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

$$v = \frac{c \times \text{number of newly infected persons}}{200 \times \begin{pmatrix} 2 \times \text{number of public health workers} - \\ c \times \text{number of newly infected} \end{pmatrix}}$$

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

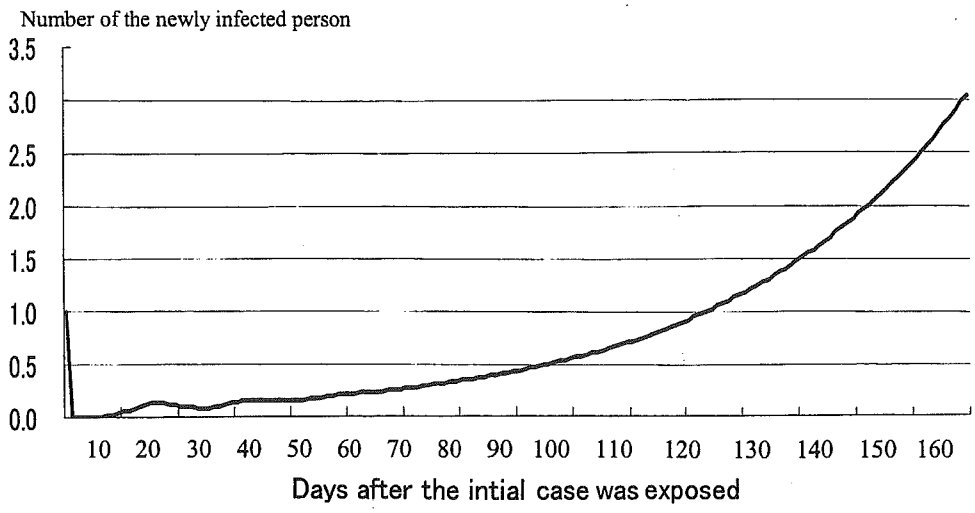

Fig. 4. Number of the newly infected person (without any intervention)

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

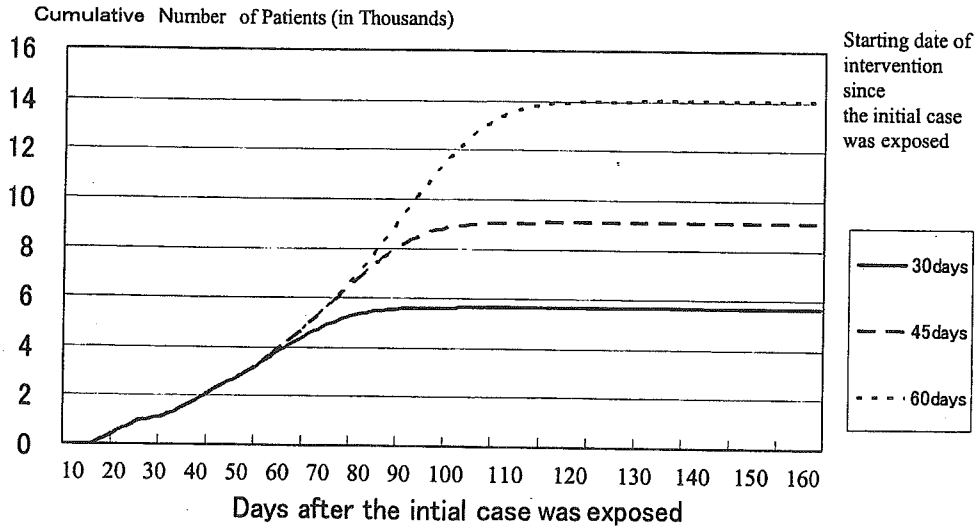

Fig. 5. Cumulative number of patients in the mass-vaccination scenario (R_0 = 1.5, number of initial-exposed cases = 1000)

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,

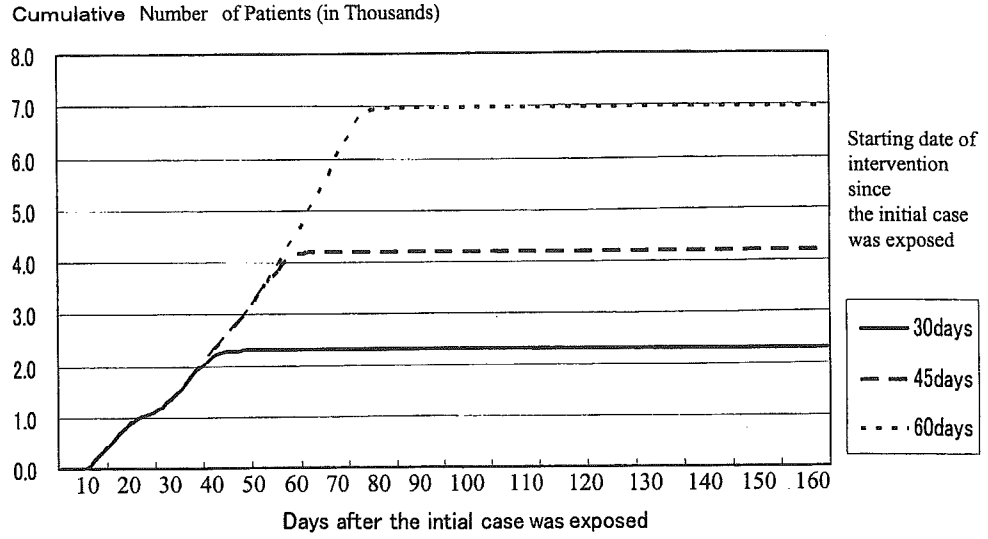

Fig. 6. Cumulative number of patients in the case of ring vaccination scenario (R_0 = 1.5, number of initial-exposed cases = 1000)

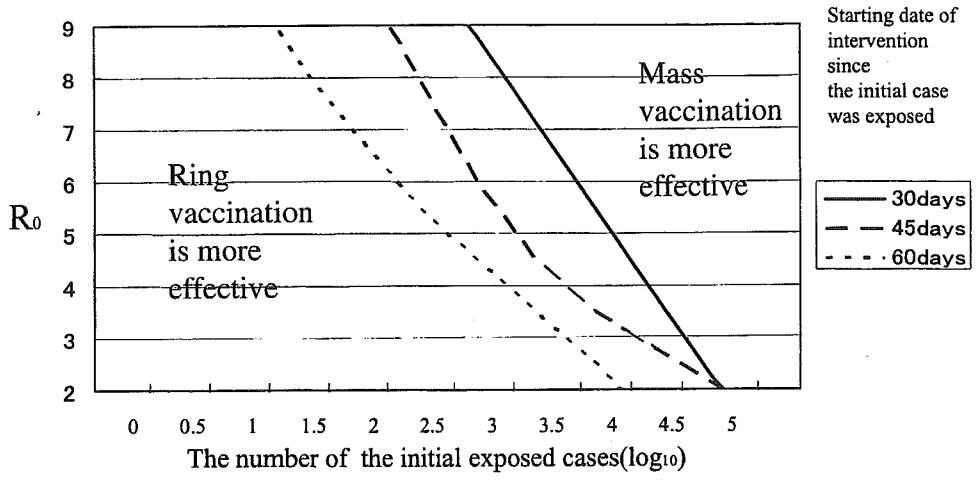

Fig. 7. Comparison of the two control measures

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.

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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

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

$$+ \sum_{j=1}^{N_1+N_2} S_n(j,t-1)\big)\Big)I_{3n}(s,t-1) + r\sum_{s=1}^{N_1} S_n(s,t-1) \tag{4}$$

$$S_{qv}(s,t) = S_{qv}(s-1,t-1) + eI_{1qv}(s-1,t-1) + vS_q(s-1,t-1) \quad (s=2,\ldots,N_1) \tag{5}$$

(6)

(7)

Transition of non-infected unquarantined contacts who are susceptible

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

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

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

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

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

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

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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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:

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

$$\text{Adjusted OTC sales in period } t = \frac{2k}{k(k+1)} \text{Replaced OTC sales in period } t + \sum_{j=1}^{k-1} \frac{2(k-j)}{k(k+1)} \text{Adjusted OTC sales in period } t\text{-}j$$

$$\text{for } t > 1 \text{ and } t \leq 6$$

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

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.

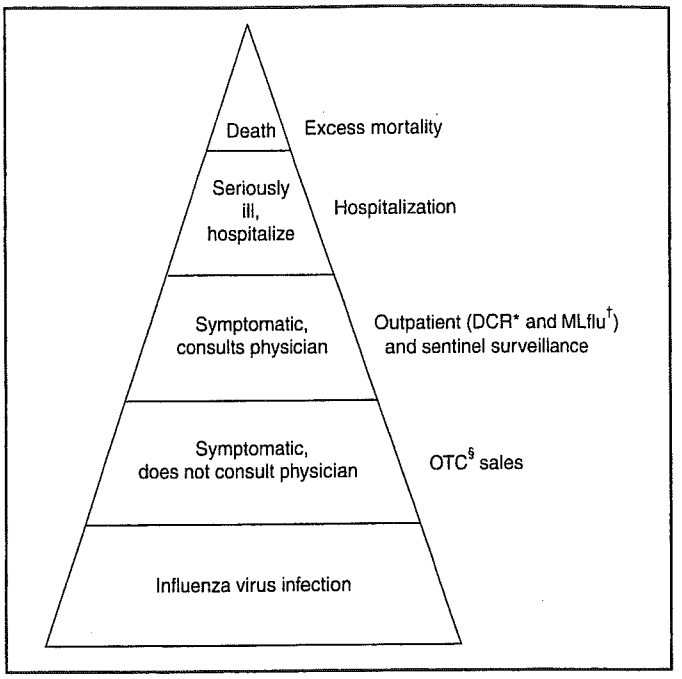
Results

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

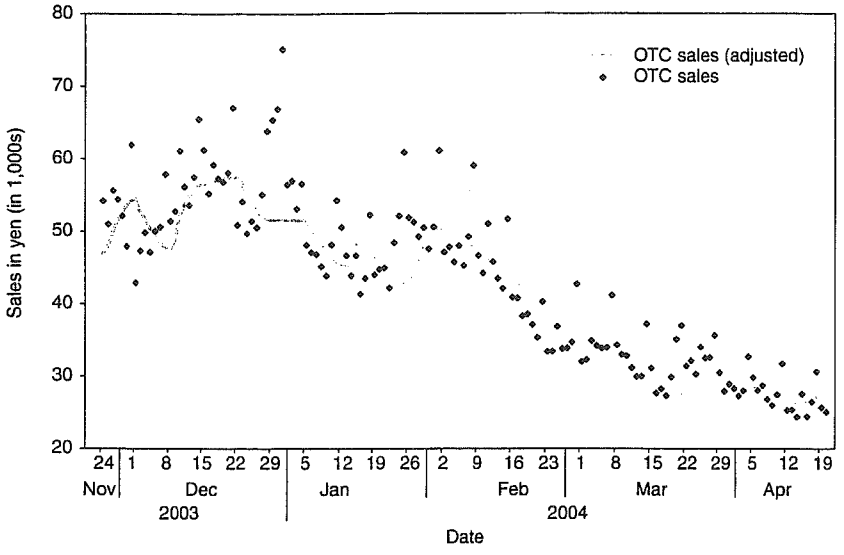
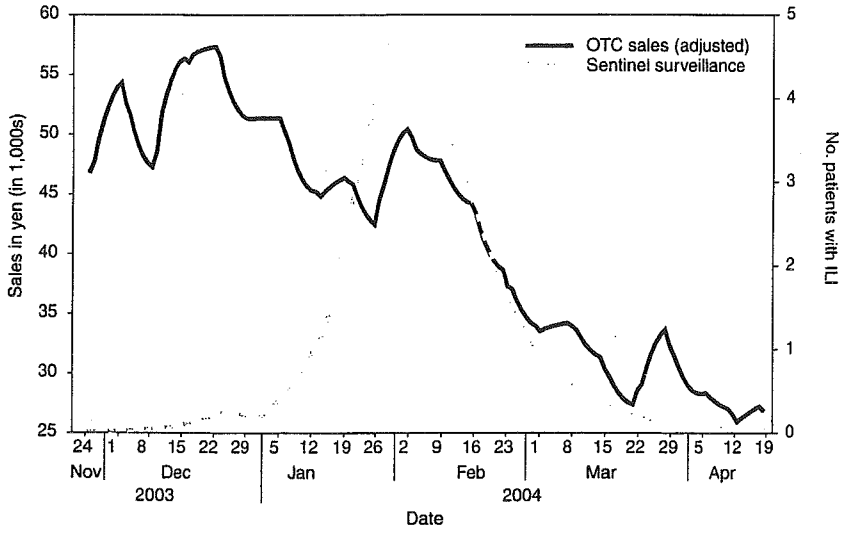


FIGURE 3. Comparison of over-the-counter (OTC) sales per pharmacy (adjusted) with number of patients with influenza-like illness (ILI) reported per sentinel point by national sentinel surveillance, by date — Japan, November 2003–April 2004



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 participants varied during the season (low at the beginning and the end of the season). Interest of the clinicians participating in MLflu was high when ILI was rapidly increasing but decreased after the peak period ended (Figure 5). The effect of this variance in the reporting rate should be considered when interpreting the results. As with the other two influenza surveillance systems, MLflu indicated a different pattern from the OTC medicine surveillance at the beginning of the influenza season (Figure 5). However, for the third peak, the rise in sales of OTC medications did not coincide with the peak of MLflu reporting. Instead, the peak observed by MLflu preceded sales by 1–2 weeks (Figure 5). No matched peak was observed for the one during March.

OTC sales data were compared with other influenza activity surveillance data to determine lead time (i.e., the number of days that OTC sales elevation preceded an increase in the number of influenza patients) (Figure 6). Fitness among DCR declined as lead time became longer. The highest adjusted R-square was obtained when OTC data led by 1 day. Conversely, fitness among sentinel surveillance and MLflu rose when lead time was longer. In the case of sentinel surveillance or MLflu, OTC sales appeared to lag behind influenza activity. A peak in OTC sales observed at the end of 2003 was suspected to reflect influenza activity.

Discussion

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

:nts who visit sentinel clinics and hos-
/ithout collecting sufficient qualitative
ıtion. These data are reported weekly,
.-week delay during which data are com-
DCR captures additional qualitative
ıtion but reports include only the date
MLflu reports the number of patients
:eive a diagnosis for influenza with rapid
In each surveillance system, timeliness,
:y, and representativeness have been
off for other advantages. The rationale
g readily available data of OTC sales for
ring is to establish routine early detec-
.rveillance for pandemics and other
:ted events to complement those surveil-
'stems.

ead time for OTC sales was compared
luenza surveillance to evaluate the time-
f sales data for detecting seasonal influ-
demics. An estimated 72% of Americans
)ugh, cold, influenza, or sore throat
urchase OTC medications early in the
)f their illnesses (*4*). Increases in OTC
:re expected to precede an increase in
visits to hospitals, assuming that con-
ehavior in Japan is similar to that in other
ed countries (i.e., persons purchase OTC
:ions when they first feel ill and then visit
)r EDs if their illness becomes more seri-
though OTC sales correlated well with
porary influenza activity (*2,3*), a clear
ıe was lacking, and analysis of OTC sales
dicated no evidence of advance detec-
influenza activity. Additionally, difficul-
re encountered in interpreting sales
:s in late December from influenza sur-
e alone. The increase appeared to reflect
tion for a long holiday season acceler-
year-end discount promotions but not
al increase in influenza activity. How-
rther analysis excluding this sales pro-
effect was also not able to determine
uenza activity in advance.

: results indicate that sales data on OTC
tions used to treat common colds have
otential for predicting increased influ-
tivity in Japan. Multiple factors might
: for this outcome. Because the analysis
:formed only on a national level, the
id not take into account regional varia-

FIGURE 4. Comparison of over-the-counter (OTC) sales per pharmacy (adjusted) with number of patients with influenza-like illness (ILI) per hospital or clinic recorded through daily case reporting (DCR) of the National Survey of Daily Influenza Outpatients (adjusted), by date — Japan, January–April 2004

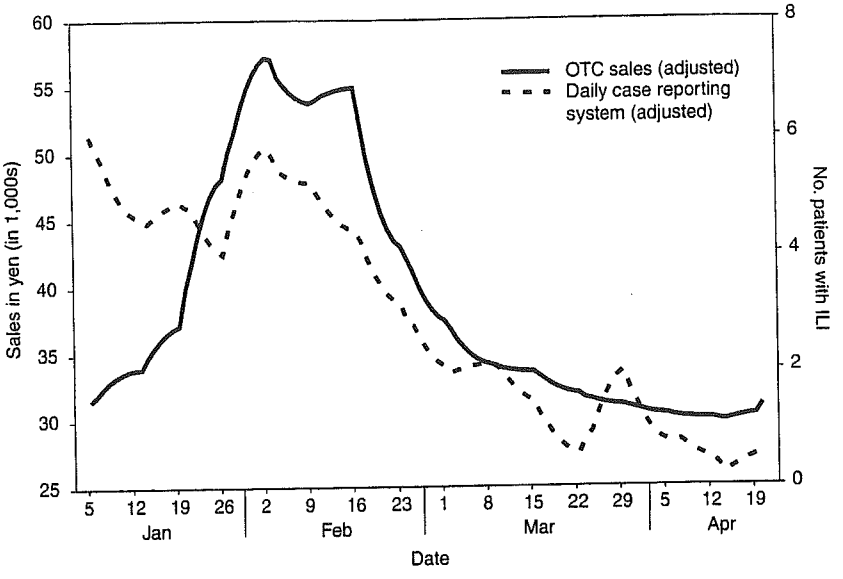
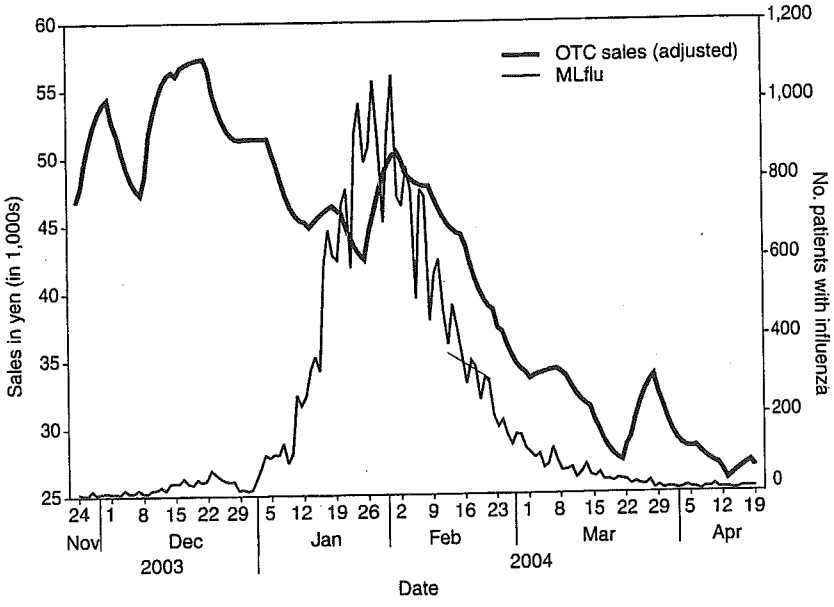
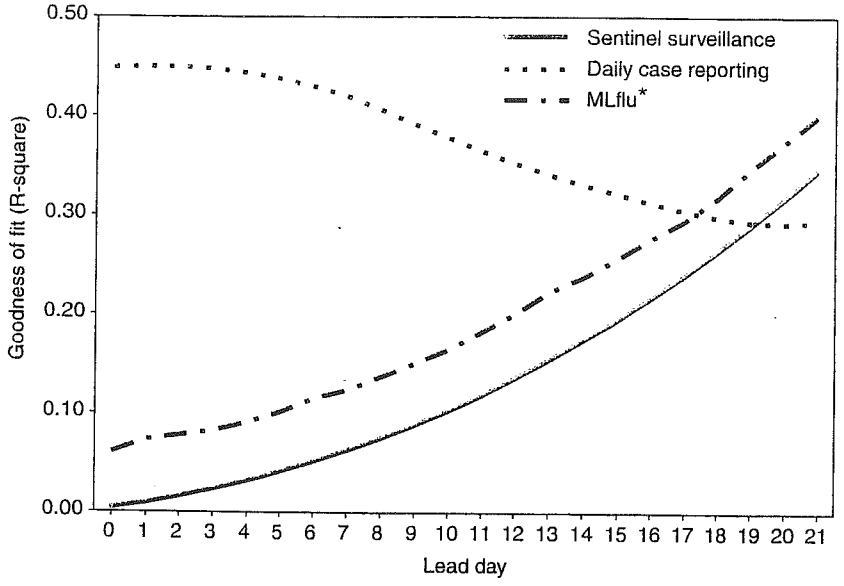


FIGURE 5. Comparison of over-the-counter (OTC) sales per pharmacy (adjusted) with number of patients with influenza reported through the Mailing List–Based Influenza Epidemic Database (MLflu), by date — Japan, November 2003–April 2004*



* MLflu reporting system was activated in November 2003 and officially launched in December 2003 for the 2003–04 influenza season.

FIGURE 6. Goodness of fit (adjusted R-square) between over-the-counter (OTC) sales and other influenza activity surveillances at different OTC lead times for 2003–04 influenza season — Japan, November 2003–April 2004



* Mailing List–Based Influenza Epidemic Database.

tions in influenza activity and variations in when the influenza season began. Variation of lead time of OTC sales to the actual disease incidence by locality has been suggested previously (*5*); therefore, to assess the real situation, smaller geographic areas must be analyzed. The next step to confirm correlations will be to break down the analysis at the prefecture level for 47 prefectures, with and without the effects of sales promotions. However, commuters cross prefecture borders frequently every day, and spatial correspondences or noncorrespondences of OTC sales and physician visits might remain biased in certain instances as a result of inexact geographic data.

The choice of OTC medications selected for this study might have contributed to the outcome. The study was limited to medications used to treat the common cold, which were already grouped in the commercialized sales reporting database. However, in certain cases of early stages of influenza, persons might purchase more symptom-oriented medications (e.g., antipyretic analgesic, antitussive, and antihistaminic medications). To include the entire sales rise attributable to ILI in the analysis, medications in those categories should be examined to formulate a suitable product group to use as precursor for detecting increased ILI as soon as data become available (*5*).

As the copayment proportion of payment for medical care by consumers continues to rise, a gradual move toward self-medication is under way in Japan. Consequently, the potential value of using OTC medication sales data as an indicator of disease outbreaks should continue to rise. However, Japanese consumers are still relatively reluctant to take an active role in decision making regarding their own health care. In addition, the majority of Japanese have easy access to medical care, and the national health insurance system provides a high degree of coverage. As a result, persons who are ill are more likely to visit a clinic at an early stage of illness. The introduction of antiviral agents (e.g., oseltamivir) that require a physician's prescription also has promoted medical assistance–seeking behavior during the influenza season. All of these factors combined might have influenced the study results.

Conclusion

The results presented in this report are tentative. Thorough data cleaning and additional analysis are required before a final decision is made concerning the use of OTC medication sales data as part of a national real-time syndromic surveillance system. Further studies are planned, including a geographic breakdown analysis, analysis with exclusion and inclusion of sales promotion effects (other than the year-end discount promotion), choice of methods for statistical analysis, and analysis taking into account bargain sales and associated promotion types and trial surveillance concerning respiratory symptoms in a limited area.

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総合診療科における不明熱患者215症例の解析

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目的：特定の診療科を決めかねる病態として不明熱がある．順天堂大学医学部附属順天堂医院総合診療科を初診し入院を要した不明熱患者215症例について，今後の診断の参考とするためその特徴を解析し検討した．

対象および方法：1994年10月から2004年8月までに当科を初診し，入院治療が必要となった成人の原因不明の発熱患者215名について検討した．対象患者の発熱の原因を疾患別に分類し検討した．また，65歳以上の高齢者と65歳未満の非高齢者での原因疾患について比較を行った．

結果：原因疾患として，感染症が102名（47.4％），非感染性炎症性疾患が40名（18.6％），悪性疾患が14名（6.5％），その他の疾患が21名（9.8％），原因不明が38名（17.7％）であった．頻度の高かった伝染性単核球症・髄膜炎・深部膿瘍・感染性心内膜炎の中で，初診時の平均年齢は深部膿瘍で有意に高く，平均体温は伝染性単核症で有意に低かった．65歳以上の高齢者では65歳未満の患者に比較し，感染症を原因とする不明熱の割合が低く，原因不明の症例が多かった．85歳以上の超高齢者も7名含まれた．

考察：不明熱の原因の約半数は感染症であった．特に，伝染性単核球症・感染性心内膜炎・深部膿瘍・髄膜炎の頻度が高く注意が必要である．HIV関連不明熱・麻疹・風疹の患者も比較的多く認められた．悪性腫瘍は多岐に渡ったが，画像検査の普及や進歩のため不明熱の原因となることは少なくなっており，過去の報告に比べ割合が低下していた．7症例は診断確定までに60日以上を要しており，周期的な発熱のみを症状とし，診断の手掛かりが得られ難かった症例であった．この中で死亡後に病理解剖により原疾患が判明した患者が2名おり，共に悪性リンパ腫と診断された．不明熱患者の診断には，感染症を中心とした多疾患にわたる知識が必要であると考えられた．

キーワード：不明熱，感染症，高齢者，総合診療

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はじめに

近年，医療の専門化・細分化が進む反面，包括的に診療することへの患者のニーズも高まっている．高度先進医療機関である順天堂大学医学部附属順天堂医院（東京都文京区本郷）においては専門診療科が整備されている．1994年10月から主に初診患者の初期診療を担うことを使命として総合診療科が診療を開始した．患者の全身的評価を行い診断・治療をし，その中で専門的診療が必要と判断された場合は専門診療科へ紹介している．診療科間の密接な関係をはかり，患者が時間的・質的に，より効率的な医療を受けられるように努力している．

特定の診療科を決めかね，かつ，外来では対処が難しい代表的な病態として原因不明の発熱がある．設立以来当科では不明熱患者の診断に力を入れている．今回われわれは，総合診療科を初診し入院を要した不明熱患者215症例について，今後の診断に役立てるためその特徴を解析・検討した．

Petersdorfらによる古典的不明熱の定義は『38.3℃以上の熱が3週間以上続き，病院での1週間以上の入院精査でも診断がつかないもの』となっている[1]．しかし，基礎疾患を有する例や抗生物質・解熱剤の既投与例など，定型的な不明熱患者は減少している．同時に，医療・社会事情の変化から，有熱状態で長期間放置されることは少なくなった．特に本邦では比較的早期に入院精査がなされる傾向がある．これらから，この定義に当てはまる患者と実際の臨床で問題となる不明熱症例との間に乖離があるという意見も多い[2)~4)]．このため今回われわれは古典的定義にこだわらず『発熱を主訴とし，外来では診断に至らず入院を要した患者』を解析の対象とした．

対象および方法

1994年10月から2004年8月までに順天堂大学医学部附属順天堂医院総合診療科を初診し入院治療が必要となった成人で，入院時において原因不明の発熱を有する患者について検討した．発熱を主訴としていても外来での検査で診断がついたもの（胸部エックス線撮影で肺炎と診断された患者など）は除外した．発熱の程度としては，腋下温37.0℃以上の微熱の患者も含めた．全入院症例3161名の中から以上の条件に合致した215名を対象とした．

対象患者の発熱の原因を疾患別に分類し検討した．また，65歳以上の高齢者と65歳未満の非高齢者での原因疾患について比較を行った．特に頻度の高かった感染症（伝染性単核球症・髄膜炎・深部膿瘍・感染性心内膜炎）については，外来初診時の年齢と体温について統計的に評価した．結果はSSPEを用いて評価して検定を行った．

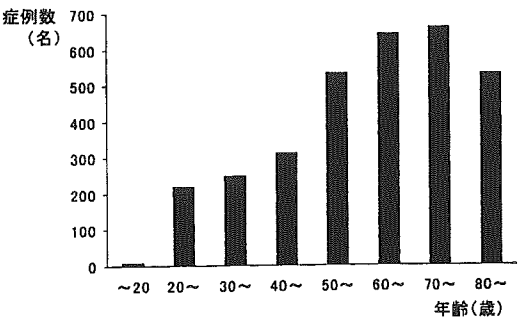

図-1a 全入院患者の年齢分布（全3161名）

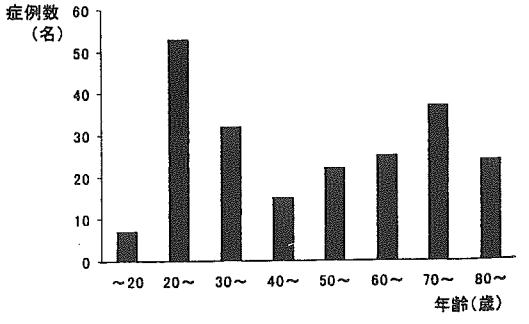

図-1b 不明熱患者の年齢分布（全215名）

表-1　各種感染症における外来初診時の平均年齢と体温

疾患名（症例数）	IM（13）	髄膜炎（11）	深部膿瘍（8）	IE（6）
平均年齢（歳）	25.1±4.50	34.4±13.0	63.0±14.9*	37.5±15.0
体温（℃）	37.5±0.595**	38.5±0.821	38.8±1.07	38.9±0.678

IM：伝染性単核症，IE：感染性心内膜炎，±標準偏差，*：$p<0.01$，**：$p<0.05$.

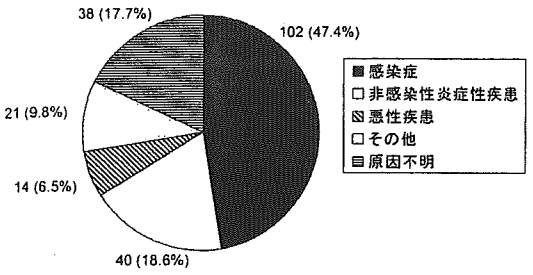

図-2　不明熱患者の疾患分類（全215名）

結　　果

今回対象となった症例は215名であり，全入院患者の6.8％であった．性別は男性111名，女性104名であり，性差は認めなかった．この中で古典的不明熱の定義を満たしているものは107名（49.8％）であった．また，他院や当院他科での外来・入院精査で診断がつかず当科に紹介入院となった患者は116名（54.0％）であった．

同期間の総合診療科全入院患者の年齢分布が60～70歳でピークを示しているのに対し（図-1a），不明熱患者は20歳台と70歳台をピークとした2峰性の分布であった（図-1b）．体温別には37℃台が66名，38℃台が84名，39℃以上が65名であった．39℃以上の高熱の患者は外来通院での精査が困難なため，入院までの期間が短い傾向を認めた．

疾患は大別して，感染症が102名，非感染性炎症性疾患が40名，悪性疾患が14名，その他の疾患が21名，診断に至らなかったものが38名であった（図-2）．

各疾患別に以下に詳述する．

Ⅰ．感染症　102名（47.4％）

感染症が約半数で不明熱の原因としては最多であった．疾患は頻度順に，伝染性単核球症13名，髄膜炎11名，深部膿瘍8名，感染性心内膜炎6名，結核5名，麻疹4名，智歯周囲炎3名，風疹2名であった．頻度の高い4疾患のうち，初診時の平均年齢は深部膿瘍で有意に高く（$p<0.01$），平均体温は伝染性単核症で有意に低かった（$p<0.05$）（表-1）．

Ⅱ．非感染性炎症性疾患　40名（18.6％）

亜急性壊死性リンパ節炎が7名，血管炎症候群が3名，ベーチェット病が3名，成人Still病，リウマチ性多発筋痛症，サルコイドーシス，亜急性甲状腺炎が各2名みられた．

Ⅲ．悪性疾患　14名（6.5％）

このうち約半数の6名は悪性リンパ腫，2名が転移性骨腫瘍（原発不明）であった．発熱による全身状態の悪化のため，精査時に消化管内視鏡検査が躊躇されていることも少なくない．しかしながら，上部消化管内視鏡検査のみで診断可能であった不明熱症例も3例認められた（膵臓癌2例，胃癌1例）．

Ⅳ．その他　21名（9.8％）

その他の原因として最も多かったのは深部静脈血栓症であった（4名）．少数ではあるが，薬剤性，詐熱，地中海熱の症例もみられた．

Ⅴ．原因不明　38名（17.7％）

診断に至らなかった症例は，自然経過または抗生物質やステロイドの投与で全例が軽快退院している．経過や血液検査所見から何らかの一過性のウイルス感染が存在したと疑われた症例が多かった．

全215症例の中で，65歳以上の高齢者は71名（33.0％）であった．高齢者では65歳未満の患者

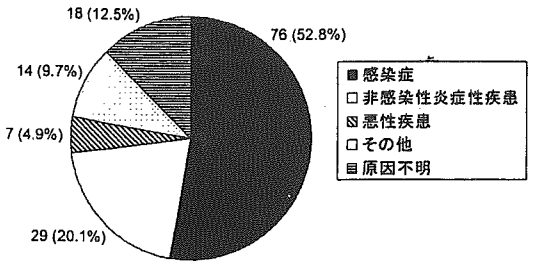

図-3a 非高齢不明熱患者（65歳未満）の疾患分類（全144名）

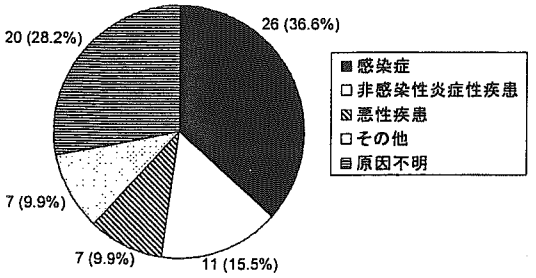

図-3b 高齢不明熱患者（65歳以上）の疾患分類（全71名）

表-2 85歳以上の超高齢不明熱患者

症例	性別	年齢	疾患名	予後
1	女性	90	急性化膿性胆管炎	軽快
2	女性	90	不明	軽快
3	女性	89	不明	軽快
4	男性	88	丹毒	軽快
5	男性	88	急性胆嚢炎	死亡
6	男性	88	転移性骨腫瘍	死亡
7	女性	86	リウマチ性多発筋痛症	軽快

（図-3a）に比較し，感染症を原因とする不明熱の割合が低かった（図-3b）．これはEBウイルス感染症・麻疹・風疹が非高齢者のみに認められた影響と思われる．また，高齢者では原因が不明であった例が多く，高齢者不明熱の診断が困難であることを示唆している．今後も高齢者独特の病因，病態を理解し，診断能力を高めていく必要がある．85歳以上の超高齢者（7名）を表-2に示した．

考　察

発熱は外来診療において最も接することの多い症候である．発熱を訴える患者の中に，原因が明らかでない患者が存在し，その原因について研究がなされてきた[5)～8)]．しかし，国内外で多くの解析の報告があるものの，200症例以上を検討した論文は検索した範囲では認めない．

今回の調査の結果，不明熱の原因として最も多かったのは各種の感染症であった．不明熱患者の診断には，広く感染症の知識が必要である．特に，伝染性単核球症・感染性心内膜炎・深部膿瘍・髄膜炎の頻度が高かった．伝染性単核球症では咽頭痛や頸部リンパ節腫脹，倦怠感などを認めるが感冒様症状と紛らわしい．しかし肝機能異常や異型リンパ球の出現が認められれば本疾患を十分疑うことができる[9)]．20～30歳において伝染性単核球症やその他のウイルス感染症が多く認められ，今回の対象患者の年齢分布は2峰性を示した理由と思われる（図-1）．

細菌感染症の中では，感染性心内膜炎と深部膿瘍で不明熱の原因となりやすいが，発熱以外の特異的な臨床症状が乏しいのが特徴である[10)]．今回の研究でも，感染性心内膜炎では発熱以外の症状は認められなかった．感染性心内膜炎の診断には歯の治療歴や弁膜症の既往についての問診や心雑音の聴取，心臓超音波検査，頻回の血液培養が必要であるが，最も感度が高い検査は経食道超音波検査である．深部膿瘍は1名が脳膿瘍で他の7名は肝膿瘍であり，やはり発熱以外の症状は乏しかった．髄膜炎は頭痛を伴っているものの髄膜刺激症状が明確でないことも多く，高熱による頭痛との鑑別が難しい症例が多かった．疑わしい場合には早期の髄液検査が必要であろう．

智歯周囲炎の症例も3名おり，感染巣が不明の時は必ず歯科の精査も行う必要がある．これらの症例ではいずれも抜歯後に解熱した．

Durackが1991年に発表した新しい不明熱の概念では，ヒト免疫不全ウイルスHuman Immunodeficiency Virus（HIV）関連の不明熱を独立し

た項目としてある[11]．今回の対象中でHIV関連不明熱は8名（3.7％）と高率であった．今後も本邦ではHIV感染患者が増加すると考えられ[12]，一般臨床医も不明熱の原因としてHIV感染症に留意する必要がある[13]．

今回の調査では，麻疹・風疹の患者が比較的多かったことも特徴であろう．成人発症の麻疹・風疹患者は非典型的な経過をとることが多く，皮疹や熱型からの診断が難しく不明熱の原因となる．診断の遅れは院内感染を引き起こす恐れもあり，早期に抗体検査を実施する必要がある．近年，麻疹・風疹のVaccine Failureが問題となっており[14]，今後本邦でもMMR（Mumps Measles Rubella）接種も含めたワクチン投与法の検討が必要と思われる．

一般には悪性リンパ腫と腎細胞癌が腫瘍熱をきたすことが多いといわれている[15]．今回の調査では腎細胞癌の症例は無く，膵臓癌・胃癌・胆管細胞癌など多岐に渡った．近年，超音波検査，CT検査を中心とした画像検査の普及・進歩のため悪性腫瘍の早期発見が可能となり，不明熱の原因となることは少なくなっている．本邦での不明熱症例の原因に悪性腫瘍が占める割合は1987年：16%[16]，1990年：14.6%[17]，1999年：8.9%[2]と低下の傾向にあった．今回の報告では6.5%とさらに低下しており，今後も減少が続く可能性がある．

不明熱患者に対する安易な副腎皮質ステロイド剤の投与は，熱型の修飾により診断を遅らせ，また，感染症の増悪を引き起こす可能性があるため避けるべきである．しかしながら，不明熱患者の中には全身状態の悪化のため診断確定前に止むを得ずステロイド投与が必要になる患者も存在する．鈴木らは，これらの症例をSR-FUO（Steroid Responsive Undiagnosed Fever of Unknown Origin）と名付け，不明熱患者の実に24％を占めたと報告している[18]．われわれの報告では4名（1.9％）であり，ステロイド投与により全例解熱し，投与終了後も再燃を認めていない．これらの症例では，何らかの自己免疫機序による発熱が存在していたことが推定される．

症状出現から診断確定までに60日以上を要した7症例を表-3に示した．周期的な発熱のみを症状とし，診断の手掛かりが得られ難かった症例が多い．症例1と2は長期の無熱期の後に診断されている．このような場合，無熱期には外来通院としながらも，特に皮疹や関節症状の出現に注意した経過観察が必要である．

原因不明のまま死亡し，病理解剖により原疾患が判明した症例は2名であり，血管内リンパ腫の症例と脾臓に限局した悪性リンパ腫の症例であった（表-3，症例2，4）．両症例とも各種の画像検査，臓器生検等で診断が付かず，最終的には悪性リンパ腫を疑い化学療法を施行したが救命出来なかった．悪性リンパ腫を疑わせる不明熱患者に対し，治療的診断として化学療法を用いることの判断は難しく，今後も検討が必要な事項である．

表-3　診断確定に60日以上を要した不明熱患者

症例	性別	年齢	疾患名	診断までの期間（日）	予後
1	男性	49	成人Still病	304	軽快
2	男性	64	血管内リンパ腫	112	死亡
3	女性	80	膵臓癌	91	不変
4	男性	36	悪性リンパ腫	88	死亡
5	男性	81	化膿性椎間板炎	84	軽快
6	男性	63	前立腺癌	82	不変
7	女性	69	悪性リンパ腫	70	軽快
8	男性	59	胆管細胞癌	62	死亡

おわりに

一概に発熱を主訴とする患者と言っても，その原因疾患は多岐にわたる．さらには時代によりその疾患頻度や診断方法が変化しており，診断には知識のアップデートが欠かせない．不明熱患者の診断の遅れは患者の生命予後に直接影響し，また，入院の長期化をもたらし医療経済的にも問題である．このため，不明熱患者が初診する総合診療科と各専門科の連携は大変重要な問題であり，今後も早期に確実な診断を目的として努力を続けるべきである．

最後に，当科設立以来から多くの専門科医師や当科で研修中の医師に診断・治療にご協力をいただいたことに感謝する．

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Summary

An analysis of the 215patients with fever of unknown origin

Objective : Idiopathic fever is one of the symptoms for which it is difficult to determine which department should treat the patient. We analyzed and reviewed the characteristics of 215 patients with idiopathic fever who required hospitalization after their first visits to the Department of General Medicine, Juntendo University School of Medicine, in order to obtain useful information to facilitate diagnosis of future cases.

Subjects and methodology : The subjects were 215 adult patients with idiopathic fever who required hospitalization for treatment after an initial visit to our department, between October 1994 and August 2004. We classified the causes of fever by disease that was eventually diagnosed. We also compared the elderly population aged 65 or older and the younger population under 65 years in terms of causal diseases.

Results : The causal diseases were infections (102 patients, 47.4%), non-infectious inflammatory diseases (40, 18.6%), malignant diseases (14, 6.5%), other diseases (21, 9.8%) and idiopathic diseases (38, 17.7%). Among the most frequent causal diseases, namely, infectious mononucleosis, meningitis, deep abscess, and infectious endocarditis, the mean patient age at initial consultation was significantly higher for deep abscess and the mean body temperature was significantly lower for infectious mononucleosis. In the population with idiopathic fever, the ratio of patients with infections was lower and that of patients with undetermined causes was higher in the group aged 65 or older, in comparison with the group under 65 years. Seven patients were very old (85 or older).

Discussion : Infections were diagnosed in about half of the cases of idiopathic fever. Infectious mononucleosis, infectious endocarditis, deep abscess, and meningitis were particularly frequent, requiring close attention. HIV-related fever of unknown origin, measles, and rubella were relatively frequent as causal diseases. Malignant tumors were wide-ranging, but these lesions now cause fewer cases of idiopathic fever because of the widespread use and advancement of diagnostic imaging systems. The ratio of malignant tumors has decreased from the levels in the past. In 7 patients, 60 or more days were required before determination of diagnosis, because periodic fever was their only symptom and other clues for diagnosis were difficult to obtain. The underlying disease in 2 of these patients was not identified until pathologic autopsy, and both were found to have malignant lymphoma. Diagnosis of idiopathic fever requires knowledge centered on infections and covering a wide range of diseases.

Key words : FUO, Infection, Aged Person, General Medicine