Peak Rotavirus Activity Shifted From Winter to Early Spring in Japan

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Background: Since 1910, there have been many studies on acute gastroenteritis in children in Japan. These diseases, namely Kasei-shoni-kolera (pseudocholera infantum) or banshu-otosho (late autumn vomiting disease), are historically known to occur in the cooler season with a peak in November or December. Earlier we confirmed their causation by rotaviruses but found peaks in January or February from 1974 to 1981. The aim of the present study was to confirm the temporal shift in peak rotavirus activity.

Methods: Under the National Epidemiological Surveillance of Infectious Diseases program from 1983 through 2003, rotavirus positive patients 0–3 years old and clinically diagnosed with "infantile vomiting and diarrhea" at sentinel clinics were examined. Fecal samples were screened by electron microscopy and/or using commercial latex agglutination kits at prefectural/municipal Public Health Institutes, and we determined the trend for the "peak" month during 21 seasons.

Results: Peak rotavirus activity shifted gradually from January to March during the 21 consecutive seasons. The mean duration from December to the peak month (mean beginning peak duration) of the rotavirus season significantly varied among 3 periods of 7 consecutive seasons (1.7 ± 0.5 months in 1982/1983–1988/1989, 2.3 ± 0.8 months in 1989/1980–1995/1996, and 3.1 ± 0.7 months in 1996/1997–2002/2003, respectively; $P = 0.0026$ by 1-way analysis of variance). This time series shift in the peak rotavirus infection was statistically significant ($P = 0.0003$ for trend).

Conclusion: Our findings confirmed that the temporal trend in peak rotavirus activity in Japan has shifted gradually from winter to early spring for unknown reasons.

Key Words: rotavirus, surveillance, gastroenteritis, seasonality

Rotavirus, the leading cause of severe pediatric gastroenteritis, is prevalent usually only in the cooler months in temperate areas, although it is common even in tropical counties.[1] In Japan, there have been many studies of acute gastroenteritis in children since 1910,[2] even before the discovery of rotavirus. *Kasei-shoni-kolera* (pseudocholera infantum) or *banshu-otosho* (late autumn vomiting disease) are forms of gastroenteritis with symptoms of vomiting, slight fever, dehydration, and whitish, watery stools,[2–5] generally occurring in infants and young children. We have confirmed these local diseases to be caused by rotaviruses,[6–8] and noted that infection often appears related to the ambient temperature but not to relative humidity.[8] In contrast to the peaks in November or December reported earlier, however, we found most rotavirus activity occurred between January and February in studies reported more than 20 years ago.

Our aim in the present study was to confirm any temporal shift in peak rotavirus activity in Japan on the basis of laboratory studies conducted during the past 21 years under the National Epidemiological Surveillance of Infectious Diseases program.

MATERIALS AND METHODS

Under the National Epidemiological Surveillance of Infectious Diseases program, the numbers of patients 0–3 years old clinically diagnosed with "infantile vomiting and diarrhea" and suspected of rotavirus infection have been reported electronically on a weekly basis from 2500 sentinel pediatricians/general physicians throughout Japan since 1981.[9–12] In addition, one-tenth to one-third (according to the locality) of the sentinel clinics send fecal samples and clinical data to 70 prefectural/municipal Public Health Institutes for laboratory diagnosis. The fecal samples are screened for rotavirus by electron microscopy and/or by using commercial latex agglutination kits. In addition, some laboratories for research work use an enzyme-linked immunosorbent assay

with polyclonal antibodies specific for group A human rotaviruses or the reverse transcription-polymerase chain reaction method for G serotyping. Rotavirus results, together with individual patient data, are reported to the Infectious Disease Surveillance Center, the National Institute of Infectious Diseases (Tokyo, Japan).

Monthly distribution of rotavirus was defined after adjusting the epidemic curves according to a 3-month unweighted moving average (mean).[13] The "peak" month during the rotavirus season was then defined as that during which the greatest number of rotavirus-positive specimens were collected.

We analyzed here the laboratory-confirmed rotavirus cases between 1982 and 2003 under the National Epidemiological Surveillance of Infectious Diseases program. We used December as the start month of the rotavirus season for convenience, given that the annual rotavirus season began between November and December during the study period. To ascertain any shift in the peak, Spearman's correlation coefficient was used for analysis of relationship between duration from December to the peak month (beginning peak duration) during the 21 consecutive seasons. Furthermore we compared mean beginning peak duration among 3 periods of 7 consecutive seasons (1982/1983–1988/1989, 1989/1990–1995/1996, and 1996/1997–2002/2003 season). Interperiod differences in the mean were tested by 1-way analysis of variance followed by the Spearman correlation test for trend and the Dunnett test for multiple comparisons. All calculations were performed with SPSS for Windows version 11.0, and significance was concluded at <0.05.

RESULTS

For the period from 1983 through 2003, we analyzed 17,583 positive cases. Rotavirus infections were reported in 400–700 patients each year from nationwide surveillance sites. Seasonal increase in rotavirus diarrhea occurred annually (Fig. 1). The annual rotavirus season began between November and December, peaked between January and

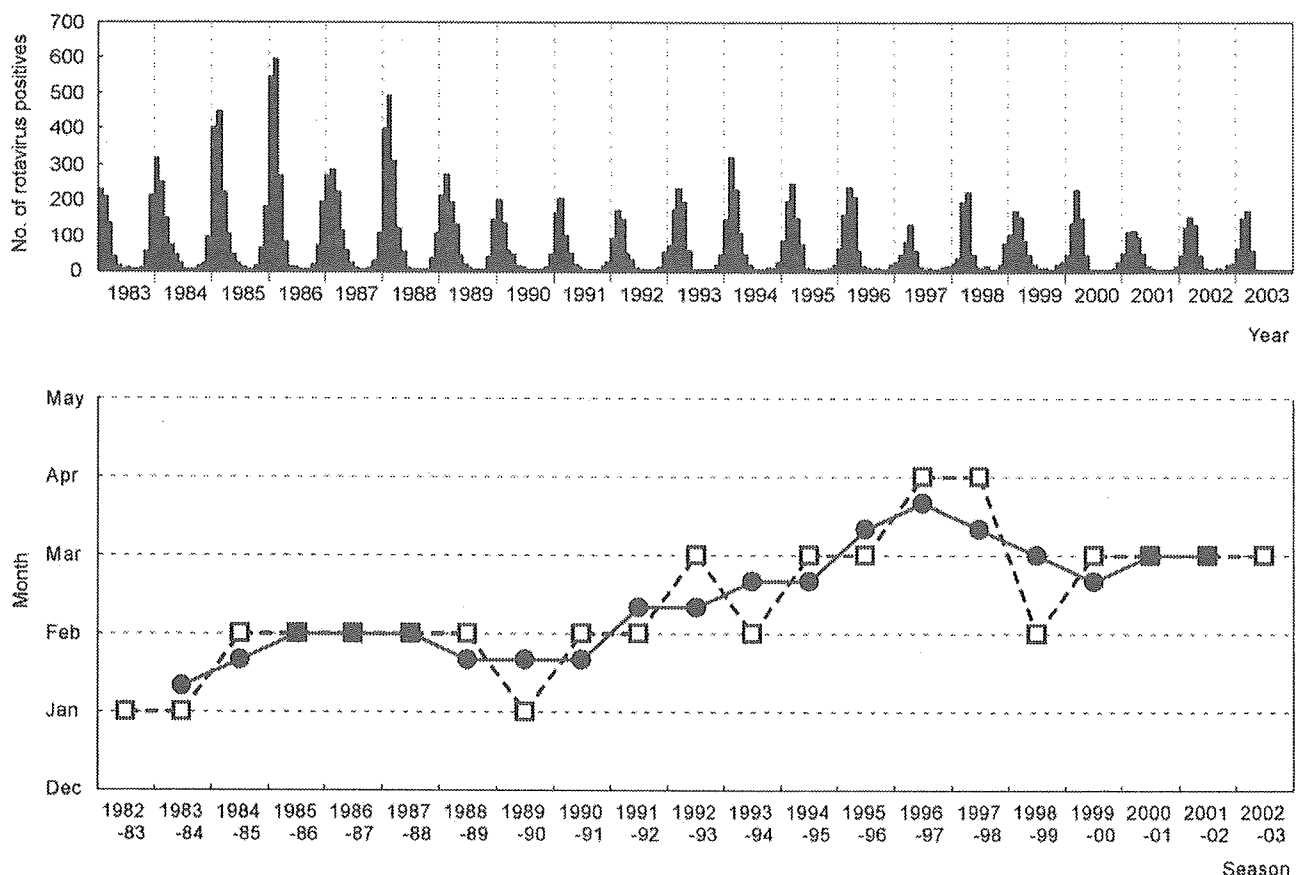FIGURE 1. Data for rotavirus gastroenteritis in Japan from 1983–2003. Upper panel, monthly distribution based on laboratory data by 3-month unweighted moving average (mean). Lower panel, peak rotavirus activity, defined as the month during which the greatest numbers of rotavirus specimens were collected (●) and after adjustment using 3-month unweighted moving averages (means) (□). $r_s = 0.77$, $P < 0.0001$.

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April, and returned to baseline by April to June for the study period. Peak rotavirus activity occurred between January and February during 1982–1991, shifting to mid-February to late-March during 1992–1995, and also from mid-February to mid-March (mostly March) in 1996–2003 (Fig. 1).

Beginning peak duration increased during the 21 consecutive seasons (r_s =0.77; $P < 0.0001$), and significantly varied among the 3 periods of 7 consecutive seasons (1.7±0.5 months in 1982/1983–1988/1989, 2.3 ± 0.8 months in 1989/1980–1995/1996, and 3.1 ± 0.7 months in 1996/1997–2002/2003, respectively; $P = 0.0026$ by 1-way analysis of variance) (Table 1). This time series shift was statistically significant ($P = 0.0003$ for trend), and the mean duration was significantly different between the earliest and the latest periods ($P < 0.01$, Dunnett test).

DISCUSSION

Our analysis based on laboratory studies during the past 21 years shows that the peak rotavirus activity shifted gradually from January to March, with statistical significance, in line with laboratory data from 7 regions of Japan for 1984 to 1999 that indicated also the clear shift of a peak rotavirus activity from February to March.[14] Thus the available information points to shift from winter to early spring during the past century in Japan.

Seasonality in disease incidence often reflects associations with weather factors. Previously we reported that rotavirus infection frequently appeared related to temperature change, being found to appear abruptly when the mean temperature of 10-day period became <5°C (November or December), and reaching a peak when it was <0°C (January and February, the coolest months) in Yamagata, Japan.[8] The coolest months in winter have not changed, but annual average temperatures have increased gradually ~1.0°C during the past 100 years with global warming in Japan,[15] apparently coinciding with a temporal shift in the peak rotavirus activity, from November to March. Our observations suggest a determining role for a single climatic factor, temperature, to explain the temporal trend, but we could not find any evi-

dence that infections with other viruses common in the cool season, such as the influenza and respiratory syncytial viruses, shifted from winter to spring in Japan. Furthermore the interrelationship of the start, peak of number of cases and alternating pattern of seasonal size of the respiratory syncytial virus epidemic reported in Stockholm[16] appears not to be a feature with our rotavirus infections.

Rotaviruses are members of the family *Reoviridae,* which contain 11 segments of double-stranded RNA within a core shell, surrounded by a double capsid. The outer capsid contains the major glycoprotein VP7, which defines rotavirus serotype G. Among group A rotaviruses, 14 distinct G serotypes have been recognized, and 4 G serotypes (G1, G2, G3 and G4) are particularly important.[17] A survey of rotavirus infection in children with diarrhea from 1984 to 1999 indicated that G1 remained the predominant serotype, with G2 was the second, and followed by G3 or G4.[18] These prevalence rates were steady and did not coincide with a temporal shift in the peak rotavirus activity. Therefore we have no evidence of any relationship between prevalence of rotavirus serotypes and the shift in peak rotavirus activity.

Noroviruses (NVs) are human enteric caliciviruses that are the most important cause of acute nonbacterial gastroenteritis in sporadic community cases as well as in outbreaks in different settings.[19] They are important causative agents of viral gastroenteritis in children and like the rotaviruses are prevalent in the cooler months in temperate areas.[9,19,20] During the period from 1993 to 1998, infections began between October and November, peaked between November and January and returned to the baseline by April–June.[11] The peak NV activity thus precedes that of rotaviruses. Until the 1993/1994 season, the epidemic curve of infantile vomiting and diarrhea cases per sentinel clinic showed 2 peaks every year correlating with rotavirus laboratory reports in trend and number.[10–12] After that, however, the first peak seemed attributable to NVs and the second to rotaviruses.[10–12] With introduction of reverse transcription-polymerase chain reaction methodology for sensitive detection of NVs, these viruses have been identified as frequently as rotaviruses in fecal specimens of Finnish children with diarrhea, as in Japan.[21,22] The pathologic role of NVs has increased not only in "infantile vomiting and diarrhea" but also in food-borne gastroenteritis,[9,11,12] probably because of demand and supply of oysters, including imports from neighboring countries. Oysters become contaminated by human pathogens in polluted waters, thus serving as a source of NV transmission to humans.[23] NVs have been the leading cause of food-borne gastroenteritis since 2001 in Japan, and >60% of cases are related to raw oyster consumption.[9] NVs may have affected the shift in peak rotavirus activity; however, because we have no culture system for NVs, we could not obtain any direct evidence in support of interference of rotavirus and NV infections with each other.

TABLE 1. Comparison of Mean Beginning to Peak Durations for Rotavirus Seasons Among 3 Periods of 7 Consecutive Rotavirus Seasons

Period	Season	Beginning to Peak Duration (mo)*
I	1982/1983–1988/1989	1.7 ± 0.5†
II	1989/1990–1995/1996	2.3 ± 0.8
III	1996/1997–2002/2003	3.1 ± 0.7‡

*Duration from the beginning of each winter season (December) to the peak month of the rotavirus season.

†Mean ± SD.

‡$P = 0.0026$ for interperiod differences by 1-way analysis of variance, and $P = 0.0003$ for trend by Spearman's correlation coefficient. $P < 0.01$ for the difference from period I by Dunnett test.

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We conclude that a temporal shift in peak rotavirus activity in Japan, from winter to early spring, has occurred for unknown reasons.

REFERENCES

1. Kapikian AZ, Hoshino I, Chanock RM. Rotavirus. In: Knipe DM, Howley PM, Griffin DE, et al, eds. *Fields Virology*. 4th ed. vol 2. New York, NY: Lippincott Williams & Wilkins; 2001:1787–1833.
2. Ito S. Pseudocholera infantum. *Jikazasshi*. 1910;125:751–757.
3. Aritomi S. Early winter diarrhea of breast-fed infants. *Rinshoshonika*. 1928;2:25–32.
4. Obara Y. Epidemic of autumn vomiting diseases in young children. *Rinshonippon*. 1933;2:440–446.
5. Yoshida S. Late autumn infantile vomiting disease. *Jikashinryou*. 1950;25:397–400.
6. Suzuki H, Konno T. Reovirus-like particles in jejunal mucosa of a Japanese infant with acute infectious non-bacterial gastroenteritis. *Tohoku J Exp Med*. 1975;115:191–211.
7. Konno T. Suzuki H, Imai A, Ishida N. Reovirus-like agents in acute epidemic gastroenteritis in Japanese infants: fecal shedding and serologic response. *J Infect Dis*. 1977;135:259–266.
8. Konno T, Suzuki H, Katsushima N, et al. Influence of temperature and relative humidity on human rotavirus infection in Japan. *J Infect Dis*. 1983;147:125–128.
9. Inoue S, Yamashita K. Yamadera S, Yoshikawa M, Kato N, Okabe N. Surveillance of viral gastroenteritis in Japan: pediatric cases and outbreak incidents. 2000;181(suppl 2):S270–S274.
10. National Institute Infectious Diseases. Viral gastroenteritis, Japan, October to December 1995. *Infect Agents Surveil Rep*. 1996;17:20–21.
11. National Institute Infectious Diseases. Viral gastroenteritis of children, Japan, 1993–1998. *Infect Agents Surveil Rep*. 1998;19:248–249.
12. National Institute Infectious Diseases. Outbreak of Norovirus infection, January 2000–October 2003. *Infect Agents Surveil Rep*. 2003;24:309–310.
13. Torok TJ, Kilgore PE, Clarke MJ, Holman RC, Bresee JS, Glass RI. Visualizing geographic and temporal trends in rotavirus activity in the United States, 1991 to 1996. *Pediatr Infect Dis J*. 1997;16:941–946.
14. Zhou T, Li L, Kim B, et al. Rotavirus infection in children in Japan. *Pediatr Int*. 2002;42:428–439.
15. Meteorological Agency. Climate in Japan in the 20th century. Japan: Printing Bureau; 2003.
16. Reyes M, Ericsson M, Bennet R, Hedlund KO, Ehnst A. Regular pattern of respiratory syncytial virus and rotavirus infections and relation to weather in Stockholm, 1984–1993. *Clin Microbiol Infect*. 1997;3:640–646.
17. Estes MK. Rotaviruses and their replication. In: Knipe DM, Howley PM, Griffin DE, et al, eds. *Fields Virology*. 4th ed. vol 2. New York, NY: Lippincott Williams & Wilkins, 2001;1747–1785.
18. Zhou T, Okitsu S, Maneekarn N, Ushijima H. Distribution of human rotaviruses, especially G9 strains, in Japan from 1996 to 2000. *Microbiol Immunol*. 2003;47:591–599.
19. Glass RI, Noel J, Ando T, et al. The epidemiology of enteric caliciviruses from humans: a reassessment using new diagnostics. *J Infect Dis*. 2000;181(suppl 2):S254–S261.
20. Mounts AW, Ando T, Koopmans M, Bresee JS, Noel J, Glass RI. Cold weather seasonality of gastroenteritis associated with Norwalk-like viruses. *J Infect Dis*. 2000;181(suppl 2):S284–S287.
21. Pang XL, Joensuu J, Vesikari T. Human calicivirus-associated sporadic gastroenteritis in Finnish children less than two years of age followed prospectively during a rotavirus vaccine trial. *Pedatr Infect Dis J*. 1999;18:420–426.
22. Pang XL, Honma S, Nakata S, Vesakiri T. Human caliciviruses in acute gastroenteritis of young children in the community. *J Infect Dis*. 2000;181(suppl 2):S288–S294.
23. Shiech YSC, Monroe SS, Frankhauser RL, Langlois GW, Brurkhardt W III, Baric RS. Detection of Norwalk-like virus in shellfish implicated in illness. *J Infect Dis*. 2000;181(suppl 2):S360–S366.

Geographic and Temporal Trends in Influenzalike Illness, Japan, 1992-1999

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From 1992 to 1999, we analyzed >2.5 million cases of influenzalike illness (ILI). Nationwide influenza epidemics generally lasted 3–4 months in winter. Kriging analysis, which illustrates geographic movement, showed that the starting areas of peak ILI activity were mostly found in western Japan. Two spreading patterns, monotonous and multitonous, were observed. Monotonous patterns in two seasons featured peak ILI activity that covered all of Japan within 3 to 5 weeks in larger epidemics with new antigenic variants of A/H3N2. Multitonous patterns, observed in the other five seasons, featured peak ILI activity within 12 to 15 weeks in small epidemics without new variants. Applying the kriging method allowed better visualization and understanding of spatiotemporal trends in seasonal ILI activity. This method will likely be an important tool for future influenza surveillance in Japan.

Influenza is a highly contagious acute respiratory disease that has caused global epidemics and pandemics. Pandemics in the 20th century have occurred at intervals of 11 to 39 years (1–3). The World Health Organization has requested each member state to produce a pandemic plan. The phasing and geographic spread of influenza pandemics have important implications for future planning, and complete global spread is now likely to occur in ≤6 months, as a result of increased travel and urbanization (4).

The National Epidemiological Surveillance of Infectious Diseases in Japan features sentinel surveillance for 27 infectious diseases, including influenza (5,6). To better understand the movement and velocity of influenza epidemic spread from 1992 to 1999 in Japan, we used a geographic information system (GIS) with generated weekly surveillance data. We focused on the kriging

method to illustrate and clarify spatiotemporal relationships in epidemiologic research, e.g., for rotavirus and influenzalike illness (7–9).

Methods

Influenza Surveillance System in Japan

The systematic surveillance of influenza and influenzalike illness (ILI) as notifiable diseases under Infectious Disease Control Law began in 1981 in Japan. Each ILI case is defined on the basis of a sudden fever ≥38°C, respiratory symptoms, and myalgia. The number of patients with ILI is reported on a weekly basis from ≈2,400 sentinel pediatric and general physicians and 663 health centers throughout Japan. The number of sentinels is decided on the basis of the size of the population of the health center area where they serve: a health center with population <75,000 would have one sentinel, a population 75,000–125,000 would have two, and populations >125,000 would have three + [(population − 125,000)/ 100,000] sentinels (10). Recruitment is on a volunteer basis. Sentinels forward clinical data to ≈60 prefectural or municipal public health institutes, and data generated are electronically reported to the Infectious Disease Surveillance Center in the National Institute of Infectious Diseases (Tokyo) (5,6).

Geographic Analysis

We analyzed surveillance data from 1992 to 1999 for 46 prefectures, excluding Okinawa Prefecture, which is approximately 800 km from the four major islands of Japan. To combine data from all prefectures and examine trends at the national level, we calculated the number of reported ILI cases per sentinel per week after adjusting the epidemic curves with a 5-week unweighted moving aver-

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age (reported ILI cases per sentinel per week [RC/S/W]) as an indicator of ILI activity. This procedure smoothed the data and simplified identification of the seasonal peak (7). The peak week during each influenza season was defined when the greatest unweighted moving average was observed in individual prefectures. For the time scale of geographic analysis, the first week was defined when the first peak was observed in any of the prefectures during the season; subsequent weeks were then numbered accordingly.

For the spatiotemporal spread of the 1992–1999 epidemics in Japan, we used the kriging geostatistical method to estimate point values by using surrounding, known point values (11,12). The address of the prefecture government was used as the representative site of prefecture surveillance data, and unweighted moving average for each prefectural peak week was applied after adjusting the time scale. Kriging uses a weighted moving average interpolation to produce the optimal spatial-linear prediction. The estimated kriging weight matrix is a product of the inverse covariance weight matrix and the distance matrix (11,12).

To make kriging maps as contour maps showing the timing of peak ILI activity, we performed the following steps. First, we created an empiric semivariogram to examine the structure of data. The empiric semivariance is 0.5 times the difference squared, when Euclidean distance is used. Second, this semivariogram estimated the theoretical model parameters through a weighted least-squares technique. The data showed a spherical pattern. Next, the weights were determined by incorporating the spherical pattern of covariance. Finally, we estimated the values at unmeasured points and made filled-contour maps from the kriging weights for the measured values. The isobars on the contour maps represent interpolated time of peak activity distributed spatially and were placed at 1-week intervals. All procedures were carried out on ArcGIS 8.2 (ESRI, Redlands, CA) and Geostatistical Analyst (ESRI) for Windows.

Statistical Analysis

To ascertain the relationship between epidemic scale and velocity of spread, we used three parameters. greatest number of ILI cases, increasing-to-peak period, and nationwide peak-duration. The first parameter was the greatest number of ILI cases, defined as the greatest number of RC/S/W in each prefecture The second parameter was the increasing-to-peak period, defined as the time from the week RC/S/W was >50% of peak to the week of the peak. Influenza epidemics usually show an elevated incidence of ILI before the peak and for some weeks after each epidemic. In our study, sharp increases in ILI cases were seen in the weeks before the epidemic; we focused on these weeks. The means for the two parameters across prefectures were calculated for each season. The third parameter was nationwide peak-duration, defined as the time between the first and last week that showed the greatest number of ILI cases among 46 prefectures in each season. Spearman's correlation coefficient was used to analyze the relationship between all pairs of the three indexes. All calculations were performed with Microsoft Excel 2002 (Microsoft Corp., Redmond, WA), and significance was determined at p < 0.05.

Results

Influenza Epidemics, 1992–1999

We analyzed 2,586,272 ILI cases during the 7-year period from 1992 to 1999. The annual influenza season began between November and December, peaked between January and February, and returned to baseline between April and June for the study period in every year at all reporting sites (Figure 1). Seasonal peaks in ILI activity occurred annually in all prefectures. Nationwide epidemics lasted for 3–4 months, but successive or overlapping waves of infection by influenza A and B sometimes resulted in a more prolonged outbreak, as in the 1996–1997 season.

The predominant circulating strain was A/H3N2 in all seasons, except in 1996, when it was A/H1N1. Larger scale epidemics were observed in the 1992–93, 1994–95, and 1997–98 seasons, when new antigenic variants of A/H3N2 as predominant circulating subtypes were isolated, namely A/Kitakyushu/159/93, A/Wuhan/359/95, and A/Sydney/5/97, respectively. A relatively large-scale epidemic was also observed in the 1998–99 season, but the predominant circulating subtype was A/Sydney/5/97, as in the previous year. The first peak arose from one predominant viral agent and was bigger than the second peak in the 1996–97 season, with a bimodal curve.
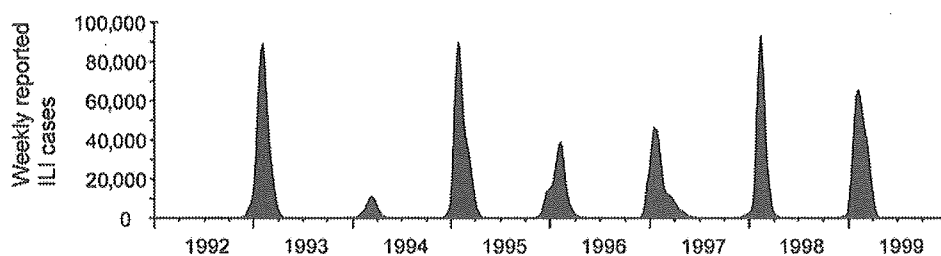

Figure 1. Moving averages of weekly reported influenzalike illness (ILI) cases.

Geographic Analysis

Kriging analysis clearly illustrated spatiotemporal movement of ILI epidemics in Japan (Figure 2). Seasonal ILI activity occurred in a sequential manner, and differences between seasons were easy to identify and characterize. The starting prefectures or areas of the peak ILI activity were mostly in the western part of Japan, except in the 1996–97 season. Trends did not change with the appearance of new variants. The most dramatic differences from year to year were in spreading pattern, as shown in the contour map of peak ILI activity by week. With the monotonous spreading pattern, peak ILI activity covered Japan within 3 to 5 weeks in large epidemics with new antigenic variants of A/H3N2, such as occurred in the 1992–93, 1994–95, 1997–98, and 1998–99 seasons. On the other hand, with the multitonous patterns, peak ILI activity covered Japan within 12 to 15 weeks in small epidemics without new antigenic variants of A/H3N2 in the other four seasons.

Statistical Analysis

During the 7-year study period, the greatest number of ILI cases, the increasing-to-peak period, and the nationwide peak duration were 4.67–40.88 ILI cases per sentinel per week, 3.43–4.83 weeks, and 3–15 weeks, respectively (Figure 3). With the larger epidemics, such as in 1992–93, 1994–95, and1997–98, and, to a lesser extent, 1998–99, the greatest number of ILI cases was >28 RC/S/W, the increasing-to-peak period was <4 weeks, and the nation-
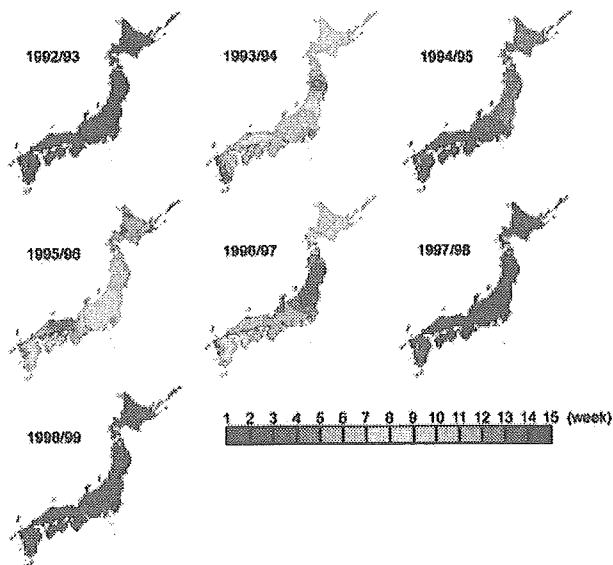

Figure 2. Timing of peak influenzalike illness epidemic activity by week in Japan. The isobars on the contour maps represent interpolated time of peak activity distributed spatially at 1-week intervals. The first week was defined when the peak week was observed first in any one of the prefectures in each season, and then the following weeks were numbered.

wide peak duration was <5 weeks. These three parameters were interrelated ($p < 0.05$).

Discussion

The size of epidemics and their relative effect reflect interplay between antigenic variation of the virus, protective immunity in the population, and relative virulence of the viruses. Kriging analysis showed several temporal and spatial patterns of influenza epidemics in Japan, which had not previously been clearly recognized.

Climate conditions, especially temperature, strongly affect influenza epidemics. Influenza in temperate areas is characterized by one annual epidemic in winter (4,13,14), and the influenza season occurs from November through April in Japan. The kriging map showed that the first epidemic areas with the greatest number of ILI cases in 46 prefectures were in western-central Japan during the 7-year study period, except in one season. The map showed nationwide epidemic patterns spreading in concentric circles from western-central Japan to eastern Japan. Mean temperature in winter is lower in eastern Japan than in western-central Japan, so cool temperatures are not essential to initiate epidemics.

Immunization coverage, increase in population density, and more frequent international and domestic traffic may have changed the course of epidemics and modified space-time spread (15–17). Immunization coverage is almost the same in all regions of Japan, while population density and traffic are higher in western-central Japan than in the eastern areas. Therefore, we can conclude that the last two factors may affect the nationwide spreading patterns of epidemics (15–17).

The kriging maps showed seasonal ILI activity occurring with two different patterns of peak ILI activity. Larger epidemics with new A/H3N2 variants as antigenic drift showed monotonous patterns, and these epidemics' peak ILI required only 3–5 weeks to cover the whole country. By contrast, small epidemics without new variants showed multitonous patterns, and peak ILI required 11–15 weeks to spread. A relatively large-scale epidemic with A/Sydney/5/97 was observed in the 1998–99 season, as in the previous year. The age distribution of ILI cases in the 1997–98 season was mostly <10 years of age, and in 1998 to 1999, the age distribution was mostly >15 years (18); these became two successive, large-scale epidemics. We conclude that kriging maps can indicate the spreading mode and velocity in conjunction with the extent of antigenic change of A/H3N2. However, the time period used for this analysis may not be representative of influenza over the long term, since we studied a period with an unusual predominance of influenza A/H3N2 viruses. Thus, we need further GIS study to know the spreading mode and velocity in conjunction with various strains.
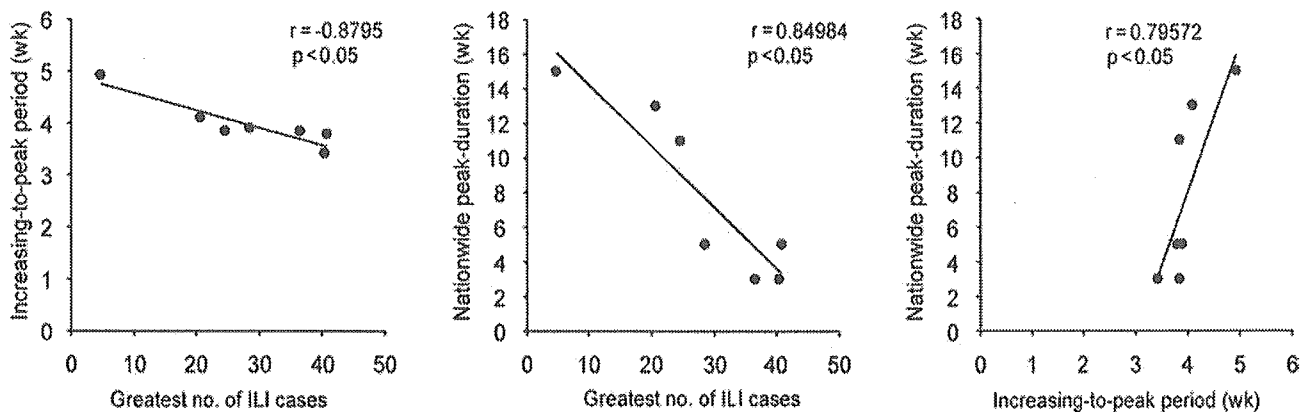
Figure 3. Correlation analysis among three parameters. Greatest number of cases refers to the greatest number of reported influenza-like illness (ILI) cases per sentinel per week (RC/S/W) in each prefecture in each season. The increasing-to-peak period refers to the period from the week when the number of RC/S/W reached >50% of the peak to the peak week. The means of the above two parameters were calculated by season and used for analysis. The nationwide peak-duration refers to the time between the first and last peak week observed among 46 prefectures.

The kriging map allowed us to better visualize and understand spatiotemporal trends in seasonal influenza activity (8,9). To confirm the GIS observations, especially the scale of epidemics and velocities, we developed three parameters: greatest number of ILI cases, increasing-to-peak period, and nationwide peak duration, which demonstrated significant interrelation (p < 0.05). We conclude that the larger the greatest number of RC/S/W found, the shorter the increasing-to-peak period and also the shorter the nationwide peak duration. As the scale of the greatest number of ILI cases obtained at the national level was connected with those from prefectural data and had an effect on the spreading mode and velocity of peak ILI activity, the greatest number of ILI cases obtained from the first prefecture in the season also is worthy of attention.

Influenza pandemics occur when a novel influenza virus emerges and most of the world's population has no immunity against it. These pandemics have been observed only with influenza A viruses, which exist in nature as a number of antigenically distinct subtypes and are due to the emergence of a novel hemagglutinin on the virus surface with or without a concomitant change in neuraminidase. In a pandemic, the number of new general practice visits for ILI can be expected to exceed 500 per 100,000 population per week; a medical practice of 10,000 patients would therefore expect to see at least 50 new patients per week (3). Under these conditions, our results indicate that the nationwide peak-duration might be <2 weeks. Therefore, once a pandemic begins, it will be too late to accomplish many key activities required to minimize its impact. Thus, preparatory activities must start well in advance (19). Stockpiling antiinfluenza drugs (1,14,20) seems a reasonable option until prophylactic strategies based on better vaccines can be implemented. Our results demonstrate that GIS is an effective surveillance tool to clarify the dynamics of influenza epidemics.

Dr. Sakai is a postgraduate student who studies the epidemiology of respiratory infectious disease using GIS at the Division of Public Health, Department of Infectious Disease Control and International Medicine, Niigata University Graduate School of Medical and Dental Sciences.

References

1. Cox NJ, Tamblyn SE, Tam T. Pandemic planning. Vaccine. 2003;21:1801–3.
2. Nicholson KJ, Wood JM, Zambon M. Influenza. Lancet. 2003;362:1733–45.
3. Oxford JS, Bossuyt S, Balasingam S, Mann A, Novelli P, Lambkin R. Treatment of epidemic and pandemic influenza with neuraminidase and M2 proton channel inhibitors. Clin Microbiol Infect. 2003;9:1–14.
4. Nguyen-Van-Tam JS, Hampson AW. The epidemiology and clinical impact of pandemic influenza. Vaccine. 2003;21:1762–8.
5. Okabe N, Yamashita K, Taniguchi K, Inouye S. Influenza surveillance system of Japan and acute encephalitis and encephalopathy in the influenza season. Pediatr Int. 2000;42:187–91.
6. Ohshiro H, Kawamoto K, Nose T. Surveillance system of infectious diseases in Japan. J Epidemiol. 1996;3 Suppl:S81–5.
7. Torok TJ, Kilgore PE, Clarke MJ, Holman RC, Bresee JS, Glass RI. Visualizing geographic and temporal trends in rotavirus activity in the United States, 1991 to 1996. Pediatr Infect Dis J. 1997;16:941–6.
8. Carrat F, Valleron AJ. Epidemiologic mapping using the "kriging" method: application to an influenza-like illness epidemic in France. Am J Epidemiol. 1992;135:1293–300.

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9. Carrat F, Flahault A, Boussard E, Farran N, Dangoumau L, Valleron AJ. Surveillance of influenza-like illness in France. The example of the 1995/1996 epidemic. J Epidemiol Community Health. 1998;52(Suppl 1):32S–8.

10. Murakami Y, Hashimoto S, Taniguchi K, Nagai M. Distributions of the numbers of monitoring station in the surveillance of infectious disease in Japan [article in Japanese]. Nippon Koshu Eisei Zasshi. 1999;46:1060–7.

11. Issaks EH, Srivastava RM. Applied geostatistics. New York: Oxford University Press; 1989.

12. Oliver MA, Webster R. Kriging: a method of interpolation for geographical information system. Int J Geogr Inf Sci. 1990;4:313–32.

13. Simonsen L. The global impact of influenza on morbidity and mortality. Vaccine. 1999;17:S3–10.

14. Hampson AW. Epidemiological data on influenza in Asian countries. Vaccine. 1999;17:S19–23.

15. Rvachev LA, Longini IM. A mathematical model for the global spread of influenza. Math Biosci. 1985;22:3–22.

16. Bonabeau E, Toubiana L, Flahault A. The geographical spread of influenza. Proc R Soc Lond B Biol Sci. 1998;265:2421–5.

17. Flahault A, Deguen S, Valeron AJ. A mathematical model for the European spread of influenza. Eur J Epidemiol. 1994;10:471–4.

18. Influenza, 1998/99 season, Japan. Infectious Agents Surveillance Report. 1999;20:289–90.

19. Gerdi C. The annual production cycle for influenza vaccine. Vaccine. 2003;21:1776–9.

20. Monto AS. The role of antivirals in the control of influenza. Vaccine. 2003;21:1796–800.

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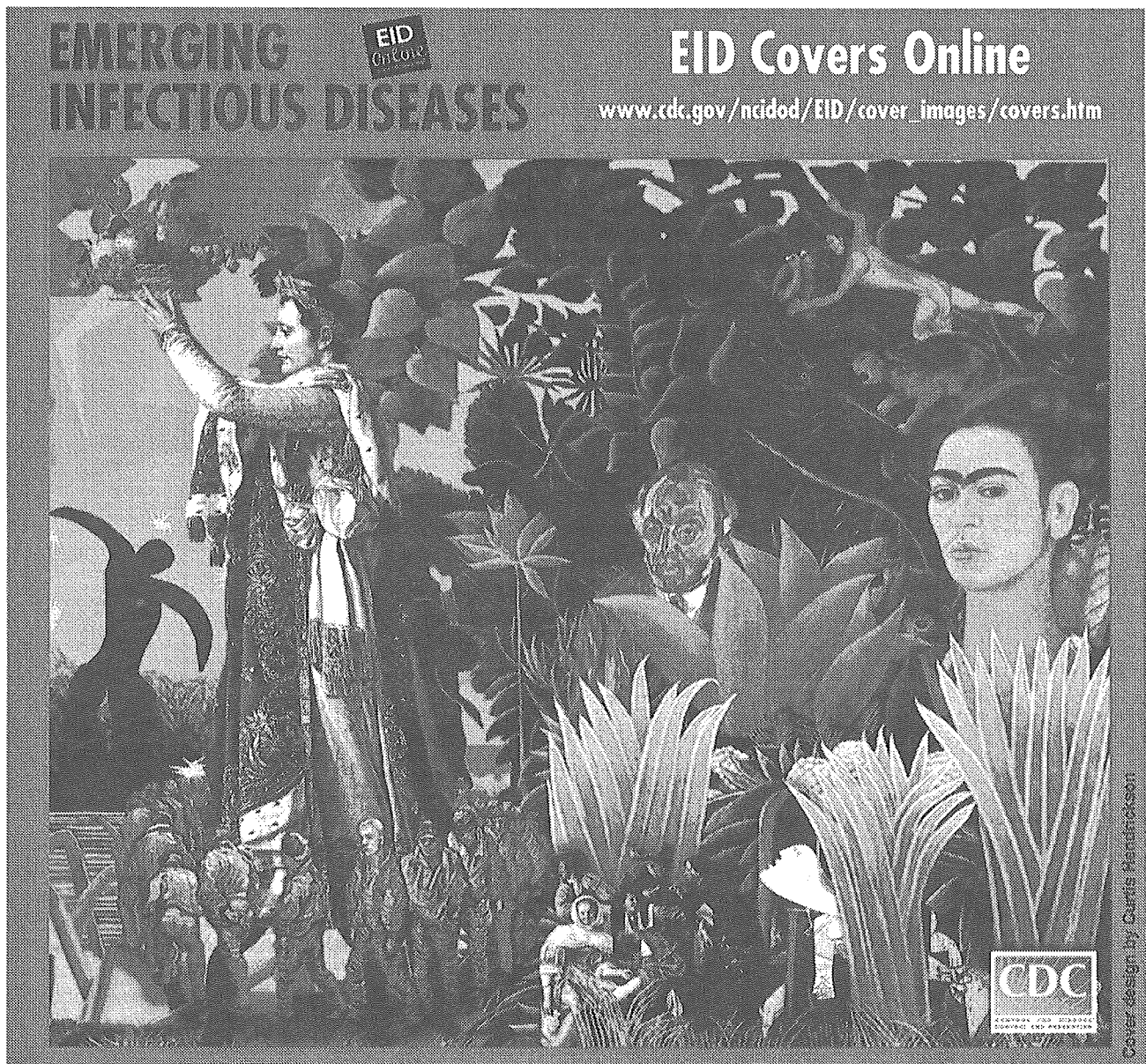
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Evaluation of a Method for Issuing Warnings Pre-epidemics and Epidemics in Japan by Infectious Diseases Surveillance

Yoshitaka Murakami, Shuji Hashimoto, Kiyosu Taniguchi,
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Original Article

Evaluation of a Method for Issuing Warnings Pre-epidemics and Epidemics in Japan by Infectious Diseases Surveillance

Yoshitaka Murakami,[1] Shuji Hashimoto,[2] Kiyosu Taniguchi,[3] Ken Osaka,[3] Hiroshi Fuchigami,[4] and Masaki Nagai.[5]

BACKGROUND: Simple methods have been developed to warn of pre-epidemics and epidemics in small areas using data of infectious diseases surveillance. Epidemic warnings are made if the index of cases per week per sentinel medical institution is greater than a defined value. A pre-epidemic warning means that an epidemic warning will be given in the following four weeks. While the methods are used routinely for surveillance in Japan, they remain to be validated.

METHODS: Infectious diseases surveillance data of influenza-like illness and 12 pediatric diseases in the fiscal year between 1999 and 2001 were used in the analysis. We examined the frequency of warnings, temporal changes in the index before and after the onset of a warning, and the sensitivity, specificity, and positive predictive value of pre-epidemic warnings.

RESULTS: For the majority of the diseases investigated, the proportion of weeks in which a warning was issued ranged between 0% and 10%. In several diseases including influenza-like illness, we observed a rapid increase and gradual decrease in the index before and after a warning. The sensitivity, specificity, and positive predictive value of a pre-epidemic warning were 90.4%, 93.7% and 23.9% for influenza-like illness, and ranged between 25.1-54.2%, 86.1-99.2%, and 2.5-20.8% for the pediatric diseases (chickenpox, rubella, measles, and mumps), respectively.

CONCLUSIONS: The study showed that the methods used for determining whether or not to issue an epidemic warning were satisfactory in some diseases, including influenza-like illness, and may need to be improved in several other diseases.
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Key words: communicable disease, surveillance, disease outbreaks, warning, evaluation studies.

The surveillance of infectious diseases is conducted in many countries.[1-9] Numerous methods for detecting and forecasting epidemics from the surveillance data have been developed and evaluated, with some of these methods being used in surveillance systems.

A surveillance system of infectious diseases has been introduced in Japan with the aim of detecting epidemics in small areas (e.g. a public health center area).[9] The application of a warning system for small areas is unique to Japan when compared with other countries. The requirement for pre-epidemic and epidemic warnings of several infectious diseases are reviewed weekly in every public health center area using surveillance data. The information on influenza-like illness is then made available to the general public through the World Wide Web (http://idsc.nih.go.jp/

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others/topics/inf-keiho/trend02.html, Accessed on February 10, 2004). In April 1999, the surveillance system was expanded by the Infectious Disease Control Law. Prior to this law change, warnings of influenza-like illness were based on reports on the number of cases each week in sentinel medical institutions, selected mainly from pediatric departments in hospitals and clinics. After this law change, the surveillance system was expanded to include sentinel medical institutions in internal medicine departments in hospitals and clinics. The criteria for determining whether to issue pre-epidemic and epidemic warnings for infectious diseases including influenza-like illness were developed using surveillance data collected prior to the law change. However, these original criteria have been evaluated on data acquired by the current surveillance system. We therefore carried out a study to evaluate the performance of these methods using surveillance data collected in Japan from April 1999 through March 2002.

METHODS

Surveillance of Infectious diseases in Japan

The National Epidemiological Surveillance of Infectious Diseases in Japan is organized by the Ministry of Health, Labor, and Welfare[9] and is operated by the Infectious Disease Surveillance Center, National Institute of Infectious Diseases. The system collects data on influenza-like illness and pediatric diseases. Prior to the introduction of the Infectious Disease Control Law in April 1999, the sentinel medical institutions in the two surveillance systems were selected mainly from pediatric departments in hospitals and clinics. Following the introduction of this law, the influenza-like illness surveillance system also includes sentinel medical institutions of the internal medicine departments in hospitals and

clinics. The number of sentinel medical institutions in April 2002 was 4,656 in the influenza-like illness surveillance system and 3,011 in the pediatric diseases surveillance system.[10] The number of sentinel medical institutions in the health center areas was approximately proportional to their population size.[11] Sentinel medical institutions were recruited on a voluntary basis, and each of the sentinel medical institutions sent weekly reports of the number of cases of notifiable diseases to the public health center. The public health center notified local government using an on-line computer network. The notifiable diseases were influenza-like illness in the influenza-like illness surveillance system and 12 diseases in the pediatric diseases surveillance system (Table 1).

The method for detecting epidemics

The warnings were based on an index calculated from the number of cases per week per sentinel medical institution. An epidemic warning in a public health center area was given if the index in the area exceeded the critical value for the onset of an epidemic and continued until the index in that area was lower than the critical value for the end of an epidemic.[12] The critical value for the onset of an epidemic fell between the 95th and 99th percentiles of the distribution of indices in 1993-1997, while the critical values for the end of epidemic were defined as the 90th percentiles of the distribution.[13] The method for issuing an epidemic warning was applied to data on influenza-like illness and 12 pediatric diseases. Like infectious disease surveillance in Japan, we made a pre-epidemic warning, which was issued before an epidemic warning, for five diseases (influenza-like illness, chickenpox, rubella, measles and mumps). These diseases would need much attention against early detection of epidemic for the public health activities. In a public health center area, a pre-epidemic warning was made only if the index in the area exceeded the critical value for a pre-

Table 1. Critical values (cases per week per sentinel medical institution) for issuing (onset) and ending epidemic warnings, and issuing pre-epidemic warning in infectious disease surveillance in Japan.

Diseases	Warning		Pre-epidemic warning
	onset	end	
Influenza-like illness	30	10	10
Pharyngoconjunctival fever	1	0.1	—
Group A streptococcal pharyngitis	4	2	—
Infectious gastroenteritis	20	12	—
Chickenpox	7	4	4
Hand-foot-mouth disease	5	2	—
Erythema infectiosum	2	1	—
Exanthema subtium	4	2	—
Pertussis	1	0.1	—
Rubella	3	1	1
Herpangina	6	2	—
Measles	1.5	0.5	0.5
Mumps	5	2	3

The numbers in the table are cases per week per sentinel medical institution.

epidemic warning. This meant that an epidemic warning would then be issued in that area in the following four weeks. The critical value was determined according to the sensitivity, specificity, and positive predictive value of a pre-epidemic warning calculated using surveillance data of 1993-1997. This method for determining a pre-epidemic warning was then applied to data on influenza-like illness and four pediatric diseases. Table 1 shows the critical values for each disease.

Evaluation of the method for detecting epidemics

We analyzed surveillance data of infectious diseases collected from April 1999 through March 2002. The public health center areas in the survey in April 1999 (583 areas) were used for the analysis. The data set consists of reports on the number of cases per week per sentinel medical institution in each public health center area(583 areas) collected over the 3 fiscal years of the study (i.e.157 weeks).

The proportion of weeks, in which epidemic and pre-epidemic warnings was issued in the 583 public health center areas during the fiscal year of 1999-2001, was calculated and compared with similar data of 1993-1997. Temporal changes in the indices before and after an epidemic warning during 1999 and 2001 were examined for the evaluation of warning. The sensitivity, specificity, and positive predictive values of pre-warning were calculated for the evaluation of pre-warning. Sensitivity was calculated as the proportion of valid pre-warnings made four weeks prior to an epidemic warning, while specificity was calculated as the proportion of weeks in which no pre-epidemic warning was issued relative to the total number of weeks without an epidemic warning including the four weeks before and after the warning. The positive predictive value was defined as the proportion of valid pre-epidemic warnings relative to the total number of pre-epidemic warnings.

RESULTS

The annual number of cases per sentinel medical institution is shown in Table 2. For many diseases, including influenza-like illness, the numbers of cases per sentinel medical institution in the fiscal years of 1999-2001 varied within or near the range of those recorded of 1993-1997. For group A streptococcal pharyngitis, chickenpox, exanthema subtium, and herpangina, the number of cases per sentinel medical institution was higher in the years 1999-2001 compared to 1993-1997. In contrast, the number of cases of rubella per sentinel medical institution was lower in the years 1999-2001 than in 1993-1997.

Table 3 shows the proportions of weeks in which an epidemic warning for influenza-like illness or the 12 pediatric diseases was issued in the 583 public health center areas during the fiscal year of 1999-2001. These proportions were similar to those recorded in 1993-1997. In exanthema subtium, pertussis, and rubella, the proportions of weeks with an epidemic warning were lower in the years of 1999-2001 than in 1993-1997.

The temporal changes in the number of cases per week per sentinel medical institution before and after a warning onset are summarized in Table 4. For influenza-like illness, the median index of weeks in which the 596 epidemic warnings were issued in 1999-2001 was 37.0. The index increased markedly in the 4 weeks before the warnings were made as seen by following changes in median values: 1.3 on the 4th week before the warnings had been issued, 3.5 on the 3rd week, 9.0 on the 2nd week, and 20.0 on the 1st week. The median index was observed to then decrease gradually, being 39.0 in the 1st week after the warning had been issued, 29.9 on the 2nd week, 18.7 on the 3rd week, and 11.3 on the 4th

Table 2. Annual numbers of cases per sentinel medical institution in infectious disease surveillance in Japan, April 1999-March 2002, compared with range of those in 1993-1997.

Diseases	Annual numbers of cases per sentinel medical institution			Range(1993-1997)	
	April 1999-March 2000	April 2000-March 2001	April 2001-March 2002	minimum	maximum
Influenza-like illness	193.13	57.01	144.50	44.75	312.12
Pharyngoconjunctival fever	4.12	7.85	7.76	1.76	4.39
Group A streptococcal pharyngitis	43.81	57.60	50.82	24.71	34.88
Infectious gastroenteritis	294.63	299.58	287.90	192.51	498.41
Chickenpox	84.02	97.85	83.54	73.40	77.98
Hand-foot-mouth disease	18.68	70.25	41.10	10.07	65.35
Erythema infectiosum	8.64	14.31	23.09	5.29	22.74
Exanthema subtium	42.79	42.67	40.70	34.22	36.75
Pertussis	1.16	1.18	0.56	1.14	2.34
Rubella	1.24	1.05	0.89	6.70	61.20
Herpangina	53.80	49.12	47.06	29.98	39.60
Measles	3.40	9.42	9.28	6.50	14.30
Mumps	30.89	58.13	83.66	29.21	62.37

Data of fiscal years are used in 3 years from 1999 through 2001.

week. These median values were higher than those measured in other weeks. For hand-foot-mouth disease and herpangina, we also observed a rapid increase in the value of median indices prior to an epidemic warning and a gradual decrease after this warning similar to that seen with influenza-like illness. However, for pertussis and rubella, these changes in the value of the median indices before and after epidemic warnings onset were not observed.

The proportions of weeks over the period of 1999-2001 in which a pre-epidemic warning was made for influenza-like illness and the 4 pediatric diseases, chickenpox, rubella, measles, and mumps in the 583 public health center areas is shown in Table 5. For influenza-like illness, the proportions of weeks with a pre-epidemic warning were 5.7%, 2.7%, and 4.6% in 1999, 2000, and 2001, respectively. These proportions were similar to those recorded in 1993-1997. For rubella, the proportion of weeks with a pre-warning warning in 1999-2001 was lower than in 1993-1997.

Table 6 shows the temporal changes in the number of cases per week per sentinel medical institution before and after a pre-epidemic warning onset. For influenza-like illness, the median index in the 1,333 in which a pre-epidemic warning was issued over the period of 1999-2001 was 13.6. The median index increased in the 4 weeks prior to this warning and was found to be 0.5 on the 4th week before the pre-warning had been issued, 1.1 on the 3rd week, 2.8 on the 2nd week, and 6.3 on the 1st week. The median index continued to increase and then decreased gradually being 19.0, 20.7, 18.0, and 12.7 on the 1st, 2nd, 3rd, and 4th weeks after the warning, respectively. These median indices were higher than

those measured in the other weeks. For chickenpox and mumps, the median indices before and after the pre-epidemic warning were also higher than in the other weeks, whereas for rubella and measles, many of the indices before and after the warning were zero, similar to that observed in the other weeks.

The sensitivity, specificity, and positive predictive values of the pre-epidemic warnings are listed in Table 7. For influenza-like illness, the sensitivity was 90.4%; the specificity was 93.7% and the positive predictive value 23.9%. For the four pediatric diseases, the sensitivity ranged between 25.1% and 54.2%, the specificity between 86.1% and 99.2%, and the positive predictive value between 2.5 and 20.8%.

DISCUSSION

This study is to evaluate a method of pre-epidemic and epidemic warning by examining a huge number of observations. For this purpose, we decided to provide a detailed description of data and not to use a method of statistical testing.

In this study, the critical values for determining when epidemic warnings should be issued at both the onset and the end of an epidemic were determined using data of the frequency of epidemic warnings from 1993 through 1997. The reason for establishing these critical values is that the definition of epidemic is not well standardized in many infectious diseases, and also that neither frequent nor very rare warnings are adequate for public health standards. In many of the diseases we investigated, including influenza-like illness, the proportion of weeks in which an epidemic warning was issued was very similar in the two study periods.

Table 3. The proportion of weeks in which an epidemic warnings were issued in public health center areas in April 1999-March 2002, compared with range of those in 1993-1997.

| | The proportion of epidemic warning weeks (%) | | | | |
| | | | | Range(1993-1997) | |
Diseases	April 1999-March 2000	April 2000-March 2001	April 2001-March 2002	minimum	maximum
Influenza-like illness	3.3	0.5	5.5	0.7	10.9
Pharyngoconjunctival fever	3.2	6.4	7.3	1.8	5.0
Group A streptococcal pharyngitis	4.6	7.7	6.4	3.6	5.2
Infectious gastroenteritis	6.5	6.9	6.0	3.6	7.3
Chickenpox	2.8	4.3	2.7	4.1	4.7
Hand-foot-mouth disease	1.7	10.5	5.2	1.0	11.9
Erythema infectiosum	1.7	3.1	6.6	1.2	8.9
Exanthema subtium	0.7	0.5	0.3	1.8	2.7
Pertussis	0.3	0.4	0.1	0.8	2.1
Rubella	0.1	0.1	0.0	1.7	19.6
Herpangina	7.8	6.2	6.7	4.2	6.7
Measles	1.2	3.8	4.5	4.2	8.2
Mumps	2.0	5.9	11.2	3.4	9.5

Data of fiscal years are used in 3 years from 1999 through 2001.
The proportion of epidemic warning weeks: the number of epidemic warnings which were issued in all the public health center area during the fiscal year 1999-2001 divided by the number of weeks in all the public health center area (583 areas) during the fiscal year 1999-2001(157 weeks).

Table 4. Median, the 25th and 75th percentile of weekly cases per sentinel medical institution before and after the issuing of an epidemic warning.

		Before warning onset				Onset week	After warning onset				Non-warning weeks
		4weeks	3weeks	2weeks	1week		1week	2weeks	3weeks	4weeks	
Influenza-like illness	median	1.3	3.5	9.0	20.0	37.0	39.0	29.9	18.7	11.3	0.0
	25th percentile	0.3	1.2	5.2	14.6	32.5	28.2	20.3	11.9	5.8	0.0
	75th percentile	4.0	7.4	14.9	25.0	44.2	52.5	44.9	30.0	18.9	0.3
	number of observation	596	596	596	596	596	595	594	586	579	84,353
Pharyngoconjunctival fever	median	0.0	0.0	0.0	0.1	1.1	0.3	0.3	0.3	0.2	0.0
	25th percentile	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
	75th percentile	0.2	0.3	0.3	0.5	1.5	1.0	0.8	0.8	0.6	0.0
	number of observation	955	955	955	955	955	949	946	942	939	80,050
Group A streptococcal pharyngitis	median	1.3	1.5	1.9	2.0	4.5	2.8	2.3	2.3	2.0	0.4
	25th percentile	0.7	0.7	1.0	1.3	4.0	1.5	1.2	1.0	1.0	0.0
	75th percentile	2.0	2.3	2.7	3.0	5.3	4.0	4.0	3.6	3.8	1.0
	number of observation	873	873	873	873	873	870	867	862	854	81,355
Infectious gastroenteritis	median	6.3	8.1	11.1	15.0	23.0	21.7	18.5	14.6	12.3	2.7
	25th percentile	3.7	5.3	8.0	12.2	21.0	16.3	12.5	9.0	8.0	0.9
	75th percentile	10.0	11.6	14.0	17.5	26.3	28.3	27.4	21.8	18.3	5.8
	number of observation	1,012	1,012	1,012	1,012	1,012	1,011	1,010	1,004	996	79,140
Chickenpox	median	2.7	3.0	4.3	3.3	8.0	4.0	5.5	4.0	4.3	1.0
	25th percentile	1.5	1.5	3.0	2.0	7.3	2.7	3.6	2.3	2.5	0.3
	75th percentile	4.0	4.4	5.5	4.8	9.0	5.8	8.0	5.8	6.5	2.0
	number of observation	628	628	628	628	628	624	620	617	613	84,541
Hand-foot-mouth disease	median	0.8	1.3	2.0	3.0	6.0	6.1	6.1	5.3	4.5	0.0
	25th percentile	0.2	0.5	1.0	2.0	5.3	3.7	3.0	2.3	2.0	0.0
	75th percentile	1.7	2.1	3.0	4.0	7.5	8.6	10.2	10.4	10.0	0.4
	number of observation	743	743	743	743	743	743	743	742	741	80,735
Erythema infectiosum	median	0.5	0.5	0.7	0.8	2.3	1.1	1.0	1.0	0.8	0.0
	25th percentile	0.0	0.0	0.2	0.3	2.0	0.5	0.4	0.3	0.3	0.0
	75th percentile	1.0	1.0	1.1	1.3	2.7	2.0	2.0	1.8	1.6	0.3
	number of observation	611	611	611	611	611	609	604	598	593	84,750
Exanthema subtium	median	1.3	1.3	1.3	1.3	4.3	2.0	2.0	1.8	1.7	0.6
	25th percentile	0.9	1.0	0.7	1.0	4.0	1.0	1.0	1.0	0.8	0.3
	75th percentile	2.3	2.0	2.0	2.5	5.0	3.0	2.7	3.0	2.7	1.0
	number of observation	133	133	133	133	133	132	131	131	131	90,158
Pertussis	median	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
	25th percentile	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
	75th percentile	0.0	0.0	0.0	0.0	1.3	0.2	0.0	0.0	0.0	0.0
	number of observation	134	134	134	134	134	133	133	133	133	90,271
Rubella	median	0.0	0.0	0.0	0.0	3.5	0.0	0.0	0.0	0.0	0.0
	25th percentile	0.0	0.0	0.0	0.0	3.0	0.0	0.0	0.0	0.0	0.0
	75th percentile	0.3	0.8	0.3	0.7	5.0	2.0	2.0	1.0	0.0	0.0
	number of observation	11	11	11	11	11	11	11	11	11	91,409
Herpangina	median	0.5	1.0	2.2	3.8	7.5	8.0	7.8	6.0	4.3	0.0
	25th percentile	0.1	0.5	1.0	2.5	6.5	5.6	4.6	3.3	2.2	0.0
	75th percentile	1.3	2.0	3.3	4.9	9.2	11.3	12.0	10.5	7.7	0.3
	number of observation	972	972	972	972	972	972	972	972	972	77,651
Measles	median	0.1	0.2	0.4	0.4	1.9	0.8	0.8	0.6	0.6	0.0
	25th percentile	0.0	0.0	0.0	0.0	1.6	0.1	0.0	0.0	0.0	0.0
	75th percentile	0.5	0.5	0.8	0.8	2.3	1.4	1.6	1.5	1.3	0.0
	number of observation	449	449	449	449	449	444	442	442	440	85,802
Mumps	median	1.5	2.5	2.7	2.5	5.7	3.0	3.7	4.0	3.0	0.5
	25th percentile	1.0	1.7	1.7	1.5	5.3	2.0	2.5	2.5	1.8	0.0
	75th percentile	2.7	3.5	3.6	3.4	6.5	4.5	5.0	5.7	4.8	1.0
	number of observation	504	504	504	504	504	495	487	480	475	83,647

The data are expressed as median, the 25th and 75th percentile of cases per week per sentinel medical institution.
The number of observations represents the total number of weeks in which indices fall into the various categories.
The period from the beginning of week in April 1999 till the end of week in March 2002 are used for the analysis.

Table 5. The proportions of weeks in which an pre-epidemic warnings were issued in public health center areas from April 1999 through March 2002, compared with the range of those in 1993-1997.

Diseases	The proportion of pre-epidemic warning weeks (%)			Range(1993-1997)	
	April 1999-March 2000	April 2000-March 2001	April 2001-March 2002	minimum	maximum
Influenza-like illness	5.7	2.7	4.6	1.9	4.5
Chickenpox	6.0	7.4	5.8	6.2	6.9
Rubella	0.4	0.2	0.2	3.4	9.5
Measles	2.3	6.2	5.8	5.2	8.2
Mumps	1.9	4.0	6.0	2.1	4.7

Data of fiscal years are used in 3 years from 1999 through 2001.

The proportion of pre-epidemic warning weeks: the number of pre-epidemic warnings which were issued in all the public health center area during the fiscal year 1999-2001 divided by the number of weeks in all the public health center area (583 areas) during the fiscal year 1999-2001(157 weeks).

Table 6. Median, the 25th and 75th percentile of weekly cases per sentinel medical institution before and after the issuing of a pre-epidemic warning.

		Weekly cases per sentinel medical institution									Other
		4weeks	3weeks	2weeks	1week	Onset week	1week	2weeks	3weeks	4weeks	weeks*
Influenza-like illness	median	0.5	1.1	2.8	6.3	13.6	19.0	20.7	18.0	12.7	0.0
	25th percentile	0.0	0.3	1.3	4.3	11.5	12.6	12.3	8.9	5.9	0.0
	75th percentile	1.4	2.6	4.8	8.2	17.1	27.4	32.5	30.0	23.0	0.1
	number of observation	1,333	1,333	1,333	1,333	1,333	1,332	1,325	1,317	1,308	79,626
Chickenpox	median	2.0	2.0	2.5	2.0	4.5	2.7	3.4	2.7	2.9	0.9
	25th percentile	1.0	1.0	1.7	1.3	4.1	1.7	2.3	1.7	1.8	0.3
	75th percentile	3.0	3.0	3.3	3.0	5.1	3.8	4.9	4.0	4.3	1.8
	number of observation	2,239	2,239	2,239	2,239	2,239	2,220	2,205	2,191	2,184	72,190
Rubella	median	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
	25th percentile	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
	75th percentile	0.0	0.0	0.0	0.0	1.5	0.3	0.2	0.0	0.0	0.0
	number of observation	154	154	154	154	154	151	150	149	148	90,185
Measles	median	0.0	0.0	0.0	0.0	0.6	0.2	0.2	0.0	0.0	0.0
	25th percentile	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0
	75th percentile	0.2	0.2	0.3	0.2	0.8	0.5	0.5	0.4	0.5	0.0
	number of observation	1,818	1,818	1,818	1,818	1,818	1,803	1,787	1,779	1,772	75,926
Mumps	median	1.5	1.7	1.7	1.5	3.3	2.0	2.0	2.3	2.0	0.4
	25th percentile	0.8	1.0	1.0	1.0	3.0	1.1	1.3	1.5	1.0	0.0
	75th percentile	2.1	2.3	2.3	2.0	3.8	2.8	3.0	3.3	3.0	1.0
	number of observation	1,444	1,444	1,444	1,444	1,444	1,435	1,421	1,408	1,395	79,159

The data are expressed as median, the 25th and 75th percentile of cases per week per sentinel medical institution.

The number of observations represents the total number of weeks in which indices fall into the various categories.

The period from the beginning of week in April 1999 till the end of week in March 2002 are used for the analysis.

*Other weeks: weeks that exclude the week of onset and before and after the onset of a pre-epidemic warning.

Table 7. The sensitivity, specificity, and positive predictive values of an pre-epidemic warning in infectious disease surveillance in Japan, April 1999-March 2002.

	Sensitivity	Specificity	Positive predictive value
Influenza-like illness	90.4	93.7	23.9
Chickenpox	54.2	86.1	17.7
Rubella	36.4	99.2	2.5
Measles	43.7	89.3	16.3
Mumps	25.1	91.7	20.8

The numbers in the table are expressed as percentage (%)

The above result is based on the analysis of all the weekly cases per sentinel medical institution in the public health center areas (583 areas), from the beginning of week in April 1999 till the end of week in March 2002 (157 weeks).

The sensitivity is the proportion of valid pre-warnings, in the 4 weeks before the onset of an epidemic warning.

The specificity is the proportion of weeks without a pre-epidemic warning relative to the total number of weeks, in which there was no epidemic warning nor the 4 weeks before and after epidemic warning.

The positive predictive value is the proportion of valid pre-epidemic warnings relative to the total of pre-epidemic warnings.

With regard to the frequency of epidemic warnings, the method for determining when an epidemic warning should be issued in the current surveillance system was as applicable as that in the previous surveillance system. However, the frequency of epidemics of exanthema subtium, pertussis, and rubella during a 3 year period from 1999 through 2001 was lower than that in 1993-1997. With regard to rubella, the number of cases per week per sentinel medical institution in 1999-2001 was considerably lower than in 1993-1997, a difference that was reflected by a lower prevalence of epidemics in 1999-2001. For exanthema subtium and pertussis, the patterns of epidemics appeared to be different between the two periods and therefore it may be necessary to modify the critical values of these epidemic warning.

In a situation when many cases occur in the weeks immediately after an epidemic warning, such warnings are useful because they initiate public health activities against the epidemic. In our study we examined the temporal changes in the numbers of cases per week per sentinel medical institution before and after an epidemic warning over the period of 1999-2001. For several diseases including influenza-like illness, we observed a gradual decrease in the index after the onset of an epidemic warning. This observation suggested that an epidemic warning may in itself result in useful public health activities against an epidemic. However, such a desirable temporal change was not observed for diseases such as pertussis and rubella.

The frequency of pre-epidemic warnings for influenza-like illness, chickenpox, measles, and mumps in 1999-2001 was similar to that recorded in 1993-1997. With regard to the frequency of

pre-epidemic warnings, the method used currently for issuing these warnings was as applicable as that used in previous surveillance system. For example, although the frequency of pre-epidemic warnings for rubella in 1999-2001 was lower than in 1993-1997 this may simply reflect that there was a lower incidence of this disease in 1999-2001.

In this study we also examined the temporal changes in the number of cases per week per sentinel medical institution before and after a pre-epidemic warning in 1999-2001. For influenza-like illness, the index continued to increase and then decreased gradually after the warning had been issued. This pattern of temporal changes is a desirable outcome of a pre-epidemic warning. In contrast, pre-epidemic warnings for the four other diseases we investigated did not result in these desirable temporal changes.

The sensitivity, specificity, and positive predictive value of the critical values selected for issuing a pre-epidemic warning were also determined using surveillance data in 1993-1997. The specificity of the pre-epidemic warnings issued in 1999-2001 for all the diseases investigated ranged between 86.1% and 99.2%. We have pointed out in a previous report that pre-epidemic warnings require a high specificity for routine infectious disease surveillance. The results of the present study confirm that pre-epidemic warnings in 1999-2001 had suitably high specificity. Our data also showed the sensitivity of the critical values was 90.4% in influenza-like illness and between 25.1% and 54.2% in other diseases. As discussed above, there may have been only the small number of rubella cases, and as we have pointed out previously, it would not be expected to find high positive predictive value when

epidemics were not frequent. Overall these results indicate that pre-epidemic warnings in 1999-2001 for influenza-like illness had sufficient sensitivity, but that detection of other four diseases at an early stage of an epidemic may not be easy. We showed the efficiency of pre-warning on influenza-like illness and extra years of observation is needed in the further examination of the other four diseases.

Our study had some inherent problems and limitations. The major problem was the definition of an epidemic with warnings being issued on the basis of the number of cases per week per sentinel medical institution. It is possible that the critical value used may vary according to the type of disease, season, and area. Although 3 years' data were available after the introduction of the expanded surveillance system, additional data are necessary in order to examine variation in the critical values.

In summary, this study examined the frequency of epidemic and pre-epidemic warnings, the temporal changes in the number of cases per week per sentinel medical institution before and after these warnings, and the sensitivity, specificity and positive predictive values of pre-epidemic warnings. We suggest other viewpoints (e.g. early detection of epidemic dispersion) may also be important for evaluating epidemic and pre-epidemic warnings.

REFERENCES

1. Tillett HE, Spencer IL. Influenza surveillance in England and Wales using routine statistics. Development of 'cusum' graphs to compare 12 previous winters and to monitor the 1980/81 winter. J Hyg (Lond) 1982;88:83-94.
2. Carrat F, Flahault A, Boussard E, Farran N, Dangoumau L, Valleron AJ. Surveillance of influenza-like illness in France. The example of the 1995/1996 epidemic. J Epidemiol Community Health 1998;52 Suppl 1:32S-8S.
3. Sprenger MJ, Mulder PG, Beyer WE, Masurel N. Influenza: relation of mortality to morbidity parameters—Netherlands, 1970-1989. Int J Epidemiol 1991;20:1118-24.
4. Matter HC, Cloetta J, Zimmermann H, and the Sentinella Arbeitsgemeinschaft. Measles, mumps, and rubella: monitoring in Switzerland through a sentinel network, 1986-94. J Epidemiol Community Health 1995;49 Suppl 1:4-8.
5. Snacken R, Lion J, Van Casteren V, Cornelis R, Yane F, Mombaerts M, et al. Five years of sentinel surveillance of acute respiratory infections (1985-1990): the benefits of an influenza early warning system. Eur J Epidemiol 1992;8:485-90.
6. Thacker SB, Stoup DF. Future directions for comprehensive public health surveillance and health information systems in the United States. Am J Epidemiol 1994;140:383-97.
7. Influenza in Canada —1996-1997 season. Can Commun Dis Rep 1997;23:185-92.
8. Del Mar C, Pincus D. Incidence patterns of respiratory illness in Queensland estimated from sentinel general practice. Aust Fam Physician 1995;24:625-32.
9. Ohshiro H, Kawamoto K, Nose T. Surveillance system of infectious diseases in Japan. J Epidemiol 1996;6:S81-5.
10. Murakami Y, Hashimoto S, Taniguchi K, Osaka K, Fuchigami H, Nagai M. Distribution of monitoring stations in the surveillance of infectious disease after the legislation of new infectious disease control law in Japan. Nippon Koshu Eisei Zasshi 2003;50:732-8. (in Japanese)
11. Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, the Ministry of Health, Labour and Welfare of Japan. The guideline for National Surveillance of Infectious Diseases (kansensho-hasseidokochosajigyo-jissiyoko). Weekly News of Public Health (Shukan-hoken-eisei) 1999;998:14-26. (in Japanese)
12. Hashimoto S, Murakami Y, Taniguchi K, Nagai M. Detection of epidemics in their early stage through infectious disease surveillance. Int J Epidemiol 2000;29:905-10.
13. Murakami Y, Hashimoto S, Taniguchi K, Fuchigami H, Nagai M. Temporal and geographical variation in epidemics determined from the results of an infectious disease surveillance system in Japan. Description of epidemic patterns by data-based criteria for epidemic periods. Nippon Koshu Eisei Zasshi 2000;47:925-35. (in Japanese)

Annual Incidence Rate of Infectious Diseases Estimated from Sentinel Surveillance Data in Japan

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JEA

Original Article

Annual Incidence Rate of Infectious Diseases Estimated from Sentinel Surveillance Data in Japan

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BACKGROUND: The estimation of incidence rates of infectious diseases based on the sentinel surveillance data is rather rare. We attempted to estimate these in 2000 in Japan by the surveillance data, and to evaluate their biases.

METHODS: We used the incidences of influenza-like illness and 12 pediatric diseases in each of the sentinel medical institutions in Japan based on surveillance data in 2000. The incidence in all medical institutions was estimated under the assumption that the sentinel medical institutions were randomly selected. The possible bias of this estimate was evaluated in comparison with the hypothetical true incidence obtained as the total incidence in all medical institutions estimated by a regression model using the numbers of all disease outpatients per day from the National Survey of Medical Care Institutions of Japan.

RESULTS: The estimated annual incidence rate was 75.6 (95% confidence interval: 72.3-78.7) per 1,000 population in influenza-like illness, and ranged from 1.1 (95% confidence interval: 1.0-1.2) to 285.2 (95% confidence interval: 270.2-300.3) per 1,000 population aged 0-19 years among 12 pediatric diseases. The ratio of the estimated incidence to the hypothetical true one was 1.06-1.26 among influenza-like illness and the 12 pediatric diseases.

CONCLUSIONS: The incidence rates of influenza-like illness and pediatric diseases in 2000 in Japan were estimated from sentinel surveillance data. The rates obtained provide some useful but not always accurate information. Thus, further research is necessary.   *J Epidemiol* 2003;13:136-141.

Key words: incidence, infectious disease, surveillance, influenza-like illness.

The surveillance of infectious diseases has been established in many countries.[1-10] The estimation of the incidence rates of infectious diseases based on the sentinel surveillance data is rather rare, although such surveillance provides some useful information regarding incidence.[11-13] In many surveillance projects including one in Japan, sentinel medical institutions (SMIs) are recruited on a voluntary basis. However, uncertainties remain as to how representative the finding are when applied to all the medical institutions in given areas. In the method for estimating incidence rates

by surveillance data, it would be assumed that SMIs are randomly selected from all the medical institutions if information on the underlying SMI population is not available.[11,14]

In Japan, the guidelines for the surveillance, introduced in 1999 by the Ministry of Health, Labor and Welfare, determine that SMIs are selected from all medical institutions in the areas as randomly and as representatively as possible (http://idsc.nih.go.jp/index.html).[15] Prefectural governments select SMIs according to the guidelines provided. The numbers of all disease outpatients per day in each

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