〔ウイルス　第55巻　第2号，pp.303-306，2005〕

Background of recent JE vaccine issues

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In Japan, more than 5,000 patients were reported in 1950, and there have been less than 10 cases annually since 1992. However, Japanese encephalitis virus caused of Japanese encephalitis (JE) are still existed highly and widely in the country, reported by National Institute of Infectious Diseases with serological examination among domestic pig population. JE immunization had been provided to children as category 1 routine immunization in Japan. However, the Ministry of Health, Labor and Welfare (HOHLW) decided not to recommend JE immunization to children as a routine immunization at May 2005. Major reason on this decision was that the Minter of MOHLW certified to pay loss of medical costs for the case of ADEM (acute disseminated encephalomyelopathy) after JE immunization, recognized as adverse events with JE vaccine, although MOHLW stated that the strict scientific evidence was unknown. MOHLW stated also that it is expected Vero cell derived JE vaccine should be replaced with the present mouse brain derived JE vaccine as the next generation, to be able to avoid theoretical possibility of neurological adverse events associated with JE vaccine. Small but increasing number of requests recently to be certified as health injuries on ADEM cases associated with JE immunization is also another reason for MOHLLW's decision. Further, fifth doses of JE vaccine given to children at 14-15 years old as a routine immunization was decided to be discontinued by MOHLW at July 2005, considering present epidemiological situation on JE and JE immunization status in Japan, although four doses has been recommended continuously as routine. The background details on JE vaccine issues decided by MOHLW in 2005 were reviewed on this paper.

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Vaccine 23 (2005) 2256–2260
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Policy evaluation for the subsidy for influenza vaccination in elderly

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Available online 18 January 2005

Abstract

Objective: In Japan, the subsidy of influenza vaccination for the elderly was introduced in November 2001. This paper examines its policy evaluation from the viewpoint of cost–benefit analysis.
Materials: The data of copayment of influenza vaccination, population and shot rate of the elderly are surveyed by telephone interview to the correspondents in the local governments of Tokyo metropolitan and other 12 big cities in Japan. The mortality due to pneumonia or influenza is obtained from Vital Statistics of Population.
Method: At first, I examine the impact of amount of copayment, through its effect on shot rate, on the percentage of elderly receiving influenza vaccinations. Using these estimation results, benefit–cost ratio (BCR) is calculated.
Results: The estimated coefficient of copayment on shot rate is −0.007 and statistically significant. Shot rate significantly reduces pneumonia and influenza mortality and its magnitude is −0.0028. The obtained net benefit (NB) is 134.9 million yen or US$ 1.08 billion and benefit–cost ratio is 22.9 and its 95% confidence interval is [2.2, 43.7].
Discussion: If copayment would be cut by a 1000 yen (US$ 8), it could avoid about 400 deaths in average big city. The benefit–cost ratio is quite high compared with the other countries or other vaccinations.
Conclusion: We found the strong evidence in a sense of cost–benefit analysis in the subsidy for influenza vaccination in the elderly.

Keywords: Influenza; Cost-benefit analysis; Vaccination; Subsidy for the elderly

1. Objective

In 7 November 2001, the vaccination law was reformed and it started to subsidize of influenza vaccination for the elderly. This policy should be confirmed by the cost–effectiveness perspectives because it costs very much. This paper examines to evaluate this policy from the viewpoint of the cost effectiveness.

2. Material

The data of copayment of influenza vaccination, population and shot rate of the elderly in 2001/2002 and 2002/2003 seasons are surveyed by telephone interview to the correspondents in the local governments of metropolitan and other 12 big cities in Japan. This survey was performed by the author.

Copayment is determined by these local governments in every year and the excess cost more than the copayment is subsidized by the central and local governments directly to the medical institutions. Total cost of vaccination, which is charge by the medical institution to the elderly and local governments, is decided through the negotiation among local governments and physicians' association in each cities. Unfortunately, it is not informed publicly. In other words, we can only know the copayment in every year and in each city, while the total cost and, thus, the amounts of the subsidy are unknown. In this sense, total cost includes all components of items for the vaccination and the profit of medical institutions.

The mortality due to pneumonia or influenza is obtained from Vital Statistics of Population in 2002 and 2003. The data of total population is obtained from National Population Census in 2000.

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doi:10.1016/j.vaccine.2005.01.042

3. Method

3.1. Estimation

Estimation is performed with the following two parts. At first, we examine the impact of the variation of copayment on shot rate. Let $R_{i,t}$, $C_{i,t}$ and T_t, respectively, denote shot rate and copayment in i area and t year, and year variable for 2002/2003 season that captures the difference between sample seasons keeping constant all other aspects. The estimation equation is:

$$R_{i,t} = \alpha_i + \alpha_c C_{i,t} + \alpha_T T_t + \varepsilon_{i,t} \quad (1)$$

The second part is to estimate the relationship between shot rate and mortality rate due to pneumonia or influenza. The estimation equation is:

$$D_{i,t} = \beta_i + \beta_R R_{i,t} + \beta_T T_t + \nu_{i,t} \quad (2)$$

where $D_{i,t}$ is pneumonia and influenza mortality rate. Unfortunately, since pneumonia and influenza mortality rate of the elderly by area and season is not reported, we use the mortality rate of the total population irrelevant to the age.

Estimation method is the weighted least square with the elderly population and the total population as a weight, respectively, in the first and the second estimation.

Note that we have to remark, if $\varepsilon_{i,t}$ and $\nu_{i,t}$ are correlated, estimated coefficient β_R certainly has bias. Moreover, the direction of bias may be positive or negative depending on $E[\varepsilon_{i,t}, \nu_{i,t}]$. For example, increase in the number of weak elderly and residents in institutions, shot rate of them usually are higher than dwelling elderly and mortality rate may be still higher due to their weakness even if shot rate are the same. This correlation may lead to the upper bias in the coefficient. Conversely, shot rate may represent overall welfare spending or situation of the elderly in that area controlled out copayment. If these spending or situation improve the elderly's health condition and reduce mortality rate, this relationship make the lower bias in the coefficient.

In both case, these are very well known as the simultaneous bias and we have to adopt the method that corrects such bias. The method, called instrumental variable method, uses the fitted variables of $R_{i,t}$ in the first estimation as an explanatory variable in the second estimation rather than the observed raw $R_{i,t}$ [1].

3.2. Benefit–cost ratio

Using these estimation results, we can evaluate the policy by net benefit (NB) and benefit–cost ratio (BCR). NB is defined simply by the difference of benefit and cost due to the policy, and BCR is defined by its ratio.

NB can be calculated as follows: the perspective is of the society and time horizon is set to be 1 year because the effect of vaccination is lower than 1 year and vaccination can extend their life 1 year at maximum. The effectiveness of vaccination is limited to the prevention of the mortality due to data limitation.

Vaccination cost is defined as the sum of copayment and subsidy, but the opportunity cost for shot is not taken into consideration because they are typically retired. Moreover, side effects of vaccination are also ignored for simplicity.

Vaccination cost is assumed to be 4500 yen (US$ 36) and benefit of 1 year increasing in life expectancy is assumed to be 6 million yen (US$ 50,000). These numbers are widely used number in US [2] and it is confirmed to be plausible even in Japan [3].

Then NB is

Monetary value of avoidance in mortality by rising shot rate

- additional cost by rising shot rate = rising shot rate due to subsidy × reduction in mortality rate due to rising hot rate × million yen
- rising shot rate due to subsidy × 4500 yen = $\frac{4000}{3}$ × reduction in mortality rate due to rising shot rate

Similarly, BCR is

$$\frac{\text{monetary value of avoidance in mortality by rising shot rate}}{\text{additional cost by rising shot rate}}$$

$$= \frac{\text{rising shot rate due to subsidy} \times \text{reduction in mortality rate due to rising shot rate}}{\text{rising shot rate due to subsidy}} \times \frac{6\,\text{million yen}}{4500\,\text{yen}}$$

$$= \frac{4000 \times \text{reduction in mortality rate due to rising shot rate}}{3}$$

4. Result

4.1. Estimation result

Summary statistics are shown in Table 1. Estimation results are summarized in Table 2.

The first and second columns in Table 2 show that the increasing in copayments significantly reduces shot rate. As its coefficient is −0.007, since it means the shot rate would rise by 0.007% point in every 1 yen subisidy, if copayment is subsidized by 1000 yen (8), then shot rate rise by 7% point. Since the coefficient for 2002/2003 season is significantly positive, shot rate rise by 8.8% point in 2002/2003 season compared with the 2001/2002 season where other situations are completely the same. All area dummies, which indicate difference from Sapporo, are insignificant. Since degree of freedom adjusted R^2 is high, it fits quite well.

The third and fourth columns in Table 2 summarize estimation results of crude weighted least square about mortality

Table 1
Summary statistics

	Average	S.D.	Minimum	Maximum
Shot rate (%)	29.6695	6.067872	18.4074	45
Copayment (yen)	1171.429	427.618	1000	2200
Mortality rate (%)	0.0409995	0.0315513	0.0033683	0.1753567

rate and they indicate that the shot rate is negatively affect mortality rate but it is not significant. On the other hand, the fifth and sixth columns in Table 2 show the results for the instrument variable method. They show significant effect of shot rate on mortality rate and its estimated coefficient is −0.003, i.e. if shot rate is raised by 10% points, mortality rate of pneumonia and influenza would decrease by 0.03% point.

4.2. Net benefit and benefit–cost ratio

Suppose calculation of the net benefit and BCR of the policy change, which raise 1000 yen (8) in subsidy. At first, this policy increase the shot rate by 7% point as mentioned above and this reduces the mortality rate of the ehold population by 0.0196 (= 7 times 0.0028)% points. It means to avoid 23,520 (= 0.000196 times 120 million) death. This benefit can be evaluated as 141.2 billion yen (US$ 1.13 billion) (=23,520 times 6 million yen) if value of life is assumed to be 6 million yen or US$ 50,000.

On the other hand, additional cost of this policy change must be the product of 7% point rise in the shot rate, 4500 yen (cost of vaccination in social per one elderly) and 20 million (population of the elderly). It expends 6.3 billion yen or US$ 50.4 million. Therefore, the net benefit must be the difference of benefit and cost and it is 134.9 million yen or US$ 1.08 billion.

Following the similar way, we can calculate its BCR easily, i.e.

$$\frac{0.0028(-1000)(-0.007)\,6\,\text{million yen}/(2000/12000)}{-1000(-0.007)4500\,\text{yen}} = 22.4 \quad (5)$$

where 2000/12,000 in the numerator is adjustment factor for the elderly because potential population of the numerator is the whole population but the counterpart in the denominator is of the elderly. Moreover, its 95% confidence interval is calculated as [2.2, 43.7] and we can confirm that this BCR is significantly greater than 1.

5. Discussion

5.1. Evaluation of estimation results

From Table 1, showing the average shot rate and average copayment, we can see that the price elasticity of shot rate is −0.2606. It appears to be higher than the results of the pre-

Table 2
Estimation result

Explanatory variable	Estimator	*p*-Value	Estimator	*p*-Value	Estimator	*p*-Value
Copayment shot rate (instrument)	−0.0066561	0.002	−0.0006669	0.304	−0.0027877	0.034
2002/2003 season	8.757308	0.000	0.0112177	0.088	0.0295542	0.015
Sendai	1.208579	0.727	−0.0047122	0.500	−0.0021133	0.780
Chiba	5.458579	0.153	0.0057438	0.475	0.0173561	0.141
Tokyo	−1.674325	0.300	0.0023957	0.727	−0.0144918	0.090
Yokohama	−0.6914208	0.781	−0.0021031	0.682	−0.0035337	0.464
Kawasaki	−5.184099	0.123	0.0056449	0.442	−0.0053089	0.455
Nagoya	−3.341421	0.222	0.0034983	0.561	−0.0035525	0.502
Kyoto	−4.723365	0.113	0.0073267	0.297	−0.0026762	0.680
Osaka	−4.441422	0.095	0.012161	0.065	0.0027774	0.618
Kobe	−4.691421	0.117	0.0034541	0.614	−0.0064597	0.325
Hiroshima	4.058578	0.225	0.0061583	0.394	0.0148015	0.141
Kitakyuushuu	−5.79142	0.076	0.0122467	0.137	0.0263081	0.548
Fukuoka	−2.991421	0.350	0.0009681	0.883	−0.0053403	0.376
Constant	34.46885	0.000	0.0437944	0.030	0.1028622	0.005
Sample size	28		26		26	
F statistics	10.81		2.53		2.60	
p-Value for *F* statistics	0.0001		0.0639		0.0537	
$\bar{R}^2$	0.8357		0.4622		0.4548	

Note: Coefficients for 2002/2003 season indicate the structural difference of it from 2001/2002 season keeping constant all other aspects. Positive coefficient means that the average is larger in 2002/2003 season than in 2001/2002 season if the situation which is represented by figure of explanatory variables are the same in both season.

vious study. That is, the study based on the conjoint analysis which is the most reliable technique with hypothetical questionnaire indicates −0.02 to −0.04 of the elasticity, and actual behavior in 2001/2002season indicates −0.1 of the elasticity [4]. Hence, the result in this paper shows that the shot rate is very elastic against price.

There may be mainly two reasons for these differences. Firstly, this study focus on the metropolitan and big cities and so it may bias toward extremely urban areas, whereas the previous studies cover the whole Japan. If the residents in the urban areas have higher price elasticity to vaccination than rural areas, our results here may be reasonable. In this sense, the previous studies seem to be more general than this research.

Conversely, the data in this paper covers all residents in an area, while the previous study relied on survey by mail and it did not cover all the residents, of course, and they may not be representative. If the respondents of the questionnaire tend to have inclination toward to vaccination for influenza compared with non-respondents, shot rate may be insensitive to price. In this sense, the result in this study seems to be more reliable than the previous one. Though, it is not sure which estimate and reasoning is more reasonable, we have to remind that our final goal, namely the analysis with the BCR, is independent of price elasticity of shot as explained the before.

On the other hand, the shot rate elasticity of mortality rate is −2.48 and, thus, mortality is elastic against shot rate. Combining with these two estimation results, if copayment would be cut by a thousand yen (US$ 8), it raises shot rate by 7% points and reduce the mortality rate due to pneumonia and influenza by 0.029% point. It seems very small number, but since the average mortality rate due to pneumonia and influenza is very small, the effect certainly is quite high. In fact, this means that this policy can reduce about 423 death in an average big city.

Since F statistics in the first equation is higher than 10, the fitted variables seems to be good instrument [5]. In other words, the reason of insignificance of shot rate in the crude weighted least square can be inferred as positive simultaneous bias, which offsets the shot rate effect on the mortality. Therefore, the instrument variable can solve this bias and it is more appropriate method for this problem.

5.2. Evaluation for BCR

The obtained BCR, 22.4, is quite high compared with the other countries or other vaccinations. In some other countries, since it is 1.93 [6] for children before school and 1.81 [7] or 2.92 [8] for healthy adults, the obtained IBCR is much higher. Comparing with the other diseases, it is 2.5 [9] in measles in Japan and it is just 1.4 [10] in the case of hepatitis B for all infants in Chinese where epidemic area. Overall, the policy of subsidy to the elderly's shot is quite cost-effective and it has concrete evidence for it.

5.3. Problem and limitation in this analysis

At first, there are some differences in the definition of population among areas for the policy targeting or/and for the shot rate calculation. Especially, this policy also subsidize the non-elderly, i.e. between 60 and 64 years old, who has heart, kidney and respiratory problem or HIV career. Moreover, each city sometimes extend targeting population more than the national policy requirement. Typically, some cities subsidize the institutionalized elderly even if they are younger than 65. These additional target populations are included in the denominator in some cities, but are not in other cities. The subsidized number in the numerator of shot rate include, such additional targeting populations and, thus, the shot rate may be different whether the denominator include such additional targeting populations or not. However, these additional targeting population is quite small compared with the elderly, and it is less than just one percentage. Therefore, such an inconsistency in the denominator of shot rate may not affect substantially on the result.

Moreover, the starting dates of subsidy are not the same among areas. In particular, it is remarkable in the first season of this policy, i.e. 2001/2002 season. Our data of shot rate only include those who received the subsidy, and does not include those who did not receive subsidy but shot. So shot rate may be lower than the actual rate in the area where subsidy was delayed to start. In this sense, data of shot rate is always lower than the actual shot rate among the elderly. This measurement error may leads upper bias of the estimated coefficient of shot rate in the second estimation. Hence, it also lead upper bias in IBCR. However, it is not sure how many elderly receive shot but are not subsidized and so we cannot evaluate this effect in detail.

On the other hand, it is questionable that our sample in the metropolitan and big cities represent whole Japan. The coverage of the elderly population in our data is 21% of whole Japan, but it may not be the average population. Especially, there may be big differences from those in the rural areas as mentioned before. So as to check the robustness of the obtained result, we should extend our analysis to the other areas.

Additionally, the effect of influenza epidemic on the mortality is measured by excess mortality which is defined by the difference between the actual number of death and the hypothetical one if there is no influenza epidemic [11–14]. Therefore, we have to replace the mortality definition from crude number of death to the excess mortality. In particular, excess death should be defined regardless of the cause of death [14] because it is very well known that influenza epidemic raises the mortality from the other causes than pneumonia or influenza and these deaths can be prevented by the vaccination and control of the influenza epidemic. Moreover, if we can limit the number of death to those of more than 65 years old, it would be more precise measure. In this sense, excess mortality of more than 65 years old in all death causes is the best measure to evaluate the vaccination effect.

At the same time, we also need more explanatory variables which affect shot rate or mortality. For example, hortative measure for vaccination may be much different among local governments and it may affect the shot rate. Even in this case, if such a measure did not change in an area in the two seasons, this effect can be controlled out by the area dummies completely and it does not affect the estimated coefficient.

On the other hand, there are many implicit assumptions in BCR. First of all, since we limit the effect of vaccination to the prevention of the mortality and, thus, it is certainly finer measurement than the prevention of the severe conditions like hospitalization as emphasized. Since it is difficult to obtain the data of the number of patients and the hospitalized, these numbers would be based on the similar estimation. Hence, these are far less precise than the number of death. In other words, we choose preciseness than broadness in the definition of effectiveness. Obviously, this limitation lower BCR. If we take the effects of vaccination on the number of patients and the hospitalized into consideration, BCR definitely become higher than that in this paper. It strengthens our conclusion in favor of the subsidy and has never change it.

Conversely, the ignorance of opportunity cost for vaccination or side effects certainly rise BCR. However, almost all of them are retired and suffered from chronic disease and, thus, they usually visit a doctor, their additional opportunity cost for vaccination seems to be small. Concerning side effects, on 28 August 2003, Ministry of health and welfare reported only 2 fatal cases and 18 severe side effects from 1998 to 2003. Therefore, we can safely ignore these costs and the obtained conclusion is probably not affected by the introduction of these costs.

Finally, we can extend the effectiveness of vaccination to the number of patients or the medical cost. The data limitation of these variables are already mentioned. Moreover, since the primary purpose of vaccination is the prevention of severe cases, if we extend to these aspects, the results may not be clear and BCR may decline. In extreme case, the fatal case may use less medical resources compared with the severe but survival case. In this sense, the limitation of effectiveness on the number of death seems to be more appropriate for considering the vaccination policy. Nevertheless, the research of the number of patients and medical cost are unambiguously important and we need to overcome the data limitation.

6. Conclusion

We find subsidy of influenza vaccination for the elderly greatly reduce mortality rate due to pneumonia and influenza. Since BCR is more than 20, we can conclude that there is strong evidence, in a sense of cost–benefit analysis, supporting the subsidy for influenza vaccination among the elderly.

Acknowledgements

This paper is a part of the outcome of 2003 grant for the research of emerging and re-emerging infectious disease by Ministry of Health, Labor and Welfare, "Policy Evaluation for Influenza Vaccination based on EBM," represented by Prof. Yoshio Hirota, Osaka City University). We appreciate deeply the cooperation for this research by the correspondents of the section of infectious disease in metropolitan and 12 city governments. Moreover, Dr. Kiyosu Taniguchi, Dr. Yuki Tada, Dr. Mika Shigematsu and Dr. Kazuki Masuda of National Institute of Infectious Disease, Dr. Masayo Sato of National Institute of Social Security and Population, and Ms. Tamie Sugawara, doctoral student of Tsukuba University. Ms. Kazuko Matsumoto is also thanked for her help.

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J Infect Chemother (2005) 11:71–80
DOI 10.1007/s10156-005-0373-3

ORIGINAL ARTICLE

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Prediction of smallpox outbreak and evaluation of control-measure policy in Japan, using a mathematical model

Received: August 26, 2004 / Accepted: January 19, 2005

Abstract Since the September 1 terrorist attacks and moreover, since the anthrax exposure events in 2001 in the United States, bioterrorism attacks seem to be a real threat. Of course, the public health authorities in Japan have started to prepare control measures for such events. We report here our attempts, using a mathematical model, to estimate outbreak size and to examine the most effective measures; comparing ring vaccination (contact tracing, isolation, and vaccination among contacts) and mass vaccination of the susceptible population in the area. The basic framework of the mathematical model follows a model used in previous research. The initial susceptible population is assumed to be 30 million persons. Concerning the important parameters, such as the number of initial-exposure cases, R_0 (infectious power, or natural history) and, the starting day of intervention after the initial exposure, we checked the robustness of our conclusions by sensitivity analysis. We found that mass vaccination is preferable to ring vaccination when the values for the initial-exposure cases and R_0 are high and when the start of intervention by public health authorities is delayed. In the base-case situation, the mass vaccination strategy needs almost 30 million vaccine doses. On the other hand, though ring vaccination needs fewer doses, it needs fewer than 50000 doses in the worst-case scenario, that with larger first exposure, higher R_0, or later start of public health authority intervention. This mathematical model can measure the prevalence of an infectious disease and can evaluate control measures for it before an outbreak. Especially, it is useful for the planning of the outbreaks of emerging diseases such as severe acute respiratory syndrome (SARS) or for bioterrorism attacks involving such diseases as smallpox. In further research, we will have to take into account the population people vaccinated of for smallpox, who account for about 70% of the total population in Japan.

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Key words Smallpox · Vaccination · Mathematical model

Introduction

Since the September 11 terrorist attacks and, moreover, since the anthrax exposure events in 2001 in the United States, bioterrorism attacks seem to be a real threat. Of course, the public health authorities in Japan have started to prepare control measures for such events. It is very well known that a mathematical model is very useful for predicting the likelihood of a disease outbreak and for evaluating control-measure planning by a public health authority, and for evaluation of these measures after an outbreak.

Mathematical modeling is widely used in planning for responses to a pandemic,[1] and in the evaluation of control measures against severe acute respiratory syndrome (SARS),[2] and in the evaluation of vaccination policies.[3,4] Especially, it is also widely used in planning responses to bioterrorism attacks in which smallpox could be used.[5–8]

By using a mathematical model, we tried to estimate outbreak size (i.e. total number of patients, outbreak duration, peak of the outbreak, and so on) and to examine the most effective measures, comparing ring vaccination (contact tracing, isolation, and vaccination among contacts) and mass vaccination of the susceptible population in the area. We report our findings here. This issue is somewhat controversial, i.e., one study found that mass vaccination was more effective,[7] while, on the contrary, another study concluded that ring vaccination was preferable.[8]

However, these studies did not take into account the human resources limitations of the public health authorities, whereas, on the other hand, a theoretical model for HIV has considered this viewpoint explicitly.[9] However, this model ignored the deaths due to HIV, and thus, we cannot extent the model to smallpox. In this article, we report our model, in which we tried to take into account the human resources limitations of public health authorities for

Table 1. Base case setting

Parameters	Setting	Sources
Model	Markov	Previous research[5–8]
R_0[a]	1.5	Previous research[5]
Duration of incubation period[b]	5–17	Previous research[5]
Duration of prodromal period	2–3	Previous research[5]
Duration of symptomatic period	11–15	Previous research[5]
Number of initial-exposure cases	1	Previous research[7]
Size of initially susceptible population	30 Million	Previous research[10]
Mass vaccination		
Number of public health workers	5000	Previous research[7]
Number of vaccination shots processed per day per public health worker	200	Previous research[7]
Ring vaccination		
Number of contacts	50	Previous research[7]
Maximum quarantine rate per day in the symptomatic period	0.5	Previous research[5]
Number of vaccination shots processed per day per public health worker	200	Assumption

[a] R_0 distribution follows data in previous research[5,11]
[b] The durations of the incubation, prodromal, and symptomatic periods are according to previous research[5]

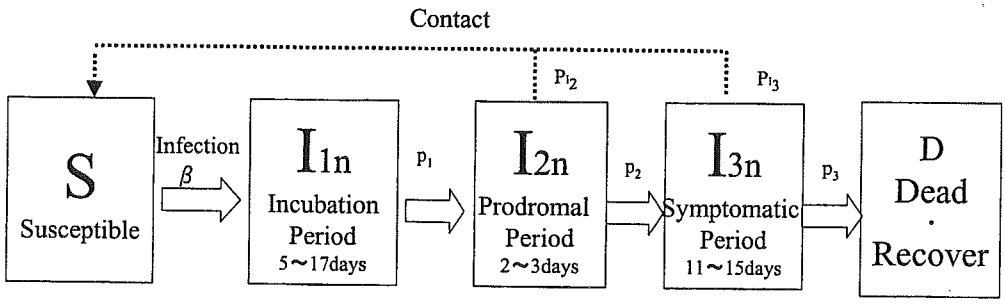


Fig. 1. Natural history of smallpox

dealing with smallpox. There is no report of this kind of research with mathematical models of control measures, (namely, mass or ring vaccination) for smallpox in Japan (S. Tokuraga: The research for technological foundation from the viewpoint of precautionary medicine [unpublished manuscript]; 2003). In this sense, this study could contribute to public health policy for the preparation of measures to deal with bioterrorism attacks using smallpox.

Materials and methods

Basic structure of the model

Some assumptions in the basic structure of the model are summarized in Table 1. We adopted the Markov model setting, following previous research,[5–8] and the epidemiological characteristics, such as R_0 (infectious power, or natural history), were borrowed from previous research,[5] the natural history of smallpox is shown in Fig. 1. In particular, we have assumed that the value for infectious power, R_0, as in an actual case[10] is 1.5, and that it is distributed potentially in the prodromal and mainly in the symptomatic period, previously reported.[5,10] We also assume that the incubation period lasts for 5 to 17 days, the prodromal period lasts for 2 to 3 days, and the symptomatic period lasts for 11 to 15 days, as in the base case. R_0 is the most commonly used and important number for infection control and is defined by the basic reproduction number (which means the number of persons who are infected from one patient if all the persons are susceptible). We have used the value of $R_0 = 1.5$, for the distribution of infectiousness, incubation, prodromal, or symptomatic period over each duration from the previous research.[5]

We have also assumed, as in the previous research, that there is one initial-exposure case, and we assume that the initial susceptible population is 30 million persons, that is, the total number of the population who were born after 1976, when vaccination for smallpox had ceased (S. Tokuraga: The research for technological foundation from the viewpoint of precautionary medicine [unpublished manuscript]; 2003).

Two control measures, mass and ring vaccination, are outlined in Figs. 2 and 3, respectively. Mass vaccination is performed by 5000 pubic health workers and each public health worker can process 200 vaccine shots per day.[7] On the other hand, patients can be in contact with 200 persons per day until isolation, even if they are not infected. However, among 200 persons, the number of potential

Fig. 2. Mass vaccination

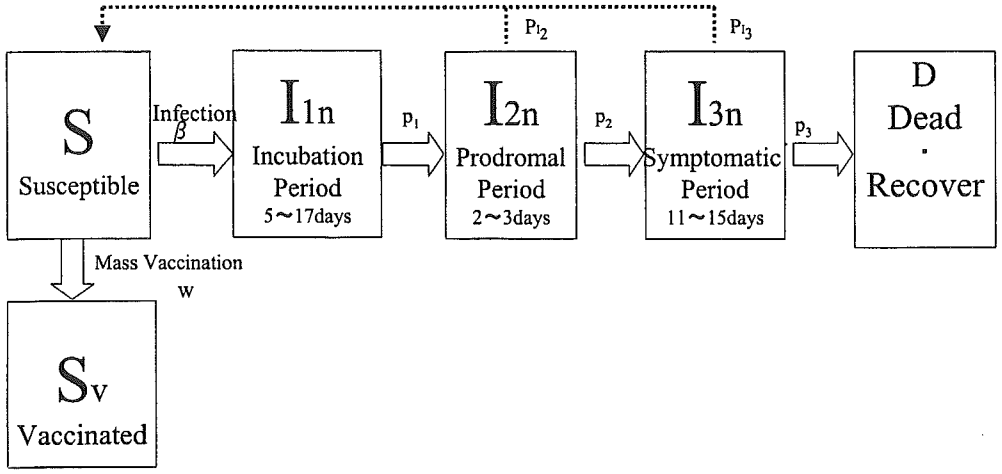
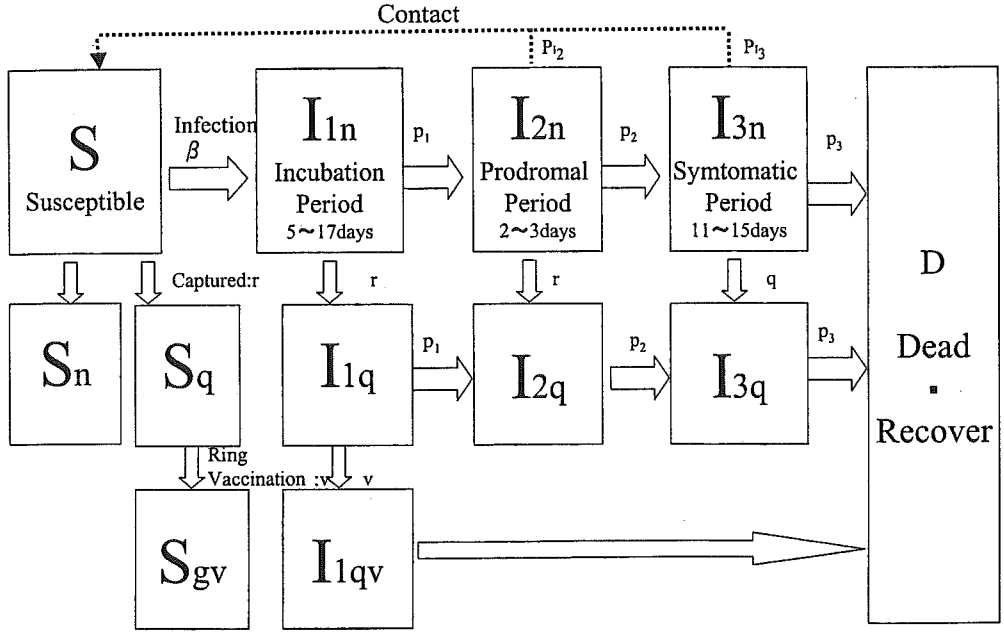


Fig. 3. Ring vaccination



susceptibles who were born after 1976 is just 50 persons. This contact number seems high, although it has been used in previous research.[7] In fact, in the episode in which a SARS-infected tourist visited Japan,[11] the public health authority had traced more than 200 contacts per day. Therefore 200 contacts per day seems to be a somewhat moderate number in our experience.

In the ring vaccination, 200 vaccine shots can be performed per day per public health worker, but the workers have to trace the contacts. Because tracing probably needs more human resources than these required for vaccine shots only, we assume that each public health worker can trace two persons per day.

Mathematical model

The mathematical model consists of the components, shown in Figs. 1–3, and the equations shown in the Appendix. Several population types are summarized in the Table in the Appendix. It is notable that, because those who recover and those who die will not again be in the susceptible population, they are identical from the model's perspective.

The non-contacted susceptible population (see Appendix) are those who do not contact with the infected population, those who contact with the infected population are removed from this category. The contacted persons are classified into four types. Namely, they must be either infected or not and either quarantined or not. Non-infected and quarantined people cannot be infected during the isolation. If they are not quarantined, they are as susceptible as non-contacted susceptible persons. The infected contacts do not have any infectious power during isolation, but if they are not quarantined, they have infectious power.

If no countermeasures are adopted. The number of newly infected persons is determined by the number of the non-isolated and infected contacts in the prodomal or symptomatic period, and R_0 multiplied by the proportion of

susceptibles in the total population ($\beta S(t)$). The symbols in parenthesis here are defined in the Appendix. We note that R_0 means the number of newly infected persons in total if contacts are all susceptible, and, thus, it is the sum of newly infected persons day by day. In other words, the number of persons newly infected from one patient is described as the product of infectious power in each stage of the prodomal or symptomatic period, and R_0 ($p_{I_2}(s)R_0$ and $p_{I_3}(s)R_0$). Equations for $S(t)$ (Eq. 1 in Appendix) or $I_{1n}(1, t)$, $I_{1qv}(1, t)$, $I_{1q}(1, t)$ (see Appendix) contain them.

The process is then developed into the next stage following the transition probability ($p_1(s)$, $p_2(s)$ or $p_3(s)$), and the remainder add 1 day within each stage. For instance, patients who are in the incubation period s days after the infection move to the prodomal stage at $p_1(s)$, and remain in the incubation period at $1 - p_1(s)$. Similarly, patients who are in the symptomatic period s days after the infection move to the dead or recovery stage at $p_3(s)$ or they remain in the symptomatic period at $1 - p_3(s)$. Besides $100q$ percent of patients in the symptomatic period are hospitalized and quarantined every day and, thus, they lose infectious power.

In ring vaccination, the public health authorities have to trace contacts, quarantine them, and perform shot vaccinations. We assume that they conduct contact tracing and isolation first. Thus, if there are many more contacts than there are staff of the public health authority, there may be some people who are not vaccinated even though they are quarantined. If more than 10000 contacts were to occur, the public health authority could not trace all contacts in 1 day, and, thus, some patients would not be isolated. Needless to say, this would depend on the size of the outbreak. Conversely, in mass vaccination, contact tracing is not required, and so the public health authorities can administer shots to 1 million persons per day. In Eq. 26 in the Appendix, the number of mass vaccinations per day per worker is described and W.

In the equations, the contacts (C) multiplied by the number of newly infected persons, divided by two multiplied by the number of public health workers is the rate of contacts captured (r). If this ratio is more than 1, r is limited to 1, and the remainder, which is the number of newly infected persons minus two times the number of public health workers, and not traced on that day. Even if this ratio is smaller than 1, but close to 1, some contacts captured by the health workers may not receive a vaccine shot. Formally, the proportion of ring vaccinations per day (v) is determined by

$$v = \frac{c \times \text{number of newly infected persons}}{200 \times \left(\begin{array}{l} 2 \times \text{number of public health workers} - \\ c \times \text{number of newly infected} \end{array} \right)}$$

Conversely, the number of mass vaccinations per day per worker is denoted by W, which is 200 times the number of public health workers.

Table 2. Setting of intervention model

Parameters	Setting	Sources
R_0	3,5,10	Previous research[5–8,11]
Starting day of intervention	30,45,60	Previous researh[5]
Number of initial-exposure cases	1000	Assumption

Starting day of intervention is defined as the number of days from the day that the initial-exposure case was exposed

Outcome indicator of control measures

We focus only on the cumulative number of patients, as the indicator of the outcome of control measures. In other words, we ignore the total number of deaths, even though this would seem to have a greater impact, because this number seems to be a proportion of the cumulative number of patients. Therefore a countermeasure that can avoid more patients than an other, alternative, measure is called effective.

Sensitivity analysis

We performed sensitivity analysis of the parameters summarized in Table 2, so as to confirm the robustness of the model and to take uncertainty of the parameters into consideration. Namely, R_0 values are assumed to be 3, 5, and 10, as used in previous research,[5–8,10] in addition to the base case. R_0 values of more than 5 were also used in previous research (S. Tokunaga: The research for technological foundation from the viewpoint of precautionary medicine [unpublished manuscript]; 2003). As an intervention parameter, the starting date is assumed to be 30, 45, and 60 days after the initial case was exposed. The number of initial-exposed cases is assumed to be 1000, as in previous research,[5] in addition to the base case.

Results

Figure 4 shows the estimated epidemic curve, which is the number of newly infected persons, in the base case, without any intervention. On the first day, one person is infected. Then there is no new patient during the incubation period of a few days in the first case. After that, the initial case has infectious power, and there is some probability of new cases. Note that, since R_0 is 1.5, and infectiousness is distributed among more than 10 days, the probability of a new infection is less than 0.2 in the earlier stage. From that time, second or third infections occur, and the number grows exponentially. The cumulative number of patients reached 122 on the final day, day 160 (Fig. 3).

Though it is not shown in Fig. 3, the peak came 2 years after the initial case was exposed, and the total number of patients reached about 17 million. Needless to say, if some intervention policy were to be implemented the course of

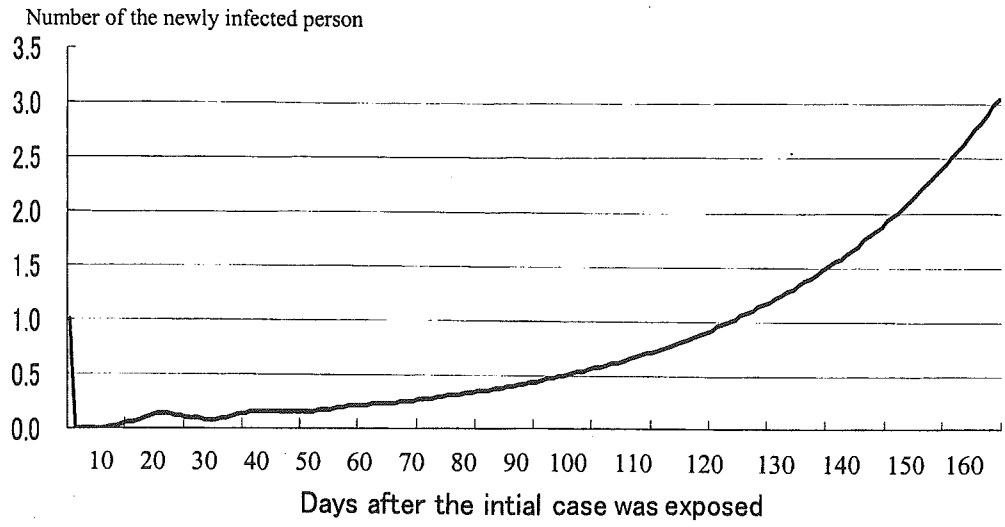


Fig. 4. Number of the newly infected person (without any intervention)

Table 3. Estimated numbers of infected persons in the mass-vaccination scenario

R_0	Number of people with initial exposure	Starting day of intervention	Number of patients			Number of vaccinations
			3 Months	6 Months	1 Year	
1.5	1	30	5.64	5.65	5.65	3.00×10^7
1.5	1	45	9.02	9.07	9.07	3.00×10^7
1.5	1	60	13.1	14.0	14.0	3.00×10^7
3	1	30	23.9	23.9	23.9	3.00×10^7
3	1	45	66.9	69.1	69.1	3.00×10^7
3	1	60	156	197	197	3.00×10^7
5	1	30	98.7	100	100	3.00×10^7
5	1	45	441	481	481	3.00×10^7
5	1	60	1.47×10^3	2.31×10^3	2.31×10^3	3.00×10^7
10	1	30	1.04×10^3	1.10×10^3	1.10×10^3	3.00×10^7
10	1	45	8.68×10^3	1.12×10^4	1.12×10^4	3.00×10^7
10	1	60	4.54×10^4	1.12×10^5	1.12×10^5	2.99×10^7
1.5	1000	30	5.64×10^3	5.65×10^3	5.65×10^3	3.00×10^7
1.5	1000	45	9.01×10^3	9.07×10^3	9.07×10^3	3.00×10^7
1.5	1000	60	1.31×10^4	1.40×10^4	1.40×10^4	3.00×10^7
3	1000	30	2.38×10^4	2.39×10^4	2.39×10^4	3.00×10^7
3	1000	45	6.67×10^4	6.89×10^4	6.89×10^4	2.99×10^7
3	1000	60	1.55×10^5	1.95×10^5	1.95×10^5	2.98×10^7
5	1000	30	9.81×10^4	9.93×10^4	9.93×10^4	2.99×10^7
5	1000	45	4.30×10^5	4.66×10^5	4.66×10^5	2.95×10^7
5	1000	60	1.39×10^6	2.01×10^6	2.01×10^6	2.79×10^7
10	1000	30	9.57×10^5	1.00×10^6	1.00×10^6	2.89×10^7
10	1000	45	5.58×10^6	5.96×10^6	5.96×10^6	2.40×10^7
10	1000	60	1.54×10^7	1.60×10^7	1.60×10^7	1.38×10^7

Number of patients (3 months/6 months/1 year) indicates the estimated number of patients at 3 months, 6 months, or 1 year after the initial case was exposed

prevalence would be affected and control may be achieved by adopting appropriate countermeasures such as quarantine and vaccination.

Table 3 summarizes the results for mass vaccination. Table 4 shows the results for ring vaccination. Each Table has 24 patterns of combinations of different R_0 values, and shows the number of initial-exposure cases, and the starting date of intervention. The numbers of patients in Tables 3 and 4 indicate the estimated numbers of patients 3 months, 6 months and 1 year after the initial case was exposed, and the necessary number of vaccination shots to be given.

In general, comparing Table 3 and Table 4, the total number of patients in the ring-vaccination scenario is smaller than that in the mass vaccination scenario for all patterns. Mass vaccination needs almost 30 million vaccine doses. Conversely, the necessary number of vaccine doses for ring vaccination is much smaller than that required for mass vaccination. If there is a larger number of initial cases, higher R_0, and later start of intervention by the public health authority, more than 24 million vaccine doses are necessary. In such a scenario, mass vaccination is preferable to ring vaccination.

Table 4. Estimated numbers of infected persons in the ring-vaccination scenario

R_0	Number of people with initial exposure	Starting day of intervention	Number of patients			Number of vaccinations
			3 Months	6 Months	1 Year	
1.5	1	30	2.30	2.30	2.30	68
1.5	1	45	4.20	4.20	4.20	101
3	1	30	3.82	3.82	3.82	140
3	1	45	11.7	11.7	11.7	395
3	1	60	34.1	34.1	34.1	1.12×10^3
5	1	30	6.21	6.21	6.21	244
5	1	45	30.6	30.6	30.6	1.15×10^3
5	1	60	147	147	147	5.52×10^3
10	1	30	14.0	14.0	14.0	549
10	1	45	143	143	143	5.47×10^3
10	1	60	1.45×10^3	1.45×10^3	1.45×10^3	5.53×10^4
1.5	1000	30	2.35×10^3	2.35×10^3	2.35×10^3	0.55×10^5
1.5	1000	45	4.35×10^3	4.35×10^3	4.35×10^3	0.98×10^5
1.5	1000	60	7.33×10^3	7.33×10^3	7.33×10^3	1.72×10^5
3	1000	30	4.34×10^3	4.34×10^3	4.34×10^3	1.64×10^5
3	1000	45	1.62×10^4	1.62×10^4	1.62×10^4	7.93×10^5
3	1000	60	6.26×10^4	6.30×10^4	6.30×10^4	3.31×10^6
5	1000	30	8.97×10^3	8.97×10^3	8.97×10^3	4.26×10^5
5	1000	45	1.04×10^5	1.05×10^5	1.05×10^5	5.58×10^6
5	1000	60	8.27×10^5	1.37×10^7	2.12×10^7	1.81×10^7
10	1000	30	1.31×10^5	2.63×10^5	2.65×10^5	1.37×10^7
10	1000	45	9.82×10^6	2.91×10^7	2.91×10^7	3.32×10^6
10	1000	60	1.98×10^7	2.92×10^7	2.92×10^7	6.91×10^5

Number of patients (3 months/6 months/1 year) indicates the estimated number of patients at 3 months, 6 months, or 1 year after the initial case was exposed

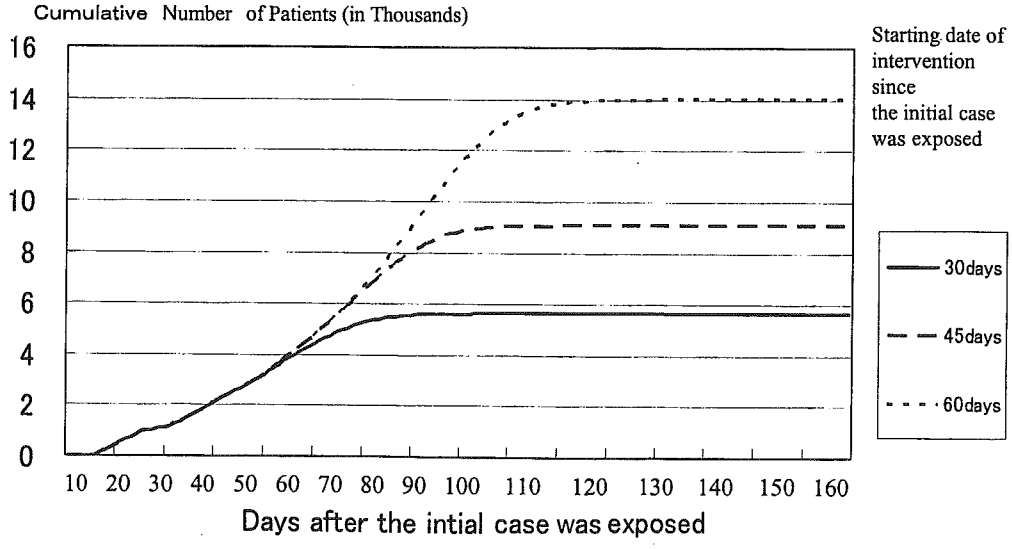


Fig. 5. Cumulative number of patients in the mass-vaccination scenario (R_0 = 1.5, number of initial-exposed cases = 1000)

Figure 5 illustrates the movement of the cumulative number of patients in the mass vaccination scenario where, R_0 = 1.5, and where the number of initial-exposure cases is 1000. It clearly shows that the total number of patients would reach 14000 if intervention was delayed. Even if the public health authority could start intervention within 30 days after the initial case was exposed, the total number of patients would exceed 5000. On the other hand, as shown in Fig. 6, ring vaccination can dramatically reduce the total number of patients. Namely, even in the worst case of delay, the total number of patients would be lower than 7000. If the public authority could start intervention within 30 days and it adopted ring vaccination, the total number of patients may be constrained to less than 2500. Therefore, we can conclude that ring vaccination is more effective when R_0 = 1.5 and the number of initial-exposure cases is 1000.

Figure 7 shows such relationships in more detail. The upper areas of the declining lines indicate that for the combination of R_0 and number of initial-exposure cases, mass vaccination is more effective than ring vaccination. The blue line indicates the combination in the scenario in which the starting date of intervention is 30 days after the initial case was exposed. The pink line and yellow line indicate the combinations for 45 and 60 days, respectively. Obviously,

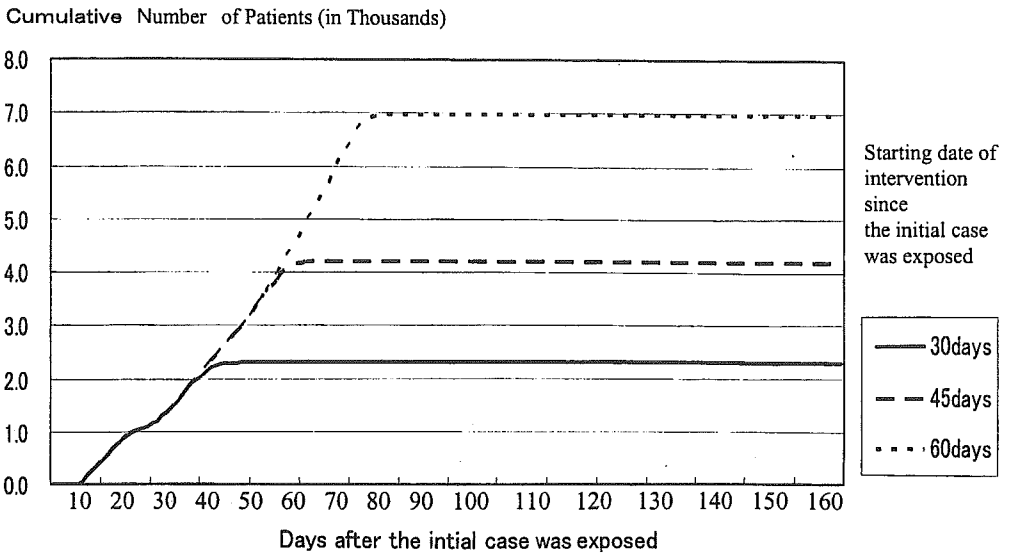


Fig. 6. Cumulative number of patients in the case of ring vaccination scenario (R_0 = 1.5, number of initial-exposed cases = 1000)

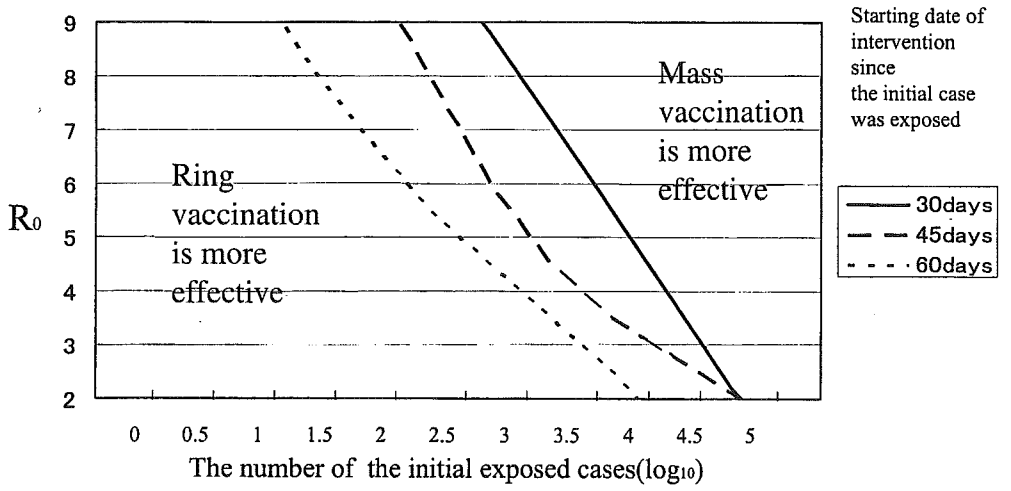


Fig. 7. Comparison of the two control measures

the later the intervention starts, the wider the area on the graph would be where mass vaccination is more effective. For instance, if the R_0 value is 9 and the number of initial-exposure cases is more than ten, mass vaccination would be more effective.

Discussion

We have considered, according to a mathematical model, which control measure, mass vaccination or ring vaccination, would be more effective to contain an epidemic of smallpox. We found that, if R_0 is higher, the number of initial-exposure cases is greater, or if the starting of intervention is delayed, the probability that mass vaccination is more effective than ring vaccination rises.

These results are qualitatively consistent with those in a previous study,[7] but, quantitatively, there are large differences. Namely, the previous research found that, even if R_0 was 1, and the number of initial-exposure cases was less than 15, or if R_0 was 1.3 and the number of initial-exposure cases was 1, mass vaccination was more effective than ring vaccination. In our results, ring vaccination was definitely more effective with these parameters. On the other hand, if R_0 is 2 and the number of initial-exposure cases is 1, our result shows that ring vaccination is more effective, whereas the previous research concluded the opposite.

These two studies (i.e., the study reported by Kaplan et al.,[7] and our present study) share a similar model framework and parameter settings, but there is a difference between them. In their study,[7] the difference in the numbers of vaccinations represents only the difference between mass vaccination and ring vaccination. Besides, the ratio of the number of vaccinations in the mass- and ring-vaccination scenarios was fixed, as 3:1. In other words, they[7] assumed that the public health authorities traced and captured contacts and then administered vaccination shots, and after that, they started searching for other contacts. On the other hand, we propose that the public health authorities trace

and capture contacts and then quarantine them, and after that, they start searching for other contacts. Vaccination is performed for the quarantined contacts after all contacts have been captured, because isolation stops further infections. Of course, vaccination can reduce the probability of disease onset in the infected period but not in the incubation period. This difference between the two models expands the area of the graph (Fig. 7) where ring vaccination is more effective than mass vaccination.

We have accounted for limitations in the numbers of public health workers and for priority setting for isolation and vaccination in the scenario for ring vaccination, factors that were not taken into account in the previous research.[7] Therefore, our model seems to be more appropriate and realistic. Moreover, the results in the previous research[7] that mass vaccination was more effective in regard to almost all parameters seems counter-intuitive. In this sense, our results may be more reliable.

Even though the value assumed for R_0, the number of the initial-exposure cases, and the natural history probably make sense, because these numbers have also been adopted in other studies and they depend on the biological characteristics of the virus or on the type of terrorist action, there is no evidence in Japan about the starting date of intervention, the human resources of the public health authorities, or other parameters of policy action. We have simply borrowed these parameters from previous studies in other countries and so we have assumed that there are no differences among policies or the human resources of the public health authorities between these other countries and Japan. We examined the sensitivity of the starting date of intervention, and it can be seen that it affected the epidemic curve dramatically, as shown in Figs. 5 and 6. Unfortunately, there is no official documentation of a detailed action plan in the case of a bioterrorism attack or of past experience in a similar situation. Therefore, we have to keep this point in mind when we interpret the results. We also have to emphasize that obtaining reliable parameters of policies in Japan is an important task for further studies. For instance, the experience of contact tracing, when a SARS patient visited Japan in May 2003, may provide good data for such studies.[11]

Moreover, we also need to mention the interpretation of our findings. As we limited the total number of patients as an outcome measure, we may have ignored important aspects of countermeasures. For instance, adverse effects of vaccination,[12,13] psychological disorders due to the isolation of contacts,[14] and so on. Therefore, our conclusion, which focuses only on the number of patients, may be biased if such ignored aspects are more important than the aspects we focused on. In principle, we have to evaluate all aspects of policy in their entirety but this seems to be a very difficult task, and it may be the next necessary step in this field. At least, we remind that this conclusion reflect only total number of patients when we interpret it.

Moreover, we have to take into account the heterogeneous population distribution or spatial spread of disease due to the movement of infected persons to evaluate movement restrictions or other control measures, even though we have considered uniform and homogenous population distribution in our model.

Moreover, if the number of vaccination doses is severely limited, we have to choose either ring vaccination or priority vaccination for medical staff and public health workers. A mathematical model could provide the answers to those questions and such a model will be one of the most important issues for the planning of measures to be taken in the event of a bioterrorism attack.

Furthermore, though we ignored about 90 million people who were born before 1976 and were vaccinated before 1980, we have to take them into account. They may keep their immunity, protecting them from infection. They may play a key role in the control measures.

Acknowledgments This research was founded by Health and Labour Science Research Grants in 2003 for Special Research, titled "Extensive Coordination among Government Offices and Medical Institutions for Large Scale Outbreak", headed by Dr. I. Okubo, Tsukuba University. We thank Mr. Kunio Tsuyuhara, Osaka University, and Ms. Tamie Sugawara, Tsukuba University, for their helpful research assistance. Needless to say, any remaining errors are ours.

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Appendix

Classification of population	Symbol
Non-contacted susceptible (unvaccinated)	$S(t)$
Non-contacted susceptible (vaccinated)	$S_v(t)$
Recovered or dead	$D(t)$
Non-infected contacts quarantined (vaccinated)	$S_{qv}(s,t)$
Non-infected contacts quarantined (unvaccinated)	$S_q(s,t)$
Non-infected contacts unquarantined (susceptible)	$S_n(s,t)$
Infected contacts unquarantined in incubation period	$I_{1n}(s,t)$
Infected contacts unquarantined in prodromal period	$I_{2n}(s,t)$
Infected contacts unquarantined in symptomatic period	$I_{3n}(s,t)$
Infected contacts quarantined in incubation period who are vaccinated	$I_{1qv}(s,t)$
Infected contacts quarantined in incubation period who are not vaccinated	$I_{1q}(s,t)$
Infected contacts isolated in prodromal period	$I_{2q}(s,t)$
Infected contacts isolated in symptomatic period	$I_{3q}(s,t)$
R_0/population	β
Distribution of infectiousness in day s of prodromal period	$p_{I_2}(s)$
Distribution of infectiousness in day s of symptomatic period	$p_{I_3}(s)$
Probability of transition from day s of incubation period to prodromal	$p_1(s)$
Probability of transition from day s of prodromal period to symptomatic	$p_2(s)$
Probability of transition from day s of symptomatic period to death or recovery	$p_3(s)$
Rate of ring vaccinations per day	v
Number of mass vaccinations per day per worker	W
Number of contacts per day	C
Rate of infected persons captured	q
Rate of contacts captured	r

Transition of non-contacted unvaccinated susceptible persons

$$S(t) = \left(1 - \sum_{s=1}^{N_2} p_{I_2}(s)\beta I_{2n}(s,t-1)\right)S(t-1) - C\sum_{s=1}^{N_2} I_{2n}(s,t) \tag{1}$$

$$+ (1-r)\left(1 - \beta\left(\sum_{s=1}^{N_2} p_{I_2}(s)I_{2n}(s,t-1)\sum_{s=1}^{N_3} p_{I_3}(s,t-1)\right)\right)S_n(N_1+N_2,t)$$

$$+ S_{qv}(N_1+N_2,t-1) - W + S_q(N_1+N_2,t-1) \tag{2}$$

Transition of those who recover of die

$$D(t) = D(t-1) + (1-r)(1-q)\sum_{s=1}^{N_3} p_3(s)I_{3n}(s,t-1) + \sum_{s=1}^{N_3} p_3(s)I_{3q}(s,t-1) \tag{3}$$

Transition of non-infected quarantined contacts who are vaccinated

$$S_{qv}(1,t) = v\sum_{s=1}^{N_3} rq\Big(C - p_{I_3}(s)\beta\big(S(t-1)\tag{4}$$

$$+ \sum_{j=1}^{N_1+N_2} S_n(j,t-1)\big)\Big)I_{3n}(s,t-1) + r\sum_{s=1}^{N_1} S_n(s,t-1) \tag{5}$$

$$S_{qv}(s,t) = S_{qv}(s-1,t-1) + eI_{1qv}(s-1,t-1) + vS_q(s-1,t-1) \qquad (s=2,\ldots,N_1) \tag{6}$$

(7)

Transition of non-infected unquarantined contacts who are susceptible

$$S_n(1,t) = \sum_{s=1}^{N_3}(1-rq)\Big(C - p_{I3}(s)\beta\big(S(t-1)\big) + \sum_{i=1}^{N_1+N_2} S_n(i,t-1)\big)\Big)I_{3n}(s,t-1) \tag{8}$$

$$S_n(s,t) = (1-r)\left(1 - \beta\left(\sum_{i=1}^{N_2} p_{I_2}(i)I_{2n}(i,t-1) + \sum_{i=1}^{N_3} p_{I_3}I_{3n}(i,t-1)\right)\right)S_n(s-1,t-1) \qquad (s=2,\ldots,N_1) \tag{9}$$

Transition of infected contacts, quarantined in incubation period, who are vaccinated

$$I_{1qv}(1,t) = rqv\beta\left(S(t-1) + \sum_{i=1}^{N_1+N_2} S_n(i,t-1)\right)\sum_{i=1}^{N_3} p_{I_3}I_{3n}(j,t-1) + rI_{1n}(1,t-1) \tag{10}$$

$$I_{1qv}(s,t) = \big(1 - p_1(s-1)\big)(1-e_0)I_{1qv}(s-1,t-1) + rI_{1n}(s-1,t-1)$$

$$+ \big(1 - p_1(s-1)\big)vI_{1q}(s-1,t-1) \qquad (s=2,\ldots,N_1) \tag{11}$$

Transition of infected contacts who are not quarantined in incubation period

$$I_{1n}(1,t) = (1-r)\beta\sum_{j=1}^{N_3}\left(\sum_{i=1}^{N_2} pI_2(i-1)I_{2n}(i-1,t-1)\right) + \sum_{i=1}^{N_3} p_{I_3}(i-1)I_{3n}(i-1,t-1)S_n(j,t-1)$$
$$+ (1-qr)\sum_{j=1}^{N_2} pI_3(j)\beta\left(S(t-1) + \sum_{i=1}^{N_1+N_2} S_n(i,t-1)\right)I_{3n}(j,t-1) + \beta p_{I_2} I_{2n}(i,t-1)S(t-1) \quad (12)$$

$$I_{1n}(s,t) = (1-r)\left(1-p_1(s-1)\right)I_{1n}(s-1,t-1) \qquad (s=2,\ldots,N_1) \quad (13)$$

Transition of infected contacts who are not isolated in prodromal period

$$I_{2n}(1,t) = (1-r)\sum_{i=1}^{N_1} p_1(i)I_{1n}(i,t-1) \quad (14)$$

$$I_{2n}(2,t) = (1-r)\left(1-p_2(1)\right)I_{2n}(1,t-1) \quad (15)$$

Transition of infected contacts who are not isolated in symptomatic period

$$I_{3n}(1,t) = (1-r)\sum_{i=1}^{N_2} p_2(i)I_{2n}(i,t-1) \quad (16)$$

$$I_{3n}(s,t) = (1-r)(1-q)\left(1-p_3(s)\right)I_{3n}(s-1,t-1) \qquad (s=2,\ldots,N_3) \quad (17)$$

Transition of non-infected quarantined contacts who are not vaccinated

$$S_q(1,t) = (1-v)rq\sum_{i=1}^{N_3}\left(C - \beta p_{I_3}(i)\left(S(t-1) + \sum_{j=1}^{N_1+N_2} S_n(j,t-1)\right)\right)I_{3n}(j,t-1) \quad (18)$$

$$S_q(s,t) = (1-v)S_q(s-1,t-1) \qquad (s=2,\ldots,N_1) \quad (19)$$

Transition of infected contacts, quarantined in incubation period, who are not vaccinated

$$I_{1q}(1,t) = (1-v)rq\beta\sum_{i=1}^{N_3} p_{I_3}(i)\left(S(t-1) + \sum_{j=1}^{N_1+N_2} S_n(j,t-1)\right)I_{3n}(j,t-1) \quad (20)$$

$$I_{1q}(s,t) = \left(1-p_{I_1}(s)\right)(1-v)I_{1q}(s-1,t-1) \qquad (s=2,\ldots,N_1) \quad (21)$$

Transition of infected contacts isolated in prodromal period

$$I_{2q}(1,t) = \sum_{s=1}^{N_1} p_{I_1}(s)(1-v)I_{1q}(s-1,t-1) \quad (22)$$

$$I_{2q}(2,t) = \left(1-p_{I_2}(s)\right)(1-v)I_{2q}(1,t-1) \quad (23)$$

Transition of infected contacts isolated in symptomatic period

$$I_{3q}(1,t) = \sum_{i=1}^{N_2} p_2(i)I_{2q}(i,t-1) + r\sum_{i=1}^{N_2} p_2(i)I_{2n}(i,t-1) \quad (24)$$

$$I_{3q}(s,t) = \left(1-(1-r)(1-q)\right)I_{3n}(s-1,t-1) + \left(1-p_3(s-1)\right)I_{3q}(s-1,t-1) \qquad (s=2,\ldots,N_3) \quad (25)$$

Transition of non-contacted susceptible persons who are vaccinated in mass-vaccination scenario

$$S_v(t) = W + S_v(t-1) \quad (26)$$

Experimental Surveillance Using Data on Sales of Over-the-Counter Medications — Japan, November 2003–April 2004

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Disclosure of relationship: The contributors of this report have disclosed that they have no financial interest, relationship, affiliation, or other association with any organization that might represent a conflict of interest. In addition, this report does not contain any discussion of unlabeled use of commercial products or products for investigational use.

Abstract

Objectives: *This report describes a study to explore the possibility of using data on sales of over-the-counter (OTC) medications as part of a routine syndromic surveillance system aimed at early detection of infections of public health concern. A retrospective evaluation was conducted of sales of OTC medications used to treat the common cold. This report discusses the correlation of these data to influenza activity in Japan during the 2003–04 influenza season and evaluates the potential of using such data to predict influenza epidemics.*

Methods: *Data from approximately 1,100 pharmacies throughout Japan collected during November 2003–April 2004 were analyzed. OTC sales data were compared with influenza incidence data (one weekly and two daily data sets) to determine correlations and predictability. Adjusted R-square was used as an index of goodness-of-fit in the estimation. Data reflecting daily influenza activity were obtained from the National Surveillance of Daily Influenza Outpatients and the Mailing List–Based Influenza Epidemic Database. National sentinel surveillance data for influenza from approximately 5,000 sites nationwide also were analyzed.*

Results: *Although a correlation was demonstrated between sales of OTC medications used to treat the common cold and concurrent influenza activity, analysis of sales data alone was not sufficient to determine influenza activity in advance even when sales promotion effects were excluded from the analysis.*

Conclusion: *Because visiting a health-care provider costs more than purchasing OTC medications, the hypothesis was formed that an ill person will purchase OTC medications first and visit a physician only if the condition does not resolve or worsens. The results of this study do not provide any clear evidence to support this hypothesis. For this reason, OTC sales do not appear to be a good candidate for a national real-time detection system for influenza epidemics in Japan.*

Introduction

In 2000, the first syndromic surveillance prototype in Japan was initiated by the Japanese Ministry of Health, Labour, and Welfare (MHLW) in the Kyushu area during the G-8 summit meeting to assist in the early detection of an act of biologic terrorism or an unusual cluster of tropical diseases imported by travelers from tropical areas (*1*). This limited-scale surveillance involved 17 medical institutes in two prefectures for <1 month. Data for the surveillance system were reported through facsimile transmissions for five syndromic categories (i.e., respiratory, gastrointestinal, neurological, cutaneous-mucous membrane-bleeding, and nonspecific). The second (and the first nationwide) syndromic surveillance system was implemented during May 20–July 14, 2002, in connection with the Japan-Korea 2002 World Cup soccer games. The Internet-based surveillance, which was conducted by MHLW and the Infectious Disease Surveillance Center of the National Institute of Infectious Diseases (NIID), grouped hospitalized patients by symptoms into the same five syndromic categories used in 2000. Both ad hoc syndromic surveillance systems operated during high-profile events and were conducted successfully, and their data were matched with those diseases with the same clinical features that were collected later by routine national surveillance. For example, this second ad hoc syndromic surveillance detected a cluster of viral meningitis and a regional outbreak of measles successfully, thereby illustrating the potential of these data in assisting with early detection of disease. However, further improvements are required to detect pandemic influenza or a possible biologic terrorist attack in time to minimize its consequences.

The goal of the early detection syndromic surveillance system is to conduct routine (not ad hoc) surveillance that complements existing surveillance systems and to detect increases in the number of patients before they report to hospitals with severe conditions. Data concerning sales of

over-the-counter (OTC) medications, emergency department (ED) visits, ambulance calls, and other factors were assessed as tentative candidates for early detection of disease outbreaks [2,3]. Because no routine syndromic surveillance for respiratory syndrome had been conducted previously in Japan, the effectiveness of OTC surveillance in early detection was compared with multiple influenza surveillance systems that were already in place. This report presents interim findings from the OTC sales surveillance.

Methods

Data Source

Commercially available data collecting reported daily sales of OTC medications in all forms (e.g., tablets, powder, granules, and syrup) used to treat the common cold from 1,100 pharmacies throughout Japan were obtained. So-called combination or general common-cold medications were chosen for examination because use of such medications has long been accepted in Japanese society as the first and most common treatment for influenza-like illness (ILI). These medications usually consist of a combination of antipyretic analgesics (e.g., acetaminophen or ibuprofen), antitussives (e.g., dihydrocodeine phosphate or noscapine), expectorants (e.g., bromohexine hydrochloride, guaifenesin, or potassium guaiacolsulfonate), exogenous enzyme (e.g., lysozyme chloride), bronchodilator (e.g., dl-methylephedrine hydrochloride), antihistaminics (e.g., carbinoxamine maleate or mequitazine), vitamins (e.g., vitamin B1, B2, or vitamin C), and others (e.g., herbal medicines or caffeine). The category also includes combined herbal medicines that are licensed for common cold treatment.

Data were collected by a private marketing company from randomly chosen pharmacies covering approximately 2.0% of the 50,000 pharmacies in Japan. The influenza season was defined as November–April. Sales data collected during November 2003–April 2004 were subjected to retrospective analysis to examine the suitability of OTC sales surveillance for early detection of unexpected rare events. OTC sales data were compared with reliable sentinel surveillance data for influenza collected during November 2003–April 2004 by the National Epidemiological Surveillance of Infectious Diseases (NESID) and with data on influenza activity collected daily by two other surveillance systems from clinics, hospitals, and health-care providers. In Japan, sentinel reporting of clinical cases of ILI is mandatory, with or without laboratory tests or confirmation. Data (e.g., the number of influenza outpatients, by age and age group) are collected weekly from 5,000 sentinel surveillance sites (including 3,000 pediatricians and 2,000 internal medicine clinics or departments) nationwide covering one tenth of all clinics and hospitals in Japan for all influenza-related visits. Two daily influenza activity information sources are 1) reported numbers of cases of ILI reported by the National Surveillance of Daily Influenza Outpatients (Daily Case Reporting [DCR]), which collects data from 10% of selected sentinel medical institutions and 2) voluntary reporting by clinicians to the Mailing List–Based Influenza Epidemic Database (MLflu). DCR is operated by NIID and began operating in January 2004 for the 2003–04 influenza season; it collects data regarding the number of outpatients who received a diagnosis of ILI either clinically or by diagnostic test from 500 sentinel sites in clinics and hospitals. Date of onset is not included in the reported data, which makes this surveillance vulnerable to the-day-of-the-week effect (i.e., few patient visits reported during the weekend and more on the following Monday). MLflu is operated by volunteer pediatricians and began operating in December 2003 for the 2003–04 influenza season; it collects data from approximately 350 pediatricians regarding outpatients who have received a diagnosis of influenza by rapid test. Cases reported through MLflu are more likely to reflect actual influenza activity. Date of onset is reported, so the surveillance system is free from the-day-of-the-week effect. However, because reporting is voluntary, the number and representativeness of participants varies during the influenza season.

Analysis

A model was created to estimate influenza activity from the OTC sales information during a 6-month period, as follows:

$$\log(\text{influenza activity in period } t) = \alpha + \beta \log(\text{OTC sales in period } t\text{-}j) + \varepsilon$$

OTC sales data were then adjusted for the-day-of-the-week effect and compared with three other different influenza activity surveillance systems (sentinel surveillance, DCR, and MLflu) to examine the number of lead-days by OTC sales. The adjusting procedure consisted of two steps, as follows:

$$\text{Adjusted OTC sales in period 1} = \text{Replaced OTC sales in period 1}$$

$$\text{Adjusted OTC sales in period } t = \frac{2k}{k(k+1)}\,\text{Replaced OTC sales in period } t + \sum_{j=1}^{k-1} \frac{2(k-j)}{k(k+1)}\,\text{Adjusted OTC sales in period } t\text{-}j \quad \text{for } t > 1 \text{ and } t \leq 6$$

$$\text{Adjusted OTC sales in period } t = 7/28 \text{ Replaced OTC sales in period } t + \sum_{j=1}^{6} \frac{(7-j)}{28} \text{ Adjusted OTC sales in period } t\text{-}j \quad \text{for } t > 6.$$

The data set was adjusted by replacing data for weekends, holidays, and the day before and after weekends or holidays with data for the nearest preceding nonholiday weekday. Then the replaced data were smoothed to the past by taking a moving average from the current period to 1 week previous, giving a relatively heavier weight to the nearer days, and gradually reducing the weight for the far past. Although this adjusting procedure did not require future data, the adjustment result might be affected (pulled) from the data used for the replacement and smoothing procedure.

Comparative analysis of OTC sales with one weekly and two daily data sets recording influenza incidence was performed to determine correlations and predictability. Adjusted R-square was used as an index of goodness-of-fit in the estimation.

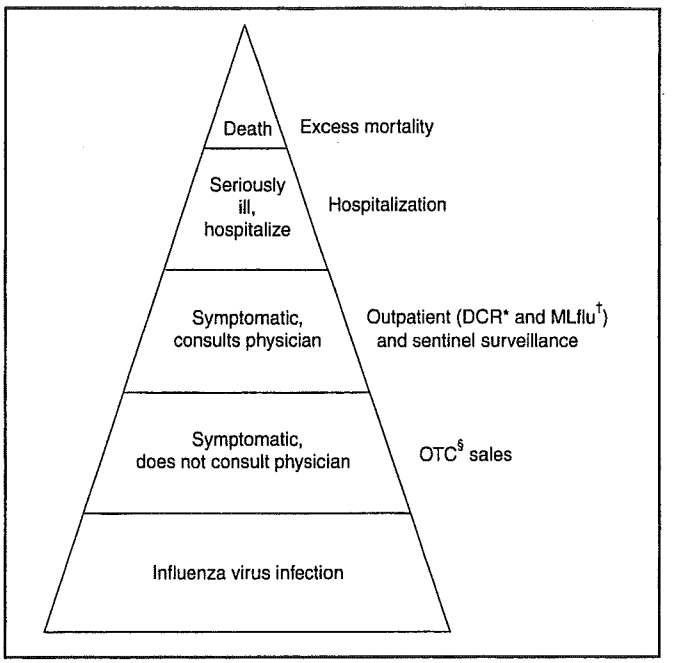
Results

Because national surveillance data do not capture the number of persons who consult a health-care provider for general respiratory symptoms, data regarding consultations for influenza symptoms were used as a substitute to assess lead time of OTC information. Influenza surveillance in Japan was designed to report all potential influenza patients from at least one system for robust detection of influenza activity other than hospitalization (Figure 1). The case definition of influenza used for both outpatient sentinel surveillance and DCR was based on clinical symptoms, which resulted in reporting of patients with ILI.

For this analysis, the hypothesis used was that the majority of persons who were infected by influenza virus and who experienced mild symptoms would choose to self-treat with OTC medications and that those persons whose condition subsequently became more serious would then consult a physician later. Data of sales of OTC medications used to treat the common cold, readily provided as commercial databases, were assumed to reflect the population of preclinical visits by persons with ILI. Data on outpatient visits were represented by sentinel surveillance, DCR, and MLflu. An increase in OTC sales of medications used to treat the common cold was assumed to indicate an initial increase of ILI, and the lead time of the sales to the influenza activity was expected to be observed.

OTC sales per pharmacy were tracked, and the time trend of sales per pharmacy, which was adjusted for the-day-of-the-week effect and then smoothed, was given as a line (Figure 2). Multiple peaks of different size were observed during the 5-month surveillance period, with the consistent underlining trend being that sales were higher in winter and decreased toward spring. Peaks observed were in early and mid-December, early February, and late March. The third peak observed occurred during late January–early February and corresponded with the peak of ILI sentinel reporting generally recorded during influenza seasons; a subsequent period of decline toward spring was also matched. However, the pattern of the early influenza season was fairly discrete between the two data sets (Figure 3).

FIGURE 1. Relationship of influenza status and influenza-related surveillance



* Daily case reporting of the National Survey of Daily Influenza Outpatients.
† Mailing List–Based Influenza Epidemic Database.
§ Over-the-counter medications.

Adjusted OTC sales data also were compared with adjusted influenza data from DCR to identify a similar pattern during the height of the influenza season (Figure 4). DCR for clinically confirmed ILI is case-based and includes the patient's age and age group, date of visit, performance of rapid test, and result of a rapid diagnostic test as a single thread of information. Because data are reported by clinics and hospitals, numbers were low on Saturdays and Sundays and high on Mondays; consequently, numbers were adjusted for the-day-of-the-week effect. As with sentinel surveillance, DCR also indicated a different pattern early in the influenza season, and the peak coincided with the third peak of OTC sales. Characteristically, no rise in DCR was observed to match the last peak of OTC sales during late March.

FIGURE 2. Time-trend of adjusted over-the-counter (OTC) sales per pharmacy, by date — Japan, November 2003–April 2004

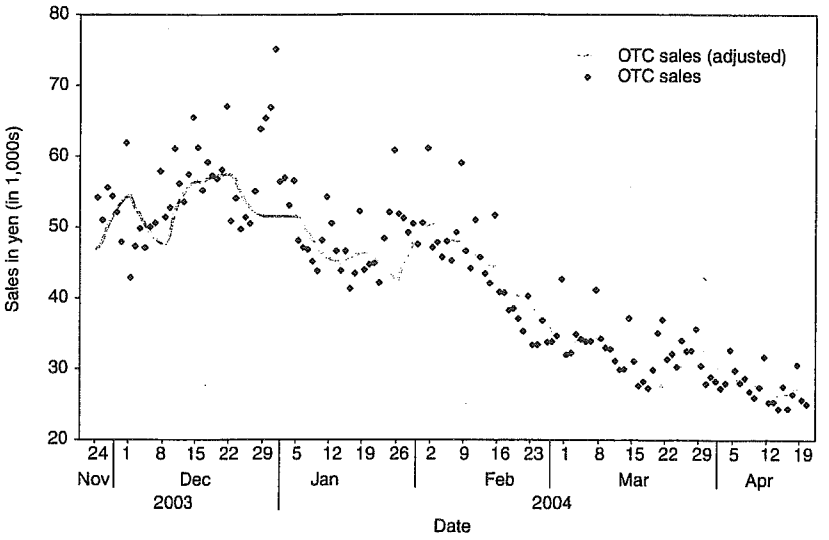
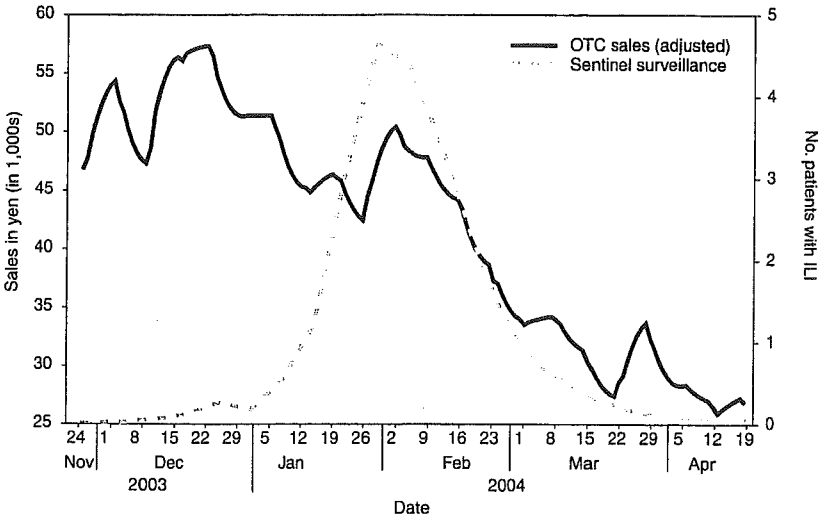


FIGURE 3. Comparison of over-the-counter (OTC) sales per pharmacy (adjusted) with number of patients with influenza-like illness (ILI) reported per sentinel point by national sentinel surveillance, by date — Japan, November 2003–April 2004



MLflu data were reported voluntarily by physicians interested in influenza preparedness. Information collected through the case-based reporting system included the patient's age, date of illness onset, date of visit, type of rapid diagnostic test used, type of influenza virus (A or B) diagnosed, and name of antivirals or other common cold medications prescribed. The date of onset was available for MLflu, which made it free from the-day-of-the-week effect. Additionally, this system was able to provide the number of laboratory-confirmed cases of influenza (i.e., those diagnosed by rapid diagnosis tests). A limitation of this system was that the number of pa ticipants varied during the season (low at tl beginning and the end of the season). Intere of the clinicians participating in MLflu was hi when ILI was rapidly increasing b decreased after the peak period ended (Figure The effect of this variance in the reporting ra should be considered when interpreting tl results. As with the other two influenza surve lance systems, MLflu indicated a different pa tern from the OTC medicine surveillance at tl beginning of the influenza season (Figure However, for the third peak, the rise in sales OTC medications did not coincide with tl peak of MLflu reporting. Instead, the pe observed by MLflu preceded sales by 1–2 wee (Figure 5). No matched peak was observed f the one during March.

OTC sales data were compared with oth influenza activity surveillance data to determi lead time (i.e., the number of days that OT sales elevation preceded an increase in the nur ber of influenza patients) (Figure 6). Fitne among DCR declined as lead time becan longer. The highest adjusted R-square w obtained when OTC data led by 1 day. Co versely, fitness among sentinel surveillance MLflu rose when lead time was longer. In t case of sentinel surveillance or MLflu, OTC sal appeared to lag behind influenza activity. A pe in OTC sales observed at the end of 2003 w suspected to reflect influenza activity.

Discussion

Syndromic surveillance in Japan has be conducted on an ad hoc basis during hig profile events (*1*). A short-term, labo intensive analysis system was used that w expensive and resource-intensive to run on daily basis. To date, several routine influenza surveillance sy tems have been implemented in Japan. However, each syste by itself is unable to provide sufficient information to prepa for the potential emergence of pandemic influenza or relat diseases. None of three currently existing influenza surveillan systems might be able to detect the early stage of a pandem because all systems detect patients only at the point of consu tation. In addition, each surveillance system has certain lim tations. For example, the national sentinel surveillance provid reliable mandatory reporting but captures only the numb