

Modelling potential responses to severe acute respiratory syndrome in Japan: the role of initial attack size, precaution, and quarantine

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Background: There has been an outbreak of the severe acute respiratory syndrome (SARS) worldwide. With the use of detailed epidemiological data from other countries, this article describes the possible reason for the SARS epidemic not appearing in Japan, and simulates the impact of different control strategies that can break the transmission cycle of SARS associated coronavirus.

Method: Mathematical modelling is used for predicting the epidemiological outcome and simultaneously for evaluating the effect of interventions on SARS. The study estimates the initial attack size that would result in failed invasion. Three different interventions have been incorporated into the public health response policies; precautionary public health measures, isolation of infected people, and quarantine of exposed humans.

Results: The maximum number of humans newly infected could be roughly estimated on the basis of the initial attack size, using simple formulas. It is seen that the introduction of only a few cases into certain communities would not lead easily to an epidemic. The possible trajectories of SARS epidemic depend on the levels of public health interventions as quarantine and precautionary public health measures greatly affected the transmissibility of the disease. It is shown that there exist threshold levels of interventions at which the SARS epidemic settles down.

Conclusion: Initial attack size is one of the determinants of whether SARS can successfully invade the community or not. Two of the most effective policy procedures to prevent new infections would be to apply stringent precautionary measures and to impose quicker and more effective quarantine of the exposed populace.

Severe acute respiratory syndrome (SARS), caused by SARS associated coronavirus (SARS-CoV or SCV), is a contagious and rapidly progressive infectious disease that can affect otherwise healthy persons, sometimes after even trivial contacts.¹ As of 11 July, a cumulative total of 8437 probable SARS cases with 813 deaths has been reported to WHO from 29 countries,² using the WHO case definition or country specific variations.³ The average overall case fatality rate for all countries has ranged from 10.4% to 14.7%.⁴ As the case toll climbed steadily this spring, many research studies have begun to appear in scientific journals on the epidemics,^{2,5,6} and on their epidemiological and clinical features.^{1,7,8} Because of the extensive public health responses to this outbreak and its possible seasonal nature, the global public health emergency caused by the sudden appearance and rapid spread of SARS is now coming to an end after almost four months.⁹

As SARS has been a worry to Japan because of its close proximity to Hong Kong, the Japanese health ministry has detailed its contingency plan for situation when SARS infected people entered into Japan.¹⁰ Although Japan experienced the entrance of an SARS-CoV infected person who had travelled to western Japan for a vacation and was later confirmed to be suffering from SARS,¹¹ Japan with its high concentrated population has so far not experienced a domestic spread of SARS. There are still great concerns over why the epidemic did not occur in Japan. Some experts put down it to largely to pure luck and partly to the washing of hands¹² by the Japanese public. The oncoming winter and spring seasons, the changes in atmospheric conditions, the possible evolution of the virulence of the pathogen, and the behaviour of

the host could lead to the re-emergence of disease. It has been predicted that there is a strong possibility¹³ that SARS will reappear in the next winter season. It has been pointed out that misdiagnosis of SARS cases would be highly likely if the incidence of influenza is high during the next winter season.

In the face of so many unknowns, several mathematical biologists have challenged the presently used models for describing the possible mechanisms for the survival and spread of SARS-CoV, as well as the assessments of the public health interventions.^{14–16} Models may be conceptualised as thought experiments, and are extremely useful tools when physical experiments are impossible to perform because of time, monetary, practical, or ethical constraints.¹⁷ They may also help us to realise which factors are the most important determinants of the development of the epidemic, and therefore which factors should be studied more closely and be measured more precisely. The purposes of this study are to clarify the possible reason for the SARS epidemic not occurring in Japan this past epidemic cycle, as well as to simulate the impact of different control strategies for breaking the transmission cycle of SARS-CoV, within a mathematical framework.

METHODS

Mathematical model

The analysis presented in this paper is based on a deterministic mathematical model for epidemic predicting the epidemiological outcome while simultaneously evaluating the effect of any specified control strategy on SARS. The model is a modification of the SEIR model¹⁸ given as a set of ordinal differential equations that are based upon specific

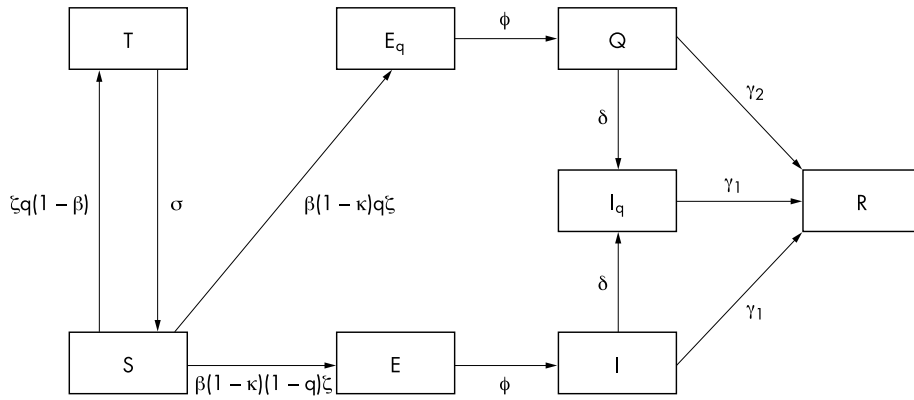


Figure 1 Transmission dynamics of the SARS taking into account the impact of precautionary measures and quarantine system. The subscript q denotes whether the new infections are quarantined or not with a proportion q . When 100% effective precautionary measures are implemented, a proportion, κ , of the potentially infected contacts is protected. S and I represent the proportion of the population susceptible and infectious; E , the proportion of untraced latent persons; E_q the proportion of traced latent contacts; T , the proportion of traced uninfected contacts; Q the proportion of infectious in quarantine; I_q the proportion of infectious isolated; R the proportion of recovered and death.

biological and intervention assumptions about the transmission dynamics of SARS (fig 1). An SARS-CoV infection of the susceptible population (S) results first in a non-infectious incubation period, which constitute the latency period (E). A proportion of the exposed persons, who had taken effective precautionary measures, would not be infected.¹⁹ The others become infectious, often being symptomatic with fever followed by rapidly progressive respiratory compromise (these being labelled (I)) and, then slowly recover or die (R).¹ While infectious, they transmit the disease to susceptible persons at a rate dependent on the basic reproductive rate, R_0 . Two of the public health interventions for interrupting the transmission are quarantining the people who are known to have been exposed and therefore may be infected but are not yet ill (denoted by the compartments T and E_q , which does each refer to “traced but not infected” and “traced and infected” in fig 1) and moving infectious people into isolation (I_q).²⁰ We assume each susceptible makes ζ contacts per day with the infectious person. Among the known contacts (in S), some would be infected with the probability of β per contacts (and enter into E_q) and $(1-\beta)$ remains uninfected (and enter into T). These processes can be modelled using an approximately parameterised set of differential equations(1) as follows:

$$\begin{aligned}
 \frac{dS}{dt} &= \zeta(q - \beta(q + \kappa - 1))SI + \sigma T \\
 \frac{dT}{dt} &= (1 - \beta)q\zeta SI - \sigma T \\
 \frac{dE_q}{dt} &= \beta q(1 - \kappa)\zeta SI - \phi E_q \\
 \frac{dE}{dt} &= \beta(1 - q)(1 - \kappa)\zeta SI - \phi E \\
 \frac{dQ}{dt} &= \phi E_q - (\gamma_2 + \delta)Q \\
 \frac{dI}{dt} &= \phi E - (\gamma_1 + \delta)I \\
 \frac{dI_q}{dt} &= \delta(I + Q) - \gamma_1 I_q \\
 \frac{dR}{dt} &= \gamma_1(I + I_q) + \gamma_2 Q
 \end{aligned}
 \tag{1}$$

Given that our model is based on the Kermack and McKendrick epidemic model,²¹ the situation just before the entrance of infectious persons into the community is given by $(S(t), E(t), I(t), R(t)) = (N, 0, 0, 0)$ and its subsequent development by:

$$\frac{dI(t)}{dt} = (\beta(1 - q)(1 - \kappa)\zeta N - (\gamma_1 + \delta))I(t)
 \tag{2}$$

where N is the size of the population in which the epidemic occurs. As the condition that SARS becomes possible to invade the community is $\beta(1 - q)(1 - \kappa)\zeta N - (\zeta + \gamma_1) > 0$, the basic reproductive rate, R_0 , is given by:

$$R_0 = \frac{\beta(1 - q)(1 - \kappa)\zeta N}{\delta + \gamma_1}
 \tag{3}$$

A description of the other principal parameters in the model and of their assigned value is presented below.

Parameter values

Table 1 contains the parameter values for our base case. Assuming that the biological variables for Japan do not differ much from those of Hong Kong because of similar population densities and lifestyles (this clearly being a rough assumption), we use the values given in the epidemic modelling of Hong Kong¹⁴ for those parameters whose values are not available for Japan. The infection rate $\beta \zeta$ is chosen so that $R_0 = 3$, which is the mean value on the order of 2 to 4 estimated in the previous studies done in similar ways.^{14 15 22} We assume that the pattern of contact is linearly related to the population size so that ζN denotes the daily number of contacts in the population. We varied R_0 while doing sensitivity analyses with regards to q and κ . We assume that an attack of 10 initial cases entered into a population of 287 000 persons, supposedly Shinjuku, Tokyo, as our baseline case but vary the attack size between 0 and 20 cases in our sensitivity analysis. It is somewhat unrealistic to expect that the population at risk would be at the national or prefectural level as it would not be possible to have 100% of this population come into possible direct or indirect contact with the disease within the short time period of concern. We have instead considered the epidemic within a city or ward sized population level, such as Shinjuku. Here, Shinjuku is assumed because of its similar population density to Hong Kong in addition to its population size.

We first estimate the number of newly infected (secondary) cases that results in a failed invasion in certain community for different initial attack size. We defined “failed invasion” as there being no secondary cases within incubation period after contacts with infectious people. We then performed a linear regression analysis to establish the linear correlation using a simple mathematical formula.

Table 1 Parameter values for transmission dynamics of SARS in Japan

Parameters	Description	Baseline values	Reference
β_s	the probability of transmission per contacts	0.0666667 person/day	14
q	the daily rate at which latent individuals are traced	0.75	14, see text
κ	the proportion of exposed person who performed effective precaution	0	See text
ϕ	the average rate at which latent individuals become infectious	0.2/day	27
σ	the rate at which the traced uninfected contacts released into the community	0.2/day	29
ζ	the daily number of contacts per capita	9/person/day	14
δ	the mean daily rate at which infectious cases are isolated	0.0333333/day	14
γ_1	the percapita rate for recovery and death	0.1666667/day	27
$(\gamma_2)^{-1}$	the mean duration for quarantine	10 days	29

Additional assumptions are that no transmission occurs from those people who are quarantined, isolated, dead, and recovered. As for the precautionary measures, we would like to point out that it may be too optimistic to assume that the measures are 100% effective so that there are no spreads of the disease among the people coming in contact with the infected. An analysis on the impact of isolation is not covered in this paper because it has already been well analysed.¹⁴

In this study, the total number of people in the population is taken to be constant during the epidemic. The background mortality rate is assumed to be negligible over the time periods examined. As the cases of “super-spread” events (SSEs), where a person may generate much more than the average number of secondary cases, has been described as a rare heterogeneous event,^{8, 23} we did not take this mode of transmission into consideration as the known values R_0 for SARS were calculated with certain adjustments of the number of secondary infections in this phenomenon and our aim is not to estimate the exact value of the basic reproductive rate but to understand, as a possible scenario in Japan, the role of initial attack size and interventions for the commonest transmission route. We assume that there is homogenous mixing among the infectious and susceptible, so that every infected person will pass the disease to exactly R_0 susceptible persons simultaneously within an infectious period of $(\gamma_1)^{-1}$ days. Simulations were performed with a time step of 0.1 days. The model has been programmed using Turbo Pascal Version 1.5 (Borland International, Scotts Valley, CA, USA) working on Microsoft Windows platform. All data from the program were analysed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA, USA) except regression analysis performed using Epi Info 2002

(Centers for Disease Control and Prevention, Atlanta, GA, USA).

RESULTS

The results of a simple scenario analysis show the probable dynamics of the SARS epidemics under different conditions (fig 2). The results in the analyses are given for up to 50 days after the onset of epidemic in the figure. It is unrealistic to estimate for longer time periods as one should not expect the health policy and control strategies as well as social reactions to remain static over longer periods. In figure 2A, four possible trajectories are shown for different initial attack sizes—that is, how many infectious persons were first introduced into a specific community having a susceptible population. The number of newly infected cases quickly rises, peaks, and then falls when more than five initial number of infectious ($I(0)N \geq 5$) are introduced while dramatic increase is not seen with one initial infectious ($I(0)N < 1$). Even though the control strategy remains the same, a more steep increase and more prolonged epidemic would be caused by bigger initial attack size. Figure 2B shows the model generated maximum number of newly infected as well as cumulative incidence over the time period examined. The maximum number of newly infected denotes the number of newly infected at the peak of the curve in figure 2A. It was found that there exists a linear correlation (coefficient of determination, $r^2 = 0.998$) between the maximum number and the initial attack size. The cumulative incidence, on the other hand, looks like a power two dependence on the initial attack size that is mathematically expected as the cumulative incidence is the area between the curves and x axis in figure 2A. From a regression analysis, the relation between

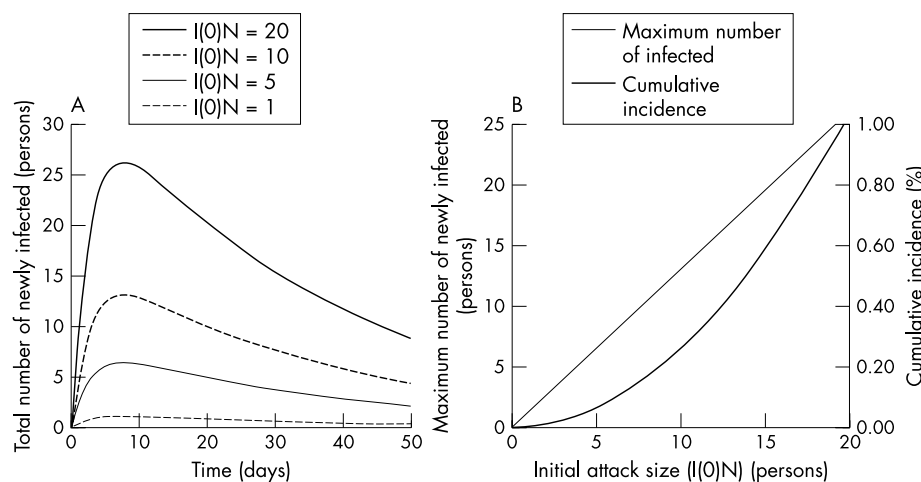


Figure 2 Dynamics of a SARS attack with the basic reproductive rate $R_0 = 3$. Effectiveness of the quarantine denoted by, $q = 0.75$, and of the precautionary measures, $\kappa = 0$. (A) Number of newly infected SARS cases according to initial number of infectious population. (B) Maximum number of newly infected SARS cases and the cumulative incidence as a function of the initial attack size (number of people initially infected).

the proportion of initial attack size ($I(0)$) and the proportion of maximum number of newly infected persons ($(E(t)+Eq(t))_{MAX}$) among total number of population, was found to be (under the assumptions leading to the epidemic)

$$(E(t) + Eq(t))_{MAX} = 1.295 \times 10^{-9} + 1.311I(0) \quad (4)$$

where 1.295×10^{-9} and 1.311 are the regression coefficient of intercept and slope, respectively. Here, 1.295×10^{-9} can be ignored as it does not lead to a large affect even though it is multiplied by total population N . Performing regression analysis by varying R_0 , the correlation was found to be represented by:

$$(E(t) + Eq(t))_{MAX} = \left(\frac{R_0}{2} - 0.167\right)I(0) \quad (5)$$

when $R_0 < 1$ because of public health interventions ($r^2 = 0.977$). When we consider the maximum number of newly infected (denoted by m , where $m = N(E(t)+Eq(t))_{MAX}$), we found that it was possible to relate this value with R_0 and $I(0)$ through:

$$I(0)N = \frac{m}{\frac{R_0}{2} - 0.167} \quad (6)$$

Next, we found the condition that would result in failed invasion (no secondary transmission) for each of the specific communities with population (N), is $m < 1$ in equation (6). Based on this, theoretically, at least 0.750 persons infected with SARS must be introduced into the population to produce secondary cases in our baseline simulation.

Figure 3A shows the number of newly infected SARS cases for various values of κ (the proportion of susceptible people who have undertaken the precautionary public health measures) and when no quarantine was carried out. Four possible trajectories are shown. Less effective precautionary measures ($\kappa = 0.30$) lead to an exponential growth of SARS. Even with relatively high proportion of people undertaking precautionary measures ($\kappa = 0.60$), a gradual increase in the number of new SARS cases is seen. When effective precautionary measures are taken by a higher proportion of the susceptible persons, one sees qualitative reductions in the number of cases. This occurs even in the absence of quarantine. The effect of a quarantine system is shown by the linear correlation with R_0 in figure 3B. It is seen that in the absence of any precautionary measures, one needs to quarantine at least 66.7% of the susceptible people who had contacts into compartment Eq and T in order for the epidemic to die down. Other information can be gained from the formula of basic reproductive rate, by noting that by interchangeable variables and q in figures 3A and 3B, we would be looking at the effects of changing the values of q with no precautionary measures being taken. Hence, the

condition to break the chain in person to person transmission of SARS can be described as:

$$(1 - q)(1 - \kappa) < \frac{1}{R_0} \quad (7)$$

This relation is shown in figure 3C. The curve shows the cut off points for R_0 to be 1. Figure 3D shows the changing pattern of R_0 for different combination of quarantine coverage and precautionary measure coverage in a three dimensional illustration. For the baseline simulation where $R_0 = 3$, the left form of equation (7) should be less than 0.33 in order to control SARS effectively.

DISCUSSION

Two important conclusions can be drawn from our analyses on the assessment of the role of initial attack size, and of the impact of interventions on possible SARS epidemic in Japan. Firstly, it is shown that the maximum number of newly infected, or the crude size of epidemic, could be roughly estimated based on initial attack size under certain public health interventions. In other words, it would be possible to predict the fate of an epidemic when SARS infected persons enter each community having approximately the same transmissibility and using the same control strategy. Secondly, the possible trajectories of a SARS epidemic depends on the levels of public health interventions as quarantine and precautionary measures greatly affect the transmissibility. There exist threshold levels of interventions to cause the SARS epidemic to settle down, and improved effective interventions can lead to dramatic decreases in its incidence.

Despite problems with the accuracy and uncertainty with the data released by WHO,²⁴ a simple dynamical model still gives reasonable simulations of the SARS dynamics. Except for the crucial parameter for the transmissibility, $\beta \zeta$, it was determined that the initial attack size is one of the most important factors to determine the course of the epidemic. It should be pointed out the cumulative incidence follows a power two law dependence on the initial attack size while the maximum number has a linear correlation with the size. Thus, a larger epidemic would be experienced if the initial attack size grows. The contribution of initial attack size to a SARS outbreak can be transliterated into equation (6). Although it is obtained within a theoretical framework based on certain assumptions without taking stochastic effect into account, and though the condition such as $I(0)N < 1$ might not be practical in the real situation, we showed that the introduction of a few cases into a given community would not necessarily lead to an epidemic using this formula—that is, successful invasion is hard to be achieved with a few initial cases. It might be possible to say that the introduction of only a few infectious persons into Japan was one of the reasons for Japan not experiencing the SARS epidemic so far. Although the fate of epidemic is determined by threshold theorem,²¹ that is, $R_0 > 1$ or not, successful or failed invasion itself can be considered using generalised formula such as ours under the condition when $R_0 < 1$. The formula could be reasonably applied to other countries.

One must be cautious about its application, however, because the formula is based on mathematical assumptions that might sometimes not be true. As each compartment, denotes the proportion of total population, it could give us the value of real number of persons to be smaller than 1. This may not be practical findings, but theoretically this notion becomes important in analyses such as ours. It should be also noted that it is based on several simple assumptions that may not be the same for all countries. The pattern of contacts between people differs from country to country.²⁵ Lipsitch *et al*

Key points

- Initial attack size is one of the determinants of whether SARS can successfully invade or not.
- It is seen that the introduction of only a few cases into certain communities would not lead easily to an epidemic.

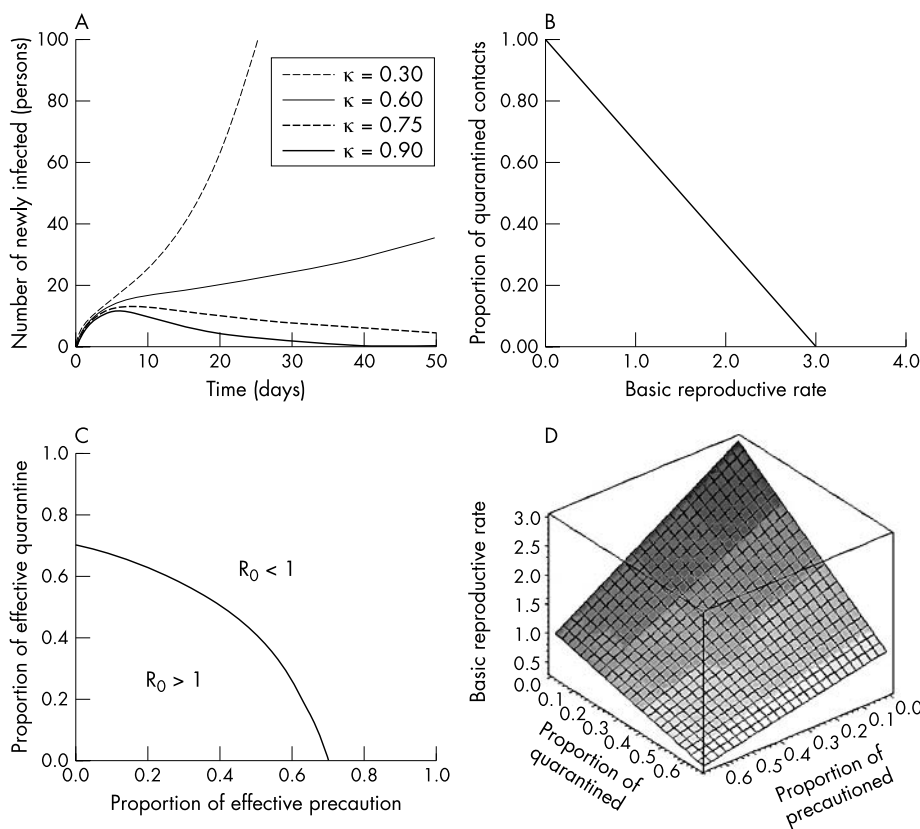


Figure 3 (A) Number of newly infected SARS cases for different proportion of susceptible persons who performed 100% effective precautionary measures for the case of $R_0=3$, and $q=0$. (B) and (C) Sensitivity analysis for model parameters whose values are unknown. Basic reproductive rate, R_0 , versus (B) the proportion of quarantined contacts, (C) both the proportion of quarantined contacts and the proportion of exposed persons who took effective precautionary measures. (D) The necessary condition to have the basic reproduction ratio lower than 1 for different values of q and κ .

described an outbreak of SARS through the use of probability theory of non-extinction of a branching process.¹⁴ Such a probability theory should be taken into account when it comes to describe the possibility of a SARS epidemic. It also should be noted that the size of the epidemic does not always depend on the initial attack size. This is clearly evident when we note that 76% of the infections in Singapore²³ were acquired in a healthcare facility. SARS can easily be spread by direct personal contact in the hospital setting.²⁶ As is well known, air borne transmission is not through the droplet nuclei but is instead through the large droplets, themselves. The wearing of a surgical mask¹⁹ can stop this.

Another example of why the initial attack size may not be the important factor is seen in Hong Kong. There we see that clusters have played an important part in the course of the epidemic in that city.²⁷ The role of close and casual contacts²⁸ and the possibility of other routes of transmission such as through touching contaminated objects or other unknown way should be incorporated into the model.

There has been an intensive assessment of the different public health interventions that contributed substantially to the eventual curtailing of the epidemic in Hong Kong.²⁷ It is well known that an effective strategy requires aggressive public health measures in combination with stringent

hospital infection control practices that meet the recommendations of World Health Organisation.²⁹⁻³⁰ The SARS pandemic has shown that governments and public health officials need to consider the use of quarantine as a public health tool to prevent the spread of infectious diseases, particularly when other preventive interventions (for example, vaccines and antibiotics) are unavailable.³¹ From our study, it is shown that either 100% effective precautionary measures or quarantine would lead to decline in the incidence. Both of them reduce R_0 in a linear way unlike the practice of isolation. The importance in the coverage should be therefore emphasised. Although recent studies with modelling¹⁴⁻¹⁵ provided us with dynamics of SARS including transmissibility as well as the impact of quarantine and isolation, the role of precautionary steps was not taken into consideration. Precautionary measures themselves are quite important especially in hospital settings because a high proportion of the SARS patients were healthcare workers as was pointed out.²³⁻²⁶

The increased amount of world travel increases the likelihood of this disease spreading faster than past worldwide epidemics. It is therefore critically important to prepare for the possible introduction of SARS into the country by introducing specific public health measures now. Two of the most effective procedures would be to introduce stringent precautionary measures and to impose better and quicker quarantine of those exposed. This would reduce the number of people who get a secondary infection from contacts with infectious persons. The important challenge is that some of the most important public health measures have to be taken outside the health sector.³² These measures include maintenance in a healthy and hygienic environment such as penalties for spitting and closely monitoring the integrity of sewage disposal systems.³²⁻³³ The government distributing free surgical masks and showing how they can be used effectively can overcome the strong fear among the general

Policy implications

- There exist threshold levels of interventions at which the SARS epidemic settles down.
- Two of the most effective policy procedures to prevent new infections would be to apply stringent precautionary measures and to impose quicker and more effective quarantine of the exposed populace.

population about this disease. In addition to infection control measures, it should be noted that case detection, reporting, clear and timely dissemination of information would play important parts in the fight against SARS.³³

Our study has several limitations, however. Firstly, one of the major problems, which the world must confront, is the absence of knowledge on SARS. In particular, it would be hard to predict the possible trajectories in Japan as the country has no experience with this epidemic. We believe that one approach to overcome the problem of risk management is to model the potential episodes with mathematical modelling. This study was conducted with only a few known parameter values. Although we used a single value of R_0 throughout an epidemic, R_0 is likely to decrease after the onset of an epidemic is detected and announced. The qualitative and quantitative patterns of diminishing R_0 , because of behavioural change (that is, if people reduce the frequency of going out), should be incorporated in further studies. We here performed sensitivity analyses of R_0 for parameters whose values are not known. Secondly, we made a simple assumption that either the precautionary measures or the quarantine were perfectly effective (an optimistic assumption) or not. Thirdly, although possible outcomes were determined for a certain population sizes, for example, that of Shinjuku, Tokyo, one should not expect the same outcome for cities of the same size because of regional variances in the age distribution, behaviour, and contact pattern. Intercommunity transportation, migration, should also be taken into account. Further research is therefore necessary. It would be important to incorporate probability theory and contact patterns into the research as the epidemic threshold parameters should be considered based on approximating the infection process, during its initial stages, by a branching process.³⁴ The mathematical model might be modified so that the effects of changing staffing policy for the healthcare facilities could be simulated. Finally, incorporating quarantine of visitors from overseas might give us more practical simulation.

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