovered class R. A recovered individual is assumed to be permanently immune to further infection. The decreases of classes E and I are represented by σE and γI, respectively. We approximately define the latent and infection periods as $1/\sigma$ and $1/\gamma$, respectively.

The key index characterizing the time evolution of these equations is the basic reproduction number R_0, which is defined as the mean number of secondary infections generated by a primary infection in a susceptible population.[7] R_0 for the SEIR model is given by

$$R_0 = \frac{\beta N}{\gamma} \tag{5}$$

where N is the total number of individuals such that $N = S(t) + E(t) + I(t) + R(t)$. If $R_0 < 1$, one infected individual will infect fewer than one susceptible individual before recovering. In this case, the infection will surely die out. If $R_0 > 1$, one infected individual will infect more than one susceptible individual before recovering. In this case, there exists a possibility of the occurrence of a major epidemic. Therefore, R_0 is considered to be the threshold that determines whether an infection can persist in a population or not.

We propose a new epidemic model with facility closure. If the proportion of infective individuals exceeds the threshold of closure θ, we assume that the facilities will be closed for d days and, for the sake of simplicity, no transmission occurs among people. The dynamics during closure can be represented as

$$\frac{dS}{dt} = 0 \tag{6}$$

$$\frac{dE}{dt} = -\sigma E \tag{7}$$

$$\frac{dI}{dt} = \sigma E - \gamma I \tag{8}$$

$$\frac{dR}{dt} = \gamma I \tag{9}$$

If the proportion of infective individuals is less than the threshold after the facility closure period of d days, the facilities will be reopened and transmission can occur again. The dynamics without closure is governed by Eqs. 1–4. Figure 1 shows the dynamics with and without closure schematically.

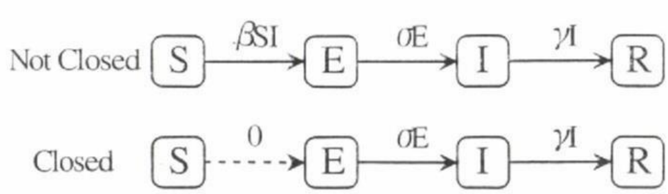

Fig. 1. Dynamics of the SEIR epidemic models with and without closure

Table 1. Parameters for transmission

Parameter	Description	Value
R_0	Basic reproduction number	2.0
$1/\sigma$	Mean latent period	1.9
$1/\gamma$	Mean infection period	4.1

Results

We performed a numerical simulation to investigate the dynamics of our epidemic model. As the initial state, we set $\{S(0), E(0), I(0), R(0)\} = \{99,1,0,0\}$. Since recent estimates of the basic reproduction number of the 1918 pandemic strain were in the range 2–3,[8] we assumed $R_0 = 2.0$. The assumed periods were also consistent with those of previous studies,[9] and the mean latent and infection periods considered were 1.9 and 4.1 days, respectively. These parameters are listed in Table 1.

Fig. 2a and b show the transition of the susceptible fraction, and those of the exposed and/or infective fraction, and the sum of the exposed and infective fractions, respectively, without facility closure. The horizontal dotted line in Fig. 2a shows that the susceptible fraction is 0.5, and the vertical dotted lines in Fig. 2a and b indicate the corresponding days. Both the exposed and infective fractions attain maximum values on about the 30th day. About 80% of the population is infected by the 180th day.

Figure 3 shows the relation between the closure threshold and the prevalence, which is the proportion of recovered individuals. We examined this relation for three values of facility closure duration d, i.e., 3, 5, and 7 days. The prevalence does not reduce monotonically with the threshold of closure regardless of the closure duration. Roughly speaking, long-term closures reduce the prevalence if the threshold of closure is fixed. However, there exists a slight possibility that a long-term closure may result in a rather higher prevalence than a short-term one.

Figure 4a and b shows the transition of the susceptible fraction and that of the sum of the exposed and infective fractions for a facility closure duration of 5 days,

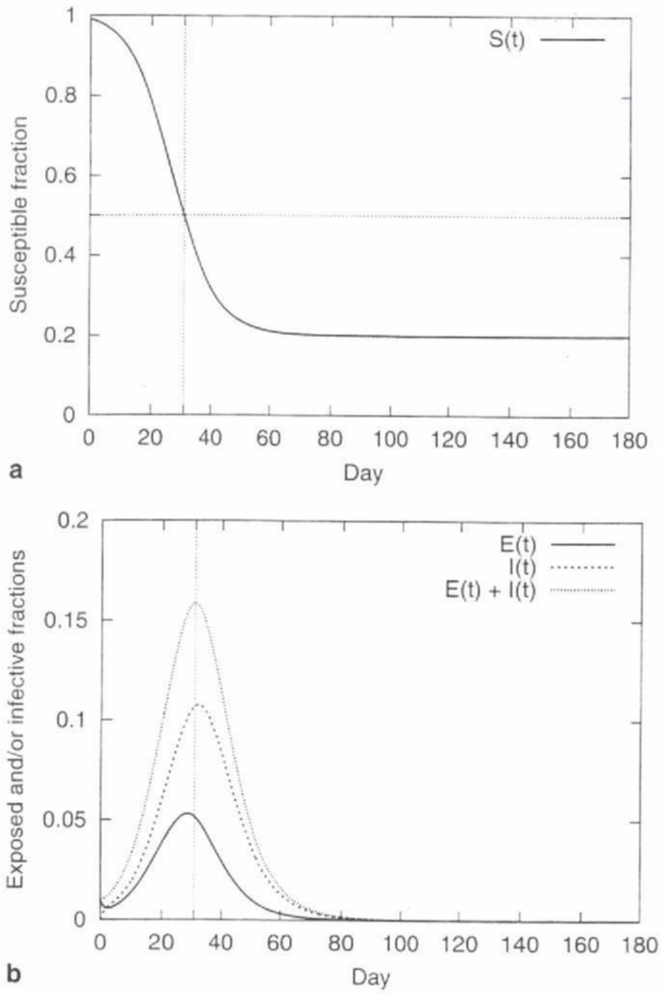

Fig. 2. Transitions of (**a**) the susceptible fraction, and (**b**) the exposed fraction, the infective fraction, and the sum of the exposed and infective fractions without facility closure

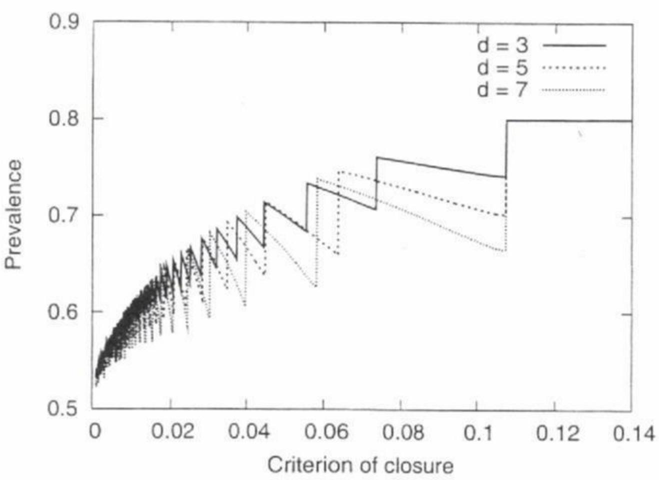

Fig. 3. Relation between the threshold of closure and the prevalence

respectively. The threshold θ of closure was assumed to be 0.06, 0.07, and 0.09, respectively. When $\theta = 0.06$, for example, facility closure was implemented twice on the 20th and 40th day.

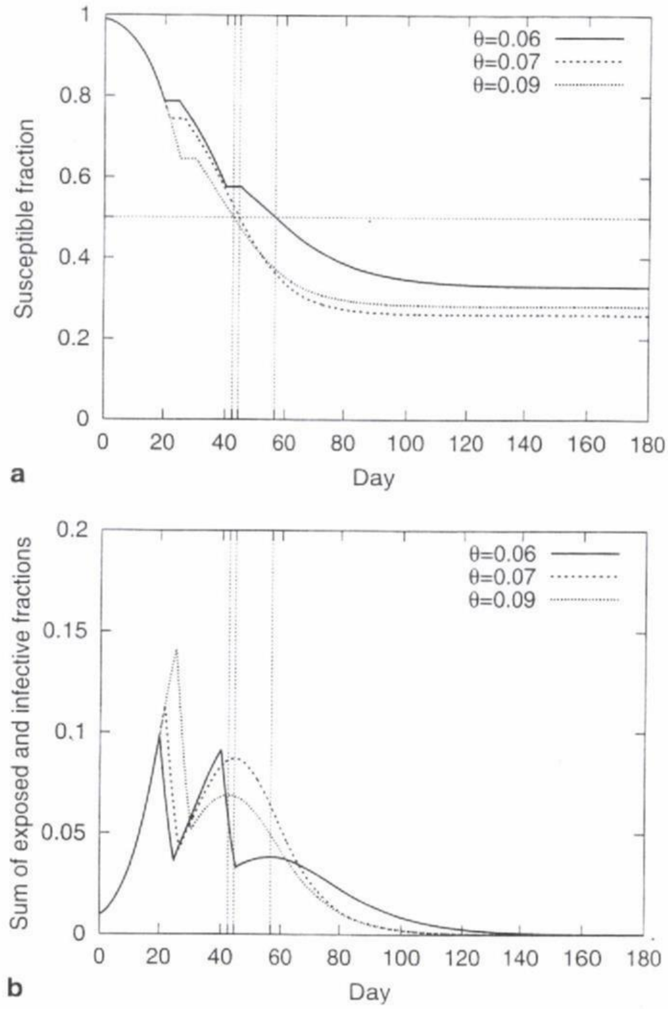

Fig. 4. Transitions of (**a**) the susceptible fraction and (**b**) the sum of the exposed and infective fractions for a facility closure duration of 5 days

Discussion

Figure 2 shows that the number of exposed and infective individuals is maximum on the 30th day. After this period, the following inequality holds:

$$\frac{dE}{dt} + \frac{dI}{dt} < 0 \tag{10}$$

From Eqs. 2, 3, and 5, we can obtain the following inequality:

$$\frac{S}{N} < \frac{1}{R_0} \tag{11}$$

The inequalities in Eqs. 10 and 11 imply that the number of exposed and infective individuals starts reducing when the susceptible fraction is less than $1/R_0$. This threshold of reduction is 0.5, since we assumed that $R_0 = 2.0$. This result is in good agreement with the simulation shown in Fig. 2.

From Eqs. 10 and 11, we can conclude that at least half the population is infected in this model. Therefore, the number of exposed and infected individuals when the susceptible fraction is equal to $1/R_0$ is an important factor to consider in reducing the prevalence.

Figure 4 explains why zigzag lines appear in Fig. 3. First, the transition of the sum of the exposed and infective fractions attains two peaks for $\theta = 0.09$ and 0.07. If the threshold changes from 0.09 to 0.07, the sum of the exposed and infective fractions reduces in the first peak but increases in the second one. In the second peak, the susceptible fractions with $\theta = 0.07$and $\theta = 0.09$ are the same at 0.5, and the increase in the prevalence due to the increase in the number of exposed and infective individuals is more for $\theta = 0.07$ than for $\theta = 0.09$. Second, if θ is reduced to 0.06, the transition of the sum of the exposed and infective fractions attains three peaks. The sum of the exposed and infective fractions at the third peak with $\theta = 0.06$ is less than that at the second peak with $\theta = 0.07$. These two mechanisms generate the zigzag lines in Fig. 3.

In this study, we show that low prevalence is generated by a small number of exposed and infective individuals when the susceptible fraction is equal to $1/R_0$. However, since the R_0 values of new influenza strains which may emerge in the future are unknown, we cannot change the number of exposed and infective individuals manually. It seems that long-term facility closure is a desirable nonpharmaceutical measure in most cases.

Conclusions

We have proposed a simple epidemic model based on the SEIR model to explore the effect of facility closure. The model has shown that the possibility of reducing the prevalence is usually higher for long-term facility closure than for the short-term closure.

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