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Evaluation for interventions against influenza of H5N1 in Sapporo-city by using an Individual Based Model

Tomoko MORIMOTO*, Tomohiro ZENIHANA*, Yusuke MAITANI*
and Hirofumi ISHIKAWA*

The spread of the highly pathogenic avian influenza (H5N1) among domestic poultry and wild birds has caused global concern over the outbreak of an influenza pandemic of H5N1. The "Pandemic Influenza Preparedness Action Plan" determines the strategy against an influenza pandemic in Japan. Simulations were carried out using an individual based model (IBM). The IBM targeted a virtual area with a population of 100,000 using the demographic data of Sapporo-city, Hokkaido. The effectiveness of targeted antiviral prophylaxis (TAP), geographical targeted antiviral prophylaxis (GTAP), school closure, and pre-pandemic vaccination were explored. Moreover, this study focused on infections among children, who have a high attack rate, and analyzed the effectiveness of interventions for school-age targeted antiviral prophylaxis (STAP). Consequently, TAP, which is recommended by the "Pandemic Influenza Preparedness Action Plan", was found to have high effectiveness in the suppression of the outbreak. Moreover, this study showed the importance of intervention among children, such as STAP and school closure, to prevent the spread of H5N1 influenza.

Keywords: *Influenza, Pandemic, H5N1, Individual Based Model (IBM), Sapporo*

1. Introduction

In recent years, the spread of highly pathogenic avian influenza (H5N1) has lead to an influenza pandemic among domestic poultry and wild birds in Asia, Europe, and Africa, and about 400 cases of the H5N1 infection in people has been reported in 15 countries, mainly in Southeast Asia, since 2003 (WHO, 2008). Therefore, there has been global concern over a pandemic outbreak of H5N1 influenza in humans (Clayton, 2003). In the past century, influenza pandemics have occurred at least three times around the world; "Spanish flu" (A/H1N1) in 1918, "Asian flu" (A/H2N2) in 1957-1958, and "Hong Kong flu" (A/H3N2) in 1968-1969. The most serious pandemic was "Spanish flu", which affected large parts of the population around the world and is thought to have killed at least 40 million people in 1918-1919 (WHO, 2003). More recently, "Asian flu" and "Hong Kong flu" also caused significant morbidity and mortality worldwide.

The Ministry of Health, Labour and Welfare of Japan (2007) has designed a "Pandemic Influenza Preparedness Action Plan" that determines the strategy against an influenza pandemic outbreak in Japan. This plan indicates that when an influenza pandemic occurs only overseas not in Japan, the inoculation of pre-pandemic vaccine will be performed for health care workers and workers in social services urgently, and that when an influenza pandemic occurs in Japan, the administration of antiviral agent oseltamivir and school closure will be performed.

Previously, there were a series of studies on influenza using stochastic models (Elveback *et al.*, 1964, 1965, 1968, 1971, 1976). Recently, an individual based model (IBM), in which every individual was assigned a role of

*Department of Human Ecology, Graduate School of Environmental Science, Okayama University, 700-8530 Okayama, Japan

infectious status in a society, was used to simulate an influenza epidemic on a more realistic basis. Longini *et al.* (2005) investigated the effectiveness of intervention of containment against an influenza pandemic for Southeast Asia, and Germann *et al.* (2006) for the United States. Ohkusa *et al.* (2007) studied the spread of influenza in a metropolitan area in Japan as a result of infection occurring on crowded trains.

This article is aimed at estimating the suppressive effectiveness of various interventions on an influenza pandemic through stochastic simulation using an IBM. A population structure in a virtual area containing 100,000 people was examined using an IBM in which every individual is assigned information on age, habitation, household, and social activity group and simulations were carried out stochastically. Sapporo-city, the capital of Hokkaido, in Japan was chosen as the target area, because there are small influxes and outflows to and from this area in comparison with other major cities in Japan (National Census of Japan, 2000). The resident information of the target area was based on the demographic data of Sapporo-city. The epidemiological parameters in the model were assessed using data of past influenza pandemics. The effectiveness of a series of interventions were explored: targeted antiviral prophylaxis (TAP), namely prescribing antiviral drugs for symptomatic patients and persons in close contact with them, school closure, and pre-pandemic vaccination as in the "Pandemic Influenza Preparedness Action Plan" (Ministry of Health, Labour and Welfare, 2007), geographical targeted antiviral prophylaxis (GTAP) by prescribing antiviral drugs for the area where one or more patients has been identified as having H5N1 influenza. The illness attack rate in children was higher than that in adults in past influenza pandemics (Chin *et al.*, 1960), because children have many opportunities to spread the infection in school. Therefore, this model focused on infections among children. The model also analyzed the effectiveness of intervention by school-age targeted antiviral prophylaxis (STAP), in which antiviral drugs were prescribed for school aged children, for the containment of influenza infections.

The simulation results show that pre-pandemic vaccination with a 10% coverage rate decreased the total number of patients to a mean of 55.44% in 100-trials compared with a no-control baseline situation. The probability of containment of influenza by TAP with a 50% coverage rate was estimated at 96%, while that in the no-control baseline was estimated at 25%. Therefore, TAP was able to suppress the outbreak. In terms of the effect of antiviral agent oseltamivir, STAP was superior to TAP with a low coverage rate (30%), because STAP can prevent the spread of infection among school-aged children who have a high attack rate. Moreover, school closure brought about a greater decrease in incidence among children, and also led to a decrease in incidence among adults.

Currently, the Ministry of Health, Labour and Welfare has declared that if one or more infected person with H5N1 influenza is identified in a prefecture, all schools in the prefecture will be closed (Mainichi Newspapers, 2008). This study showed the importance of intervention among children, which contributed to the successful containment of the H5N1 influenza outbreak in the present model.

2. Materials and Methods

2.1. Natural history and transmission parameters

In the past century, influenza pandemics have occurred at least three times around the world; "Spanish flu" (A/H1N1) in 1918, "Asian flu" (A/H2N2) in 1957-1958, and "Hong Kong flu" (A/H3N2) in 1968-1969. Because the natural history of a future influenza pandemic is unknown, observational data was used from these previous pandemics to estimate the values of transmission parameters. The latent and infectious periods were estimated on the basis of "Asian flu" (A/H2N2). New infected people with influenza pass through the latent period for 1.9 days on average and then the infectious period for 4.1 days on average, and thereafter they recover with immunity or die (Elveback *et al.*, 1976). These periods vary among individuals; the probability distributions are shown in Table 1.

Infected individuals were classified into symptomatic cases with typical symptoms and asymptomatic cases that are assumed to have half the infectivity compared with symptomatic cases (Elveback *et al.*, 1976). Based on the result of Bridges *et al.* (2002) for the H5N1 virus, it was assessed that 67% of infected people will become symptomatic and the other 33% will be asymptomatic.

In "Asian flu" (A/H2N2), the illness attack rate was very high for children in comparison with adults (Chin *et al.*, 1960). On the other hand, the illness attack rate for "Hong Kong flu" (A/H3N2) was observed to be approximately the same for all age group (Davis *et al.*,

Table 1. Natural history of influenza. **(A)** Latent period and **(B)** infectious period.

(A)

Latent period (day)	Probability (%)*
1	30%
2	50%
3	20%

(B)

Infectious period (day)	Probability (%)*
3	30%
4	40%
5	20%
6	10%

*Derived from Elveback *et al.* (1976)

Table 2. Illness attack rate for a future influenza pandemic.

	Illness attack rate (%)*
Young children	32%
Older children	46%
Adults	29%
Overall	33%

*Derived from Longini *et al.* (2005)

1970). Although the illness susceptibility profile for a future influenza pandemic is unclear, it was reported in the sporadic transmissions of H5N1 virus from bird to human in Southeast Asia that the susceptibility in children was higher and that the age-specific illness susceptibility was similar to H2N2 virus. Therefore, the present model adopted the estimated illness attack rate of "Asian flu" (Longini *et al.*, 2005) (Table 2).

2.2. Intervention effectiveness

Currently, it is regarded that the administration of antiviral agent oseltamivir has high effectiveness in the treatment and prophylaxis of influenza (Ministry of Health, Labour and Welfare, 2008). For treatment, it is required to take two tablets a day for 5 days, and for prophylaxis to take one tablet a day for 7-10 days (Chugai Pharmaceutical, 2008). It was assumed that each medication course consists of 10 tablets for 5 days of treatment or 10 days of prophylaxis. Oseltamivir takes therapeutic effect by alleviating symptoms, reducing infectiveness, shortening the infectious period, and also a prophylactical effect for prevention of infection. Longini *et al.* (2005) expressed the above effects quantitatively, so their estimated values were adopted in the present model; (1) the attack rate of susceptible persons dosed with antiviral agent prophylactically decreases to 0.30 compared with a susceptible person without dosing (relative susceptibility=0.30); (2) the probability that an infected person dosed with antiviral agent prophylactically will develop the symptoms of influenza decreases to 0.60 compared with an infected person without dosing; (3) the infectiveness of an infected person dosed with antiviral agent prophylactically or therapeutically decreases to 0.62 compared with an infected person without dosing (relative infectiousness=0.62); (4) the infectious period in an infected person dosed with antiviral agent prophylactically or therapeutically reduces to 1 day compared with an infected person without dosing. It was assumed that antiviral efficacy lasts during the course, but that there remains no residual effect thereafter.

Vaccination is an important intervention method for an influenza pandemic (Ministry of Health, Labour and Welfare, 2008). There are two kinds of vaccines; pre-pandemic vaccine that will be manufactured on the basis of virus isolated in bird-to-bird transmission or bird-to-human transmission, and pandemic vaccine, which will be manufactured on the basis of virus isolated in human-to-human transmission. Generally, pandemic vaccine seems to show higher efficacy than pre-pandemic vaccine. However, pandemic vaccine cannot be manufactured until human-to-human transmission actually occurs, and it requires a long time to manufacture pandemic vaccines. Therefore, it is not suitable to deal with pandemic vaccine in a short-term simulation. This model focused on pre-pandemic vaccination that will be performed before an outbreak. However it will take 2 weeks to boost immunity level using pre-pandemic vaccine, and the effect of pre-pandemic vaccination is maintained for 3-6 months after inoculation (Matsumiya *et al.*, 2006). It was estimated that the attack rate of susceptible vaccinated people decreases to 0.30 compared with susceptible people without vaccination (relative susceptibility=0.30), and the infectiveness of an infected person with vaccination decreases to 0.50 compared with an infected person without vaccination (relative infectiousness=0.50) (Longini *et al.*, 2005).

2.3. Control strategies

The effectiveness of three kinds of interventions for an influenza epidemic was explored: antiviral agent oseltamivir, school closure, and pre-pandemic vaccina-

tion, and for oseltamivir treatment, three medication methods were examined: Targeted Antiviral Prophylaxis (TAP), Geographical Targeted Antiviral Prophylaxis (GTAP), and School-age Targeted Antiviral Prophylaxis (STAP).

2.3.1. Targeted Antiviral Prophylaxis (TAP)

In the TAP intervention, symptomatic patients and persons in close contact with them are treated with antiviral drugs, in accordance with the "Pandemic Influenza Preparedness Action Plan" (Ministry of Health, Labour and Welfare, 2007). Symptomatic patients begin to be treated with antiviral drugs just after diagnosis of influenza. A person belonging to the same social activity group as a symptomatic patient is traced. When he/she is identified as a close contact, he/she is treated with antiviral drugs (Germann *et al.*, 2006). It was assumed that all members of his/her household were identified and treated, persons in the same social activity group were treated with antiviral drugs within two days after identification of the close contact, but no members in the casual contact group could be traced. The advantage of TAP intervention is the use of fewer doses of antiviral drugs because of their distribution only among persons in contact with infected patients.

2.3.2. Geographical Targeted Antiviral Prophylaxis (GTAP)

In the GTAP intervention, when symptomatic patients with influenza occur in an area beyond a certain level for the initiation of GTAP, antiviral drugs are distributed throughout the area (Longini *et al.*, 2005). The advantage of GTAP intervention is that many people can be treated at once. However, this approach needs a large supply of antiviral agents. The present model adopted 10 symptomatic patients in area as the criterion for the initiation of GTAP.

2.3.3. School-age Targeted Antiviral Prophylaxis (STAP)

When more symptomatic patients with influenza occur in a school than a set criterion, STAP is initiated and antiviral drugs are distributed at the school to prevent school-aged children, who have high attack rate from becoming infected. In the model, it was assumed that when one child in a school is diagnosed with influenza, STAP will be performed.

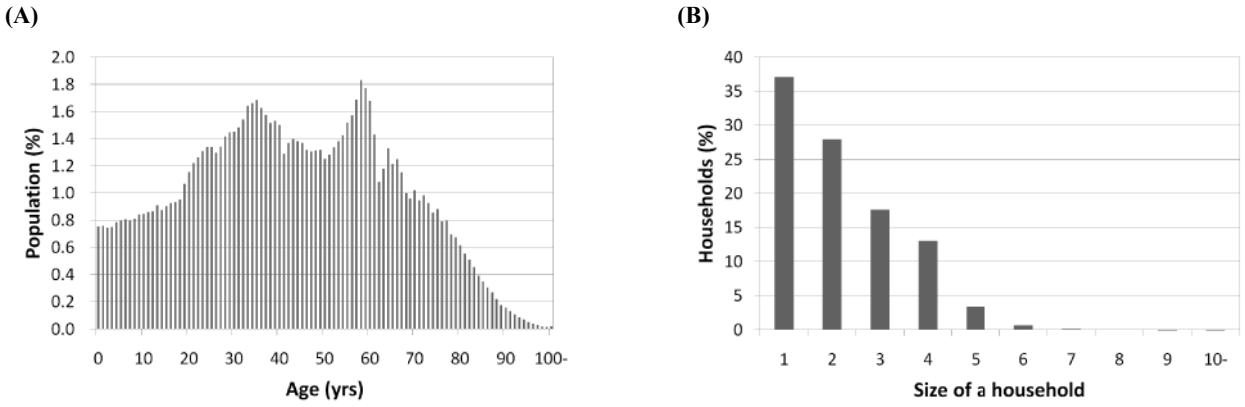

Fig. 1. Population structure. **(A)** Age distribution and **(B)** structure of households.

Table 3. Household, social activity groups and casual contact group.

Group		Household	Playgroup	Elementary school	High school	College	Workgroup	Casual contact group
Age (yrs)	3-6	○	○					○
	7-12	○		○				○
	13-18	○			○			○
	19-22	○				○		○
	22-70	○					○	○
	Other	○						○
Group size		1-10	5	35	40	20	20	20
No. of groups		61,021	622	148	144	373	2,688	4,686

2.3.4. School closure

School closure as performed in the model when more symptomatic patients with influenza occur in a school than a set criterion in accordance with the "Pandemic Influenza Preparedness Action Plan" (Ministry of Health, Labour and Welfare, 2007). In the model, it was assumed that when one child in a school is diagnosed with influenza, school closure will be performed.

2.3.5. Pre-pandemic vaccination

Pre-pandemic vaccination is assumed to be performed before the outbreak of the epidemic. This model simulated the situation that the inoculation is performed one month before an index patient is diagnosed with influenza (H5N1) in a virtual area.

2.4. Population structure

In order to generate a more realistic situation, the population structure in a virtual area was built heterogeneously using IBM, in which every individual is given information on their age, habitation, household and social activity group. Sapporo-city, Hokkaido was chosen as the target area, because there is limited influx and outflow to and from the areas in comparison with other cities (National Census of Japan, 2000). The demographic data of Sapporo-city was used. It was assumed that the target area has a population of 100,000 and is divided into 10 administrative districts as in Sapporo-city. The population density for every administrative district was assessed in proportion to the demographic data of Sapporo-city. The traffic densities among the administrative districts were set on the basis of the National Census of Japan (2000).

The age structure in the target area was determined from Resident Registrations (2008), which are shown in Fig. 1(A). It was assumed that a single-person household consists of an adult aged 19 and over, and that two or more persons in a household consist of at least an adult aged 19 and over. The distribution of household sizes is shown in Fig. 1(B) on the basis of the National Census of Japan (2005).

Social activity groups, such as playgroup, elementary school, high school, college, and work group, were set. An individual may belong to such a group according to age. Casual contact groups, such as markets, trains, neighborhoods and other places where people mix and make untraceable contacts, were also set. It was assumed that casual contact groups change members every day unlike social activity groups. The sizes of the social activity groups, such as schools, colleges, and workgroups were set so as these individuals make contacts of sufficient duration or closeness and can transmit influenza virus at that location. Moreover, the enrollment age at college and the employment rate per age group were set on the basis of the Employment Status Survey (2002). The list of the groups corresponding to each age, their group size, and their numbers are shown in Table 3.

Table 4. Daily contact rates for household, social activity groups and casual contact group.

Group	Contact rate*
Household (child to child)	0.6
Household (child to adult)	0.3
Household (adult to child)	0.3
Household (adult to adult)	0.4
Playgroup	0.25
Elementary school	0.0435
High school	0.0375
College	0.0315
Workgroup	0.0575
Casual contact group (0-4 years)	0.0000181
Casual contact group (5-18 years)	0.0000544
Casual contact group (19-64 years)	0.000145
Casual contact group (65 years-)	0.0002175

*Derived from Germann *et al.* (2006)

An individual was assumed to mix randomly in a group. In the model, use contact rates per day for households, social activity groups and casual contact groups, which had a probability of sufficient contact to transmit influenza (Germann *et al.*, 2006) (Table 4). It was noted that the contact rate in a household is higher than the other contact types, and that the contact rate in casual contact groups is quite low.

3. Results

Simulations were carried out for scenarios for execution of control interventions. It was assumed in every scenario that an initial child patient with symptom was introduced into Chuo-ward, which is located in the center of Sapporo-city. For every scenario, 100-trial simulations were carried out over 360 days. The effective reproductive number (R_t) was calculated following the formula of Germann *et al.* (2006). It was considered that an epidemic was successfully contained if the total number of

patients (the epidemic size) fell below 1,000, which is proportionate to 0.1% of the total population.

3.1. Baseline scenario

The baseline scenario (scenario 0) stands for the situation with no-intervention. Fig. 2 shows the profile of the number of patients (A), the number of patients by age and age-specific incidence (B), and the profile of the effective reproductive number (C). The number of patients reached a peak at about 100 days after introduction of the initial patient, thereafter the number decreased gradually and the epidemic was eradicated after about 7 months (Fig. 2(A)). Children (7-18 years) had the highest illness attack rate (Fig. 2(B)), and the effective reproductive number (R_t) for 30 days after introduction of initial patient was estimated at 1.5 (Fig. 2(C)).

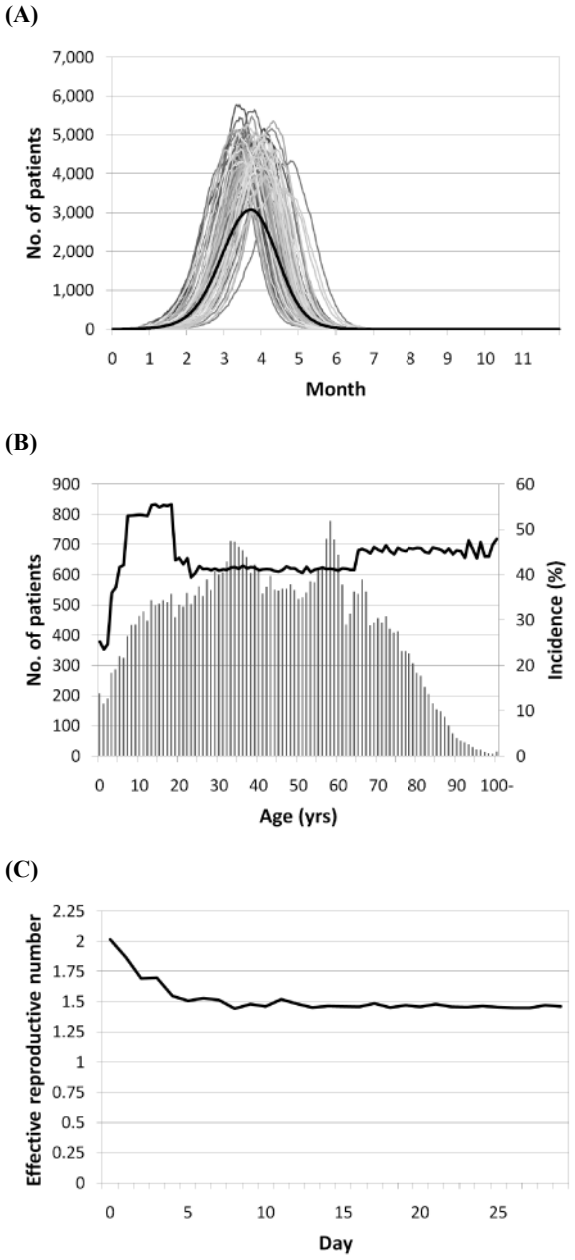

Fig. 2. Baseline scenario. **(A)** Profile of the number of patients in 100 trials (grey lines) and their average number (black line), **(B)** the number of patients by age and age-specific incidence, and **(C)** changes in the effective reproductive number.

3.2. Intervention scenarios

Twelve scenarios involving interventions were examined: medication of antiviral agent by TAP, GTAP, or STAP, school closure, and inoculation of pre-pandemic vaccine (Table 5). In TAP intervention, two rates of tracing of persons in contact with a patient in the same group, except for the same household (30%, 50%), were investigated. In GTAP and STAP, three kinds of coverage rate (30%, 50%, and 80%) were investigated. In the pre-pandemic vaccination strategy, two kinds of coverage rate (10%, 30%, and 50%) were investigated.

The mean epidemic size, mean epidemic period, mean amount of antiviral agent oseltamivir, and probability of containment in all scenarios (scenarios 0-9) are shown in Table 6. Figs. 3-6 show the profiles of the number of patients and the age-specific incidence in scenarios 1-2 (Fig. 3), scenarios 3-5 (Fig. 4), scenarios 6-8 (Fig. 5), and scenario 9 (Fig. 6), respectively.

Fig. 7 shows the profiles of the number of patients and total patients with pre-pandemic vaccination for 90 days after the introduction of an initial patient in scenarios 10-12, because the effect of pre-pandemic vaccination lasts for only 3-6 months.

4. Discussion

In this model, the population structure was described in a virtual area containing 100,000 people, which was based on the demographic data of Sapporo-city, and simulations were carried out using an IBM. Sapporo-city, the capital of Hokkaido in Japan, is suitable for simulating the spread of infection, because there are small influxes and outflows to and from the areas in comparison with other major Japanese cities (National Census of Japan, 2000). Moreover, IBM is able to give every person individual age-dependent behavior pattern, which lead to a more realistic situation.

Illness attack rate was assessed by comparison with past influenza pandemics. Infected individuals are classified into symptomatic cases with typical symptoms and

Table 5. Scenarios.

Scenario	Intervention	Coverage
1	TAP	30%
2	TAP	50%
3	GTAP	30%
4	GTAP	50%
5	GTAP	80%
6	STAP	30%
7	STAP	50%
8	STAP	80%
9	School closure	—
10	Pre-pandemic vaccination	10%
11	Pre- pandemic vaccination	30%
12	Pre- pandemic vaccination	50%

asymptomatic cases (Elveback *et al.*, 1976). It was estimated that 67% of infected people will develop symptoms for the H5N1 virus (Bridges *et al.*, 2002). Although this proportion has been observed on bird-to-human transmission of H5N1 virus, not on human-to-human transmission, this proportion was used in the model, as is impossible to determine the actual proportion before an influenza pandemic occurs. It was defined that the intervention could contain an epidemic successfully if the total number of patients fell below 1,000, which corresponded to 0.1% of the total population.

Firstly, the no-control baseline scenario (scenario 0) was investigated (Fig. 2). In the baseline scenario, it was shown that 75% of 100-trials could eradicate an outbreak over time and the other 25% could stamp out the outbreak immediately without spreading infection. The incidence in school-aged children (7-18 years) went up to 55%, while the incidence in adults (19 years-) could remain at 40% (Fig. 2(B)). These results come from the high illness attack rate of children and the high contact rate in school. In the beginning of the outbreak, the effective reproductive number (R_t) is estimated at 2.0, thereafter it decreased gradually to 1.5 after about 10 days (Fig. 2(C)).

Secondly, the effectiveness of TAP with two levels of tracing rate (30%, 50%) (scenarios 1-2) was investigated (Fig. 3). TAP could decrease the epidemic size to a mean of 35.24% (scenario 1) and 0.60% (scenario 2) compared with the baseline scenario. The probabilities of containment in scenarios 1 and 2 were estimated at 59% and 96%, respectively, while that in the baseline scenario was estimated at 25% (Table 6), which indicated the high effectiveness of TAP. Scenario 1 (50% tracing rate) could save the amount of oseltamivir doses needed by 4.60% as much as the mean in scenario 2 (30% tracing rate). This saving in high coverage TAP is due to the attainment of containment of the infection at an early stage of the outbreak. However, because it is very hard to trace people who have close contact with symptomatic patients, it is difficult for TAP to gain a high rate of tracing.

Thirdly, the effectiveness of GTAP with three kinds of the coverage rates (30%, 50%, and 80%) (scenarios 3-5) was investigated (Fig. 4). The profiles of the number of patients showed that GTAP could cause a delay in reaching the peak of the outbreak and reduced the number of patients at the peak (Fig. 4(A)). However, the mean epidemic size in scenarios 5 and 6 could only slightly decrease the number of patients to 94.15% and 92.91% compared with the baseline scenario (Table 6).

Table 6. Result of simulations for scenarios.

Scenario	Mean epidemic size	Mean epidemic period (days)	Mean amount of antiviral agent (doses)	Probability of containment
0 (Baseline)	43042.19	155.46	0.0	25%
1	15167.66	153.11	123446.7	59%
2	258.50	34.36	5681.2	96%
3	43476.12	167.42	227671.7	24%
4	40524.47	169.27	354709.4	29%
5	39991.62	187.60	581193.8	30%
6	29778.30	114.65	17374.2	48%
7	24627.19	97.69	24550.6	57%
8	13758.17	57.14	20361.2	76%
9	14834.49	80.74	0.0	70%

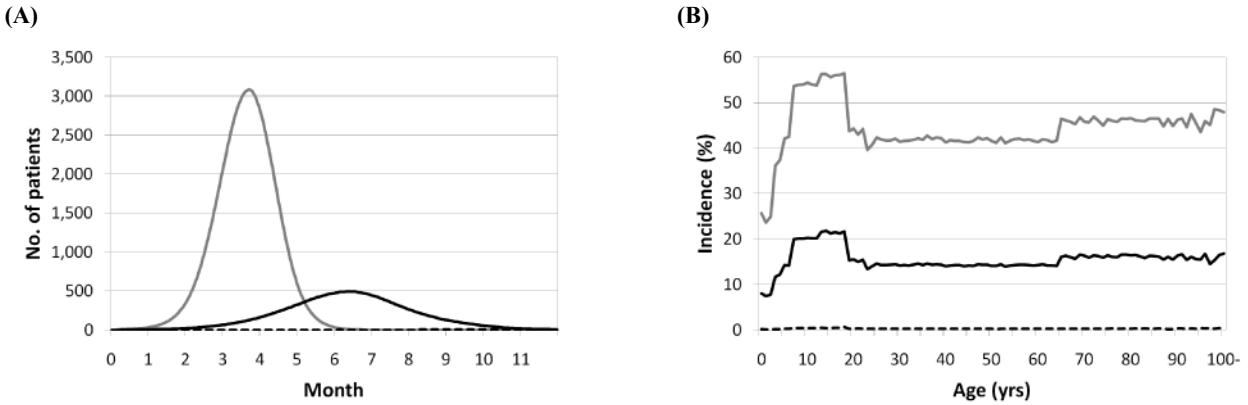

Fig. 3. Results for scenarios 0-2. Grey and black solid lines and dashed line show the situations in baseline, TAP for coverage rates of 30%, 50%, respectively. **(A)** Changes in the number of patients and **(B)** age-specific incidence.

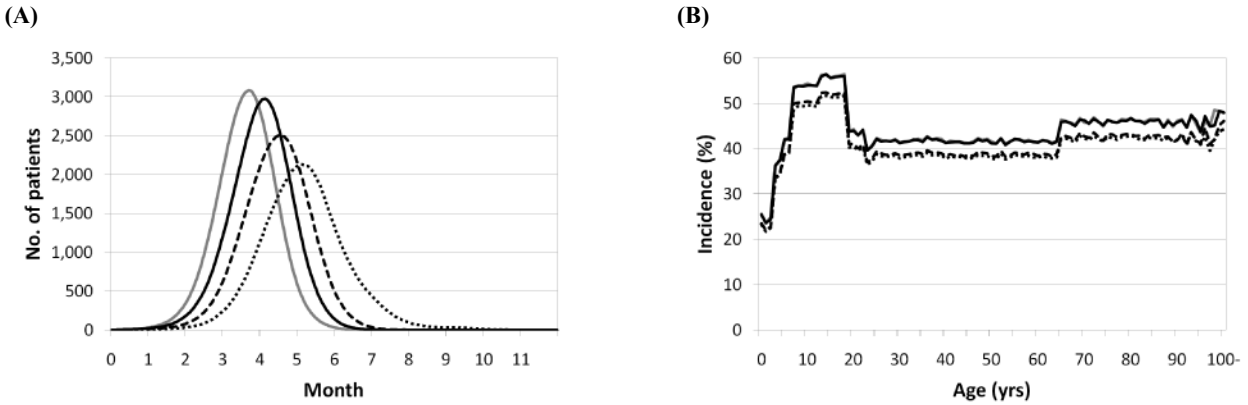

Fig. 4. Results for scenario 0 and scenarios 3-5. Grey and black solid lines and dashed and dotted lines show the situations at baseline and GTAP for coverage rates of 30%, 50%, and 80%, respectively. **(A)** Changes in the number of patients and **(B)** age-specific incidence.

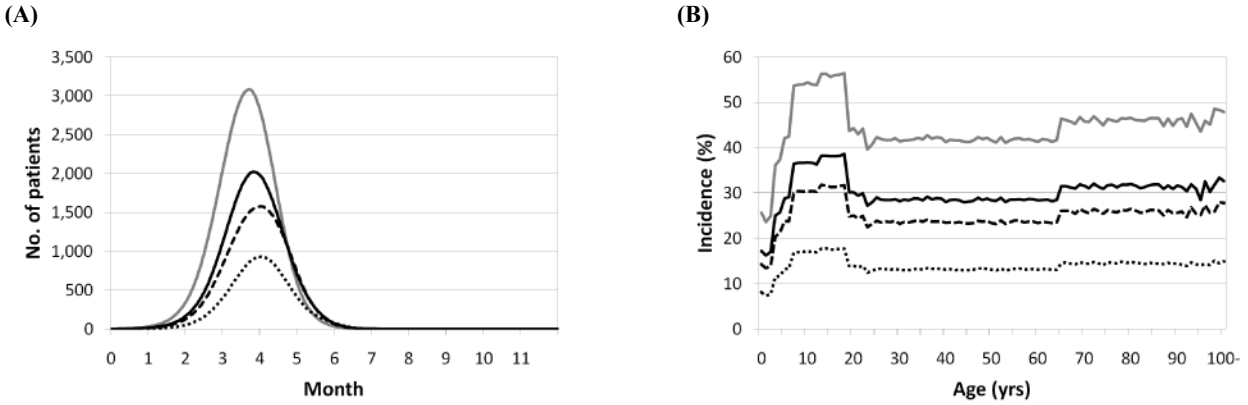

Fig. 5. Results for scenario 0 and scenarios 6-8. Grey and black solid lines and dashed and dotted lines show the situations at baseline and STAP for coverage rates of 30%, 50%, and 80%, respectively. **(A)** Changes in the number of patients and **(B)** age-specific incidence.

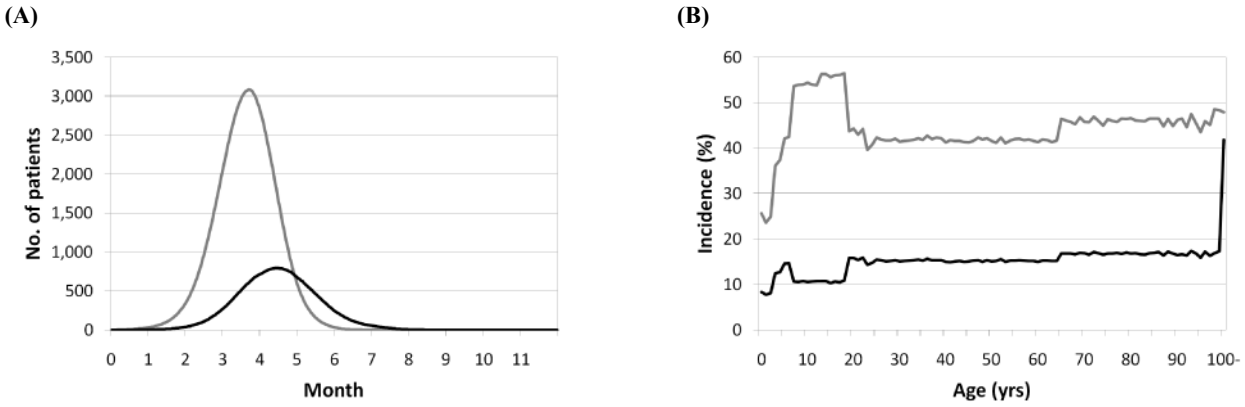

Fig. 6. Results for scenario 0 and scenario 9. Grey and black lines show the situations at baseline and after school closure. **(A)** Changes in the number of patients and **(B)** age-specific incidence.

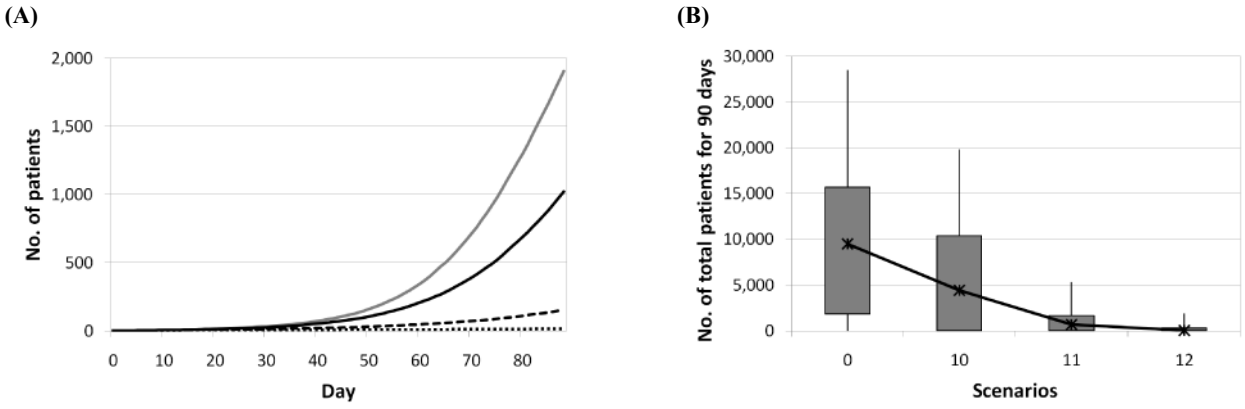

Fig. 7. Results for scenario 0 and scenarios 10-12. **(A)** Changes in the number of patients. Grey and black solid lines and dashed and dotted lines show the situations at baseline and pre-pandemic vaccination for coverage rates of 10%, 30%, and 50%, respectively. **(B)** The distribution of the total number of patients for 90 days in 100 trials. The lines, boxes, and the marks show the range between minimum and maximum, lower-upper quartile, and the median in scenarios.

GTAP had little effect in spite of spreading plenty of antiviral agents, because the influenza infection spread by the movement of inhabitants among several districts before GTAP has been performed. To improve GTAP intervention, it is necessary to begin GTAP as soon as a symptomatic patient can be identified.

Fourthly, the effectiveness of STAP with three kinds of the coverage rates (30%, 50%, and 80%) (scenarios 6-8) was investigated (Fig. 5). In spite of intervention with only children, STAP could decrease the incidence for all age groups (Fig. 5(B)) and the mean epidemic size was limited to 69.18% (scenario 6), 57.22% (scenario 7), and 31.96% (scenario 8) compared with the baseline scenario (Table 6). The ripple effect of the administration of oseltamivir in STAP on the reduction of the number of patients was estimated as 7.63-fold (scenario 6) and 7.50-fold (scenario 7), while that in TAP with low coverage (scenario 1) was 2.26-fold. From this point of view, STAP may be superior to low coverage TAP (30%).

Fifthly, the effectiveness of school closure (scenario 9) was investigated (Fig. 6). The probability of containment in scenario 9 was estimated as 70% (Table 6). The incidence in children under school closure was assessed as 10%, which was lower than in other age groups, but noting that incidence could ascend to 55% of the baseline (Fig. 6(B)). School closure, which can also decrease the incidence among adults, could prevent or slow down the spread of infection.

Finally, the effectiveness of pre-pandemic vaccination with three kinds of the coverage rates (10%, 30%, and 50%) (scenarios 10-12) was investigated (Fig. 7). The total number of patients during 90 days after the beginning of the outbreak showed mean decreases to 55.44% (scenario 10), 10.53% (scenario 11), and 2.19% (scenario

12) compared with the baseline scenario. Pre-pandemic vaccination was introduced at an early stage of an outbreak to prevent infection. Because the effect of pre-pandemic vaccination lasts for only 3-6 months, an outbreak cannot be suppressed by only one vaccination. Therefore, it is necessary to take other measures, such as additional inoculation with pre-pandemic or pandemic vaccine, administration of antiviral agent, and school closure.

The simulation results showed that TAP, as recommended by the "Pandemic Influenza Preparedness Action Plan" (Ministry of Health, Labour and Welfare, 2007) could suppress the outbreak. The fact that STAP (scenarios 6-8) and school closure (scenario 9) bring about a decrease in incidence among not only children but also adults suggested the importance of intervention among children. This study will contribute to intervention strategies against a future influenza pandemic in Japan.

The basic reproductive number (R_0) in past pandemics was estimated in various studies; Mills *et al*. (2004) estimated R_0 as 1.5-3.5 for "Spanish flu" (A/H1N1) in 1918, Longini *et al.* (2004) estimated R_0 as 1.68 for "Asian flu" (A/H2N2) in 1957-1958. The present study estimated the effective reproductive number (R_t) as 1.5 in the baseline scenario (Fig. 2(C)). However, in the crowded urban environment of Japan, higher risks of infection in crowed trains, theaters, shopping malls and so on will accelerate the spread of infection (Ohkusa *et al.*, 2007). Further studies on intervention against an influenza pandemic with a high effective reproductive number will be needed.

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