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Mathematical Modeling of Severe Acute Respiratory Syndrome Nosocomial Transmission in Japan: The Dynamics of Incident Cases and Prevalent Cases

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***Abstract*: An outbreak of Severe Acute Respiratory Syndrome (SARS) occurred in Hong Kong in late February 2003, resulting in 8,096 cumulative cases with 774 deaths. The outbreak was amplified by nosocomial transmission in many hospitals. Using mathematical modeling, we simulated the number of new incident and prevalent cases of SARS after one infected person was admitted to a hospital (index case). The simulation was tested stochastically using the SEIR model based on previously reported Gamma distributions. We estimated the duration time until 10 beds in negative pressure rooms in Chiyoda-ku, one of the 23 wards in Tokyo, were fully occupied with SARS-infected patients. We determined the impact of an increasing number of days on the number of prevalent cases until the index case was isolated. The prevalent cases increase exponentially along with the increase of the non-isolation period of the index case, and all the beds were fully occupied if the index case was not isolated until more than 6 days. However even 2 days non-isolation period of the index case could fill up all the beds when 16% of secondary infections are transmitted outside the hospital. There is a possibility that an epidemic will occur with the isolation of the index case even at early days if the infection is transmitted outside the hospital. The simulation results revealed that it was important to recognize and isolate SARS patients as early as possible and also to prevent the transmission spreading outside the hospital to control an epidemic.**

***Key words*: SARS, Nosocomial transmission, Stochastic model, Simulation**

We had a worldwide outbreak of Severe Acute Respiratory Syndrome (SARS) that was initiated in Hong Kong in late February 2003 (2). This outbreak affected 27 countries resulting in 8,096 cumulative cases with 774 deaths. Although the causative agent of SARS had been unknown during the initial outbreak, SARS-associated coronavirus (SARS-CoV) was identified as the pathogen (6, 7, 10). Although SARS-infected patients transmitted the disease to approximately three persons on average, nosocomial transmission possibly contributed to a rapid increase in the number of infected people (9, 20). Super spreaders (SSs) are defined as patients who produce more than 10 secondary infections (3). SSs represent a variety of patients with different environmental, genetic and pathogenic influences. The super spreader events (SSEs) are probably caused by either brief contact with highly infectious patients or close contact with moderately infectious patients. SSEs occurred frequently in hospitals with close contact. In fact, medical staff comprised approximately 20% of all reported cases of SARS infection (21).

Especially during first phase of SARS outbreak, it was difficult to diagnose the SARS outbreak because of the similarity of clinical symptoms among SARS and other known diseases such as influenza; thus the medical staff was vulnerable (4). This characteristic of SARS hindered control of the infection. As a result, an explosive increase of SARS patients including medical staff,

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Abbreviations: SARS, severe acute respiratory syndrome; SARS-CoV, SARS-associated coronavirus; SS, super spreader; SSE, super spread event; WHO, World Health Organization.

inpatients and visitors eventually made hospitals close (11, 14).

Several mathematical models of SARS have estimated the number of infected inpatients. Riley et al. estimated the number of most recently infected persons in Hong Kong, focusing on the importance of controlling nosocomial transmission of SARS (15). Webb et al. developed a compartment mathematical model to address the role of hospitals in transmission of the SARS epidemic in Canada (19).

In this study, we estimated the influence of the delay in the preventive measures against SARS in a hospital on the incident and prevalent cases caused by one infected patient, because the delay led to an increase SARS-prevalent cases (8). Therein, an incident case and a prevalent case mean those who newly contract the disease and those who have already got the illness, respectively. We used a stochastic model to simulate SARS nosocomial transmission, because a stochastic model can predict both an average trend and a variation of prevalence. In addition to the transmission in a hospital, we examined the situation in which the SARS spreads outside the hospital through visitors and healthcare workers who are infected in a hospital. In fact, patients who were infected with SARS at Tan Tock Seng Hospital brought the disease into Singapore General Hospital in Singapore (8). Moreover, we estimated the size of the SARS epidemic to estimate the period in which the negative pressure rooms will be filled, when a single SS is admitted to a hospital in Chiyoda-ku, one of the 23 wards in Tokyo, Japan, with the detailed epidemiological data from Hong Kong reported by Donnelly et al. and Leung et al. (5, 12).

Thus, nosocomial transmission may also contribute to disease spread when medical staff and visitors make close contact with SARS-infected patients. Our model is inferred to be helpful for the design of SARS control strategies.

Materials and Methods

Hospital-derived transmission model. This article describes the nosocomial transmission dynamics when a single SARS-infected person is admitted to a hospital. In the model, the process of transmission is simulated stochastically. The susceptible population is divided into two groups: (1) individuals that work in the hospital or are resident patients (*Nq*) and (2) people living and working outside the hospital (*No*). We chose the epidemiological data from the 2003 SARS epidemic in Hong Kong reported by Donnelly et al. and Leung et al. (5, 12) because the daytime population density and the area of Chiyoda-ku, one of the 23 wards in Tokyo (73,000 people/km^2(2000)) (17), are similar to those of the most affected region of SARS in Hong Kong (Kwun Tong: 51,000 people/km^2(2001)).

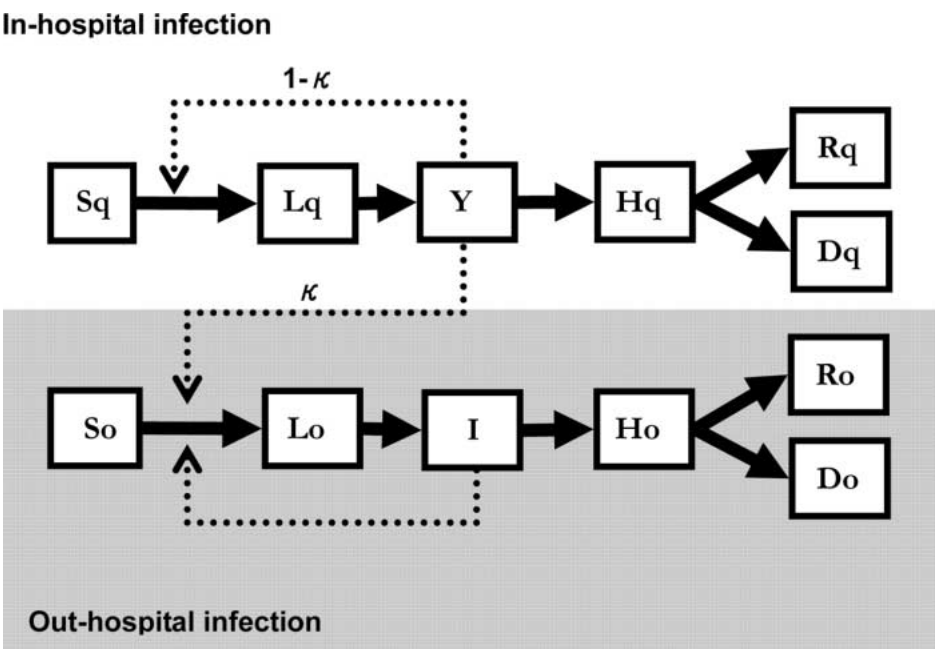

Fig. 1. Hospital-derived transmission model. Schematic flow diagram of the hospital-derived transmission model used in this study. The parent population was divided into two groups: (1) inpatients and people who work in the hospital (*Nq*) and (2) people outside the hospital (*No*). We designate SARS transmission in the former "In-hospital infection" and in the later "Out-hospital infection."

In the nosocomial transmission model, *Nq* denotes all individuals affected by infection in a hospital, including inpatients, medical staff and all the people who spend a significant amount of time in the hospital. *Nq* is segregated into six categories according to the SEIR model (1). *Sq* defines a fully susceptible population. When an individual of *Sq* becomes infected, he/she enters a latent category (*Lq*) that is composed of infected, asymptomatic individuals. During the outbreak, frequently unprotected or inadequately protected patient-to-health-care worker contacts and grouping large numbers of ill persons greatly amplifies the chance of infection in a hospital (8, 18, 20). The patients who are not isolated transmit the infection and produce new patients. *Y* denotes the category of infectious and symptomatic patients who are not isolated, and *Hq* denotes the category of isolated patients. The categories *Rq* and *Dq* identify recovered and dead individuals, respectively. In the early phase of the epidemic, the transmission occurs within hospitals. In the late phase, we assume that hospitals have identified the SARS epidemic, isolated infected patients, and implemented infection control. During this late phase at *p* days after admission of the first infected person (the index case), *Lq* individuals pass category *Y* and move directly into category *Hq*. Therefore, this model assumes that the first hospitalized SARS patients are left unisolated until infection control starts at *p* days. Figure 1 shows the scheme of the model (Fig. 1: In-hospital infection).

In the transmission outside hospitals, the population (*No*) is also segregated into six categories; *So* and *Lo* denote susceptible and latent categories, respectively. *Lo* individuals progress to category *I*, which includes symptomatic and infectious patients who are not yet hospitalized, followed by progression to category *Ho*, that includes patients who are hospitalized and completely isolated. *Ro* and *Do* denote the recovered and the dead categories, respectively. Figure 1 diagrams the transmission outside hospitals (Fig. 1: Out-hospital infection).

In In-hospital infection, *Y* individuals transmit SARS to susceptible individuals of both *Sq* and *So*. In Out-hospital infection, *I* individuals transmit SARS to susceptible individuals of *So*, but not *Sq* because of the simplicity of the model.

We refer to a coalescence model of both "In-hospital infection" and "Out-hospital infection" as "hospital-derived transmission model."

Control model. We introduce the control model to compare the dynamics of SARS transmission among the general public outside a hospital with that of the hospital-derived transmission model. We segregate the total population (*No*) into susceptible (*So*), latently infected (*Lo*), infectious (*I*), hospitalized (*Ho*), recovered (*Ro*), and dead individuals (*Do*) as described in Out-hospital infection in the hospital-derived transmission model (Fig. 1: Out-hospital infection). In the control model, we assume the following: one infected person (the control index case) transmits the SARS to the general public outside the hospitals; there are no SSs, and no In-hospital infection occurs.

For both the hospital-derived transmission model and the control model, we assume that only the index case or the control index case is infected with SARS and that there are no other SARS carriers (*Lq*, *Lo*) in the population (*Nq*, *No*) in the beginning.

Stochastic model. We base our analysis on a stochastic model. Generally, stochastic models predict both average trends and variations of the calculated results of a designated model, so we can estimate changes caused by chance and changes reflecting the impact of the dynamics each day. A stochastic model is useful for a small population. Our stochastic model proceeded day by day with infection events and transition among infectious stages; the number of secondary infections and the transition among infectious stages are governed by Poisson distribution and Gamma distribution, respectively. These parameters are described below. We carried out 60,000 time simulation trials to calculate the averages and quartile points. The model was programmed using Microsoft Visual Studio.NET 2002 (Microsoft Corporation, Redmond, Wash., U.S.A.). All data from the simulation were analyzed using Microsoft Excel 2003 (Microsoft Corporation).

Underlined deterministic model. To explain our stochastic model clearly, we introduce the underlined deterministic model, which is formulated by a system of differential equations. Generally, a deterministic model is adaptable for a large population. The average results of many trials in the stochastic model tend toward the result in its underlined deterministic model when stochastic simulation trials increase in number. The underlined deterministic model of our hospital-derived transmission model uses the following nonlinear system of differential equations (1).

$$\frac{dSq(t)}{dt} = -(1-\kappa)\cdot Rin\_d \cdot Y(t)\cdot \frac{Sq(t)}{Nq}$$

$$\frac{dLq(t)}{dt} = (1-\kappa)\cdot Rin\_d \cdot Y(t)\cdot \frac{Sq(t)}{Nq} - \frac{Lq(t)}{tLq}$$

$$\frac{dY(t)}{dt} = \frac{Lq(t)}{tLq} - \frac{Y(t)}{tYo(t)}$$

$$\frac{dHq(t)}{dt} = \frac{Y(t)}{tYo(t)} - \left[(1-\sigma)\frac{Hq(t)}{tHq\_R} + \sigma\cdot\frac{Hq(t)}{tHq\_D}\right]$$

$$
\begin{aligned}
\frac{dRq(t)}{dt} &= (1-\sigma)\cdot\frac{Hq(t)}{tHq\_R}\\
\frac{dDq(t)}{dt} &= \sigma\cdot\frac{Hq(t)}{tHq\_D}\\
\frac{dSo(t)}{dt} &= -Rout\_d\cdot I(t)\cdot\frac{So(t)}{No}-\kappa\cdot Rin\_d\cdot Y(t)\cdot\frac{Sq(t)}{Nq}\\
\frac{dLo(t)}{dt} &= Rout\_d\cdot I(t)\cdot\frac{So(t)}{No}+\kappa\cdot Rin\_d\cdot Y(t)\cdot\frac{Sq(t)}{Nq}-\frac{Lo(t)}{tLo}\\
\frac{dI(t)}{dt} &= \frac{Lo(t)}{tLo}-\frac{I(t)}{tI}\\
\frac{dHo(t)}{dt} &= \frac{I(t)}{tI}-\left((1-\sigma)\frac{Ho(t)}{tHo\_R}+\sigma\cdot\frac{Ho(t)}{tHo\_D}\right)\\
\frac{dRo(t)}{dt} &= (1-\sigma)\cdot\frac{Ho(t)}{tHo\_R}\\
\frac{dDo(t)}{dt} &= \sigma\cdot\frac{Ho(t)}{tHo\_D}
\end{aligned}
\qquad (1)
$$

Estimation of parameter values. To establish the stochastic model for nosocomial transmission, we defined the means and variances of several epidemiological parameters. For the In-hospital infection model, we defined four periods of time: infection to onset (*tLq*), onset to discharge (*tHq_R*), onset to death (*tHq_D*) and the period of hospitalization without isolation (*tYo*). *tYo* is determined by $p-t$ ($t \leqq p$) where t and p are the days post admission of the index case and time when isolation started, respectively. We also define four periods for the Out-hospital infection model: infection to onset (*tLo*), onset to admission (*tI*), admission to discharge (*tHo_R*) and admission to death (*tHo_D*). The same symbols are also used in the control model. These parameters except for *tYo* are treated as probability parameters according to Gamma distributions as described previously (5, 12). The sets of means and variances for these parameters were respectively estimated to be 4.6 days and 15.9 days^2 for *tLq* and *tLo*, 23.5 days and 62.1 days^2 for *tHo_R*, 35.9 days and 572.9 days^2 for *tHo_D*. The means and variance for the period from onset to admission (*tI*) changes with the amount of time (t) since the index case was admitted: 4.85 days and 12.19 days^2 ($0 \leq t \leq 28$), 3.83 days and 5.99 days^2 ($29 \leq t \leq 35$), 3.67 days and 10.71 days^2 ($36 \leq t$) (Fig. 2). *tHq_R*, *tHq_D* denote the cumulative days of *tI* and *tHo_R*, *tI* and *tHo_D*, respectively. The symbol σ represents the mortality rate caused by SARS which was estimated at 0.1 based on the data from World Health Organization (21). The parameter κ represents the rate of newly infected patients who are outside the hospital divided by the total secondary cases occurring in the hospital. These patients mediate SARS transmission from inside to outside the hospital.

Each parameter value (*tLq*, *tLo*, *tI*, *tHo_R*, *tHo_D*) was chosen stochastically on the basis of Gamma distribution with the above-mentioned mean and variance by a random number obtained from the pseudo random number generating routine in Microsoft Visual Studio.NET 2002.

Reproductive number. Hospital-derived transmission model: Basic reproductive number is defined as the average number of secondary cases generated by one primary case in susceptible individuals (16). In this model, we defined the basic reproductive number for

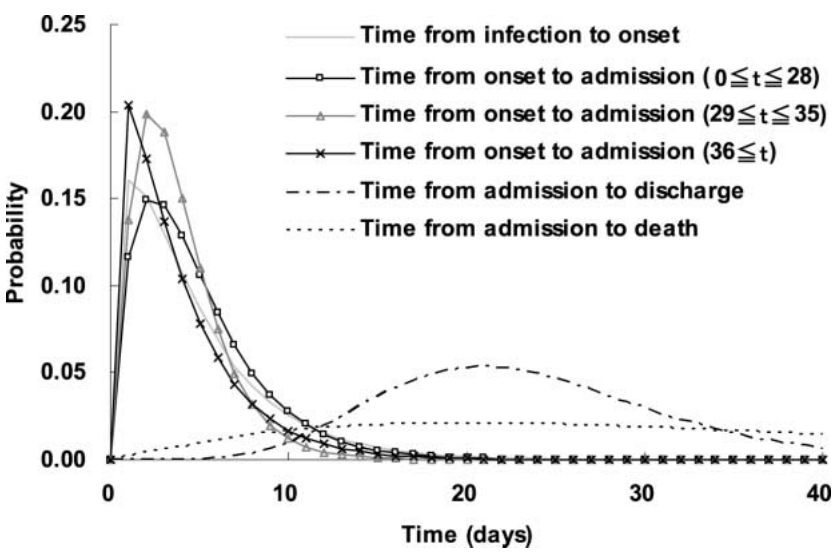

Fig. 2. Gamma distributions applied to this model. The graphs of probability density function for the distribution for the following periods: infection to onset (straight line), onset to admission ($0 \leq t \leq 28$) (straight line with square), onset to admission ($29 \leq t \leq 35$) (straight line with triangle), onset to admission ($36 \leq t$) (straight line with cross), admission to discharge (dashed line) and admission to death (dotted line).

In-hospital infection during p days of patient hospitalization without isolation as *Rin*. Thus, the average number of secondary patients per day caused by one primary case is obtained from *Rin/p*, which is represented by *Rin_d*, called "a daily secondary patients number." Before infection control, we fixed $Rin\_d=2$ as reported in previous reports (8) and the numbers of secondary infections were calculated stochastically from Poisson distribution.

Control model: We designate the reproductive number for the control model as *Rout*. SARS-infected patients transmit the disease to susceptible people from their infection onset to hospital admission (tI). Therefore, the number of daily secondary patients is given by $Rout\_d=Rout/tI$. *Rout* is estimated as 3 ($0\leq t\leq 30$), 1 ($31\leq t\leq 51$), and 0.15 ($51\leq t$) (15). In this model, the numbers of secondary patients are also calculated stochastically from Poisson distribution.

Results

We carried out stochastic simulations with 60,000 trials for the situation of SARS patients increasing inside a hospital and spreading outside a hospital. We gave the means of the incident and prevalent cases in simulations as the gravity in 60,000 trial data, and also the range among the first-third quartile points because it is unknown what kind of distribution the trial data that have asymmetry would follow.

The Effects of the Non-Isolation Period of SARS-Infected Patients on Hospital Transmission

The non-isolation period of SARS-infected patients (p) will affect In-hospital infection. Therefore, we investigated the dynamics of the number of incident and prevalent cases by varying p (2, 4, 6, 8, 10, 12) under the condition that no inpatients transmit SARS outside the hospital ($\kappa=0$).

Incident cases. Figure 3 (A) shows the changes in the number of incident cases in SARS epidemics for up to 60 days ($t=60$) with the situation of $p=2$, 4, 6, 8, 10, and 12. As a result, the maximum number of newly infected cases (the day of maximum new incidence, 25th percentile of observations [the first quartile point], median, 75th percentile of observations [the third quartile point]) were 7.3 (31, 0, 4, 11) for the control and 0.4 (2, 0, 0, 1), 1.0 (4, 0, 1, 2), 2.1 (6, 1, 2, 3), 4.3 (8, 2, 4, 6), 9.1 (10, 5, 8, 12), and 18.9 (12, 11, 17, 25) for the case of $p=2$, 4, 6, 8, 10, and 12, respectively. It was found that these maximum numbers could satisfy the experimental equation: $y=0.21\exp(0.76p)$. The simulations showed that the maximum number of cases in the In-hospital infection model was higher than that of the control if parameter value p was more than 10. After 60,000 time simulation trials, the average of cumulative incident numbers was determined to be 166.2 for the control model, and 2.7, 7.0, 15.7, 33.8, 71.9, and 150.9 for $p=2$, 4, 6, 8, 10, and 12 for In-hospital infection, respectively. The cumulative number of incident cases for the In-hospital infection for any p value was lower than that for the control, but when $p=12$ the In-hospital infection model yielded case numbers very close to the control.

Prevalent cases. Figure 3 (B) shows the transition of the number of prevalent cases for up to 120 days ($t=120$) in the case of $p=2$, 4, 6, 8, 10, 12. The maximum number of prevalent cases (the day of maximum prevalence, the first quartile point, median, the third quartile point) was 111.3 (53, 1, 64, 173) for the control and 3.4 (12, 2, 3, 4), 7.3 (15, 5, 7, 9), 15.3 (17, 10, 14, 20), 32.0 (19, 20, 29, 41), 66.8 (21, 41, 62, 85), 139.4 (23, 86, 127, 181) for $p=2$, 4, 6, 8, 10, 12, respectively. These results indicate that when $p=12$ the number of prevalent cases for In-hospital infection with $\kappa=0$ were more than those for the control.

Outcome of SARS Infection Spreading Outside the Hospital

People who live outside the hospital but visit the hospital, such as outpatients and pharmaceutical businessmen, may contact SARS patients and get infected with SARS. Once the person is infected, he/she may carry SARS outside the hospital. In fact, there are many reports of visitors becoming infected when they visited hospitals with SARS infected inpatients, for example, in the Tan Tock Seng Hospital case, Singapore (8). The parameter κ is defined as the rate of persons outside hospitals becoming infected while visiting the hospital and represents a portion of the total infection cases occurring in the hospital. To assess the impact of infections spreading outside the hospitals, we investigated the maximum number of newly infected incident cases and prevalent cases by varying the rate of κ. Simulations were performed for the case of $p=2$, 4, 6, 8, 10, and 12.

Maximum incident cases. Figure 4 (A) shows the changes in the number of maximum incident cases for up to 60 days ($t=60$) at rate κ (0.0–1.0) and for the periods $p=2$, 4, 6, 8, 10, and 12. The maximum values of incident cases (κ with maximum new incidence, the first quartile point, median, the third quartile point) were 3.62 (1.0, 0, 2, 6), 6.62 (1.0, 2, 5, 10), 9.15 (0.98, 4, 8, 13), 11.64 (0.84, 6, 10, 16), 15.6 (0.66, 8, 14, 21), and 22.0 (0.52, 12, 20, 29) for $p=2$, 4, 6, 8, 10, 12, respectively, and the maximum value realized was 35 days after the hospitalization of the index case for all

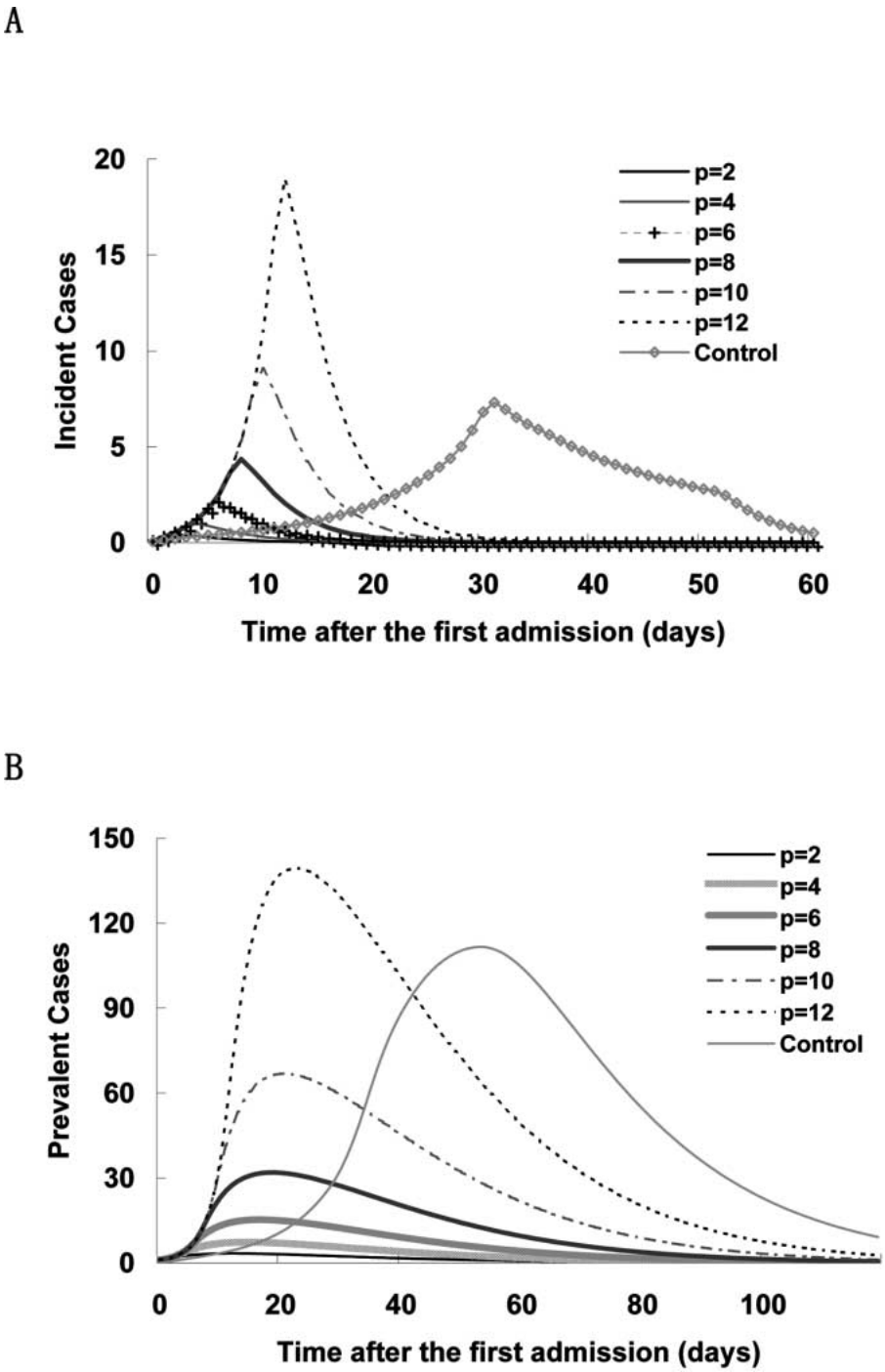

Fig. 3. Influence of increasing days until SARS patient isolation on the number of incident and prevalent cases. The effect of an increasing number of days until patient isolation on the number of newly infected SARS cases (A) and SARS infected prevalent cases (B). p denotes the number of days from admission of the index case until patient isolation (p=2, 4, 6, 8, 10, 12).

simulations. The higher the number of non-isolated days (p) in the hospital, the smaller the spreading ratio outside the hospital (κ) and the greater the number of the maximum incident cases. A p value greater than 10 with κ=0 in the In-hospital infection model yielded higher maximum incidence numbers than in the control model, but when p=6 and infection spread outside the hospital (κ=0.98) in the hospital-derived transmission model, the maximum number of incident cases was almost the same (Fig. 3 (A) and Fig. 4 (A)). This suggested that spreading SARS outside the hospital contributed to more infections, and that under these condi-

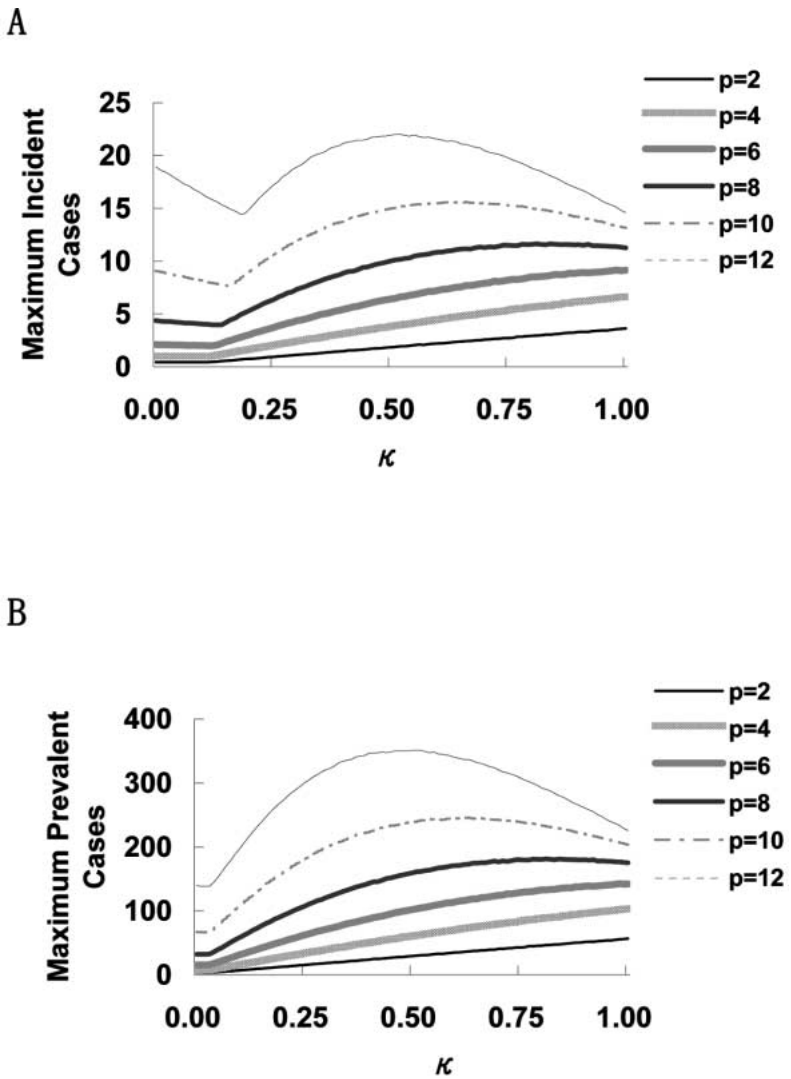

Fig. 4. Effect of SARS spreading outside the hospital on the number of incident and prevalent cases. Changes in the maximum number of newly infected SARS cases (A) and maximum number of prevalent cases (B) as the rate of secondary infection outside the hospital changes for each p value. κ indicates the rate of infected people from inside to outside the hospital.

tions, the maximum number of incident cases can accomplish that in the control model with a shorter number of days of isolation (p), especially for small p values ($p \leq 8$). The average cumulative cases at the rate κ which gave the maximum number of incident cases were 84.4, 154.2, 212.4, 270.0, 366.0, and 525.1 for $p=2$, 4, 6, 8, 10 and 12, respectively.

Maximum prevalent cases. Figure 4 (B) shows the relationship between the maximum number of prevalent cases and the rate of leaked infected cases from the hospital (κ) in the situation of $p=2$, 4, 6, 8, 10 and 12 for up to 120 days. The estimated maximum prevalent cases for κ (κ with maximum prevalence, the first quartile point, median, the third quartile point) were 56.6 (1.0, 3, 35, 86), 103.2 (1.0, 39, 85, 148), 142.4 (0.98, 71, 126, 195), 181.2 (0.81, 98, 161, 243), 245.6 (0.63, 138, 221, 325), and 351.1 (0.50, 202, 315, 462) for $p=2$, 4, 6, 8, 10 and 12, respectively. All the maximum values occurred 48 days after hospitalization of the index case. Figure 4 (B) indicates that the maximum number of prevalent cases for the hospital-derived transmission model was more than the number of cases for the control model (111.3) when $p=6$ and $\kappa=0.98$, or when $p=12$ and $\kappa=0.0$ (Fig. 3 (B)).

Simulation on Tokyo, Japan

We investigated the situation when a SARS epidemic occurs in Chiyoda-ku, one of the 23 wards in Tokyo, Japan, using the epidemic data from Hong Kong, where the daytime population density and the city area are

similar to those of Chiyoda-ku. There were 10 beds in negative pressure rooms, which can hold SARS patients of Chiyoda-ku (Sep 1st, 2003). The result of the simulation in the In-hospital infection model ($\kappa=0.0$) indicates that the beds can accommodate all the patients that arise in the case of $p=2$, 4 (the maximum number is 3.4 and 7.3, respectively), while they will be filled at the 8th day for $p=6$. This result suggests that prolonging the non-isolation period of patients (p) exponentially increases the number of new incident cases and total prevalent cases. When taking into account SARS transmission outside the hospital in the hospital-derived transmission model ($\kappa\geq0.0$), the beds are filled at the 42nd day even for $p=2$ ($\kappa=0.16$). The simulation shows that even a short period of non-isolated days (p) can extend the epidemic when transmission expands outside the hospital.

Discussion

SARS is a newly emerging infectious disease caused by a novel virus, the SARS-CoV (13). Many nosocomial transmissions of SARS have been reported. In Singapore, SARS-infected patients were not isolated for 6 and 8 days, resulting in 24 and 27 transmission cases, respectively (8).

Webb et al. treated the nosocomial transmission of SARS in Canada by a mathematical model using the actual data from the SARS epidemic in Canada (19). They classified the population into two groups: health care workers and patients with high transmission risk and the general public at low risk. Their analysis pointed out that the hospital infection control procedure contributed to containment of the SARS epidemic in Canada, but they did not consider the influence of the delay of hospital infection control. In this study, we first investigated the impact of the delay of infected patient isolation and quarantine on the hospital transmission of SARS (p).

It is somewhat unrealistic to expect that the population at risk of infection would include an entire country or prefecture as not everyone in the population would come in contact with the disease within a short time period. Therefore, we instead considered an epidemic within a city- or ward-sized population, such as Chiyoda-ku, one of the 23 wards in Tokyo. In such a small population, the stochastic model is regarded as better than the deterministic model, because it can provide both the average and range from individuals. We therefore made a stochastic model. We investigated the dynamics of the new incident number and prevalent number of cases, assuming that the SARS epidemic occurred in Chiyoda-ku.

First, we simulated the transmission dynamics assuming that SARS spread only inside a hospital. The results indicated that the maximum number of incident cases exponentially increased with quarantine delay (p) (Fig. 3 (A)). The maximum number of incident cases resulting from In-hospital infection ($\kappa=0$) at $p=10$ was higher than the number of cases in the control model, and the day giving the maximum number of incident cases ($t=10$) was much earlier than that of the control ($t=31$). In addition, in the In-hospital infection model, the maximum number of prevalent cases simultaneously increased and were higher than that of the control for $p=12$ (Fig. 3 (B)). The result revealed that a prolonged preisolation period (p) would cause an exponential increase of incident cases and prevalent cases without infection spreading outside the hospital.

Secondly, we investigated the maximum number of incident and prevalent cases, taking into account SARS spreading outside the hospital. Nosocomial transmission may occur when visitors and outpatients visit the hospital where SARS patients are staying. They are at risk of contracting SARS during their visits to the hospital and consequently transmitting it outside the hospital. In fact, there are many reports of outpatients and visitors being infected in the hospital and serving as a new source for SARS transmission (8, 20). Therefore, we assessed the relationship between the number of maximum incident cases or maximum prevalent cases and the rate of secondary infections (κ) in which inpatients transmit SARS to visitors and outpatients. The simulation showed that transmitting SARS outside the hospital contributed to SARS infection, especially for small p ($p\leq8$). The p values in the In-hospital infection model ($\kappa=0$) were estimated to be 10 and 12 when the number of maximum incident and prevalent cases was greater than that of the control, while p values in the hospital-derived transmission model ($\kappa=0.98$) were estimated to be 6 in both situations. Thus, when SARS leaked outside the hospital, even a small value p could cause a SARS epidemic (Fig. 4 (A, B)). These case results indicate that it is important to diagnose and isolate SARS patients as early as possible to control the epidemic and prevent further infections.

The curves of the maximum incident or prevalent cases have a cusp point near $\kappa=0.15$ (Fig. 4 (A)) or 0.50 (Fig. 4 (B)), where the predominance of incident or prevalent cases changes from In-hospital infection to Out-hospital infection. For a small κ, most incident cases proceed from In-hospital infection because $Rin>Rout$. On the other hand, if the transmission cycle of Out-hospital infection serves for SARS infection for some κ, most incident cases proceed from Out-hospital infection because of the large number of latent individu-

als (*Lo*).

This model was made under limited conditions. First, although we fixed *Rin_d*=2 for the daily secondary patients number in this model, this value may shift higher or lower depending on hospital circumstances. Secondly, the simulation results using limited Gamma distributions may include some errors. As the distributions used in this model were referred from an initial SARS epidemic in 2003, the number of cases was limited. Thirdly, there were some substituted parameters in the model. We used the sum of days from infection onset to hospital admission (*tI*) and from admission to discharge (or death) (*tHo_R*, *tHo_D*) as the hospitalization period of inpatients (*tHq_R*, *tHq_D*) because such data were not available for the hospital-derived transmission model. That would reduce the accuracy of the model. Indeed, the simulated curve for prevalent cases has more variance and less smoothness as the value *p* gets bigger.

Emerging infectious diseases have occurred constantly in our history. Recently, human immunodeficiency virus and avian flu have emerged and remain a health threat. Estimating the damage of an epidemic is important for determining how to control the infection, how to use hospital wards and how to prepare medical equipment and supplies for infected patients, etc. In-hospital infection has a critical impact on the outbreak, especially for SARS. Although the simulation used in this study is limited to a particular SARS scenario, our model has great value for learning how to control SARS epidemics. By changing the parameter values, this model will help calculate new infections and indicate how to treat them accordingly.

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