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The magnitude of variation in temperature within a year has an effect on the seasonal variations of chickenpox incidence in Japan

A. KOKAZE*, M. YOSHIDA, Y. SEKINE, M. ISHIKAWA, T. KUROKOCHI, Y. UCHIDA, N. MATSUNAGA AND Y. TAKASHIMA

Department of Public Health, Kyorin University School of Medicine 6-20-2, Shinkawa, Mitaka-shi, Tokyo, 181-8611, Japan

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SUMMARY

We investigated the epidemic pattern of chickenpox incidence among 47 prefectures in Japan. There were two peaks in chickenpox incidence in all prefectures. The first peaks appear at almost the same time in a year, while the second peaks occur at different times with relatively different types of size and shape. The feature of the second peak might characterize the epidemic pattern of chickenpox. We first introduced the second peak index, that is, the ratio of the difference between the incidence at the point of the second peak and the minimum incidence between the first and second peaks to the difference between the incidence at the point of the second peak and the minimum incidence in the year. There was a close correlation between the second peak index and the magnitude of variation in temperature within a year corresponding to the difference between the maximum and the minimum of the monthly mean of the highest daily temperature. This is the first article focusing on the close relationship between the second peak of epidemic pattern of chickenpox incidence and the variation of temperature within a year.

INTRODUCTION

Chickenpox (varicella) occurs worldwide, and is a mild, highly infectious disease, chiefly of children, characterized clinically by a vesicular eruption of the skin and mucous membranes [1]. This infectious disease is caused by varicella-zoster virus (VZV) and is the acute disease that follows primary contact with the virus. Over 95% of infections with VZV result in symptomatic infection known as chickenpox, and over 90% of individuals in temperate countries are infected with VZV before the age of 15. From an epidemiological point of view, chickenpox is also a common epidemic disease of childhood in Japan, and shows a marked seasonality, namely high prevalence in winter and spring rather than in summer. The epidemics of chickenpox occur at an optimal temperature, depending on temperature. Shoji et al. reported that it was possible to explain the seasonality of chickenpox incidence as mono- or bi-phase occurrence of epidemics throughout Japan, based on the data of the chickenpox epidemics and meteorological factors in Miyagi Prefecture [2]. It has been reported that there were two peaks, the first peak in winter and the second peak in spring, in the epidemic pattern of chickenpox incidence in every prefecture. Although some studies have been made on the chickenpox incidence in Japan [2–5], little attention is paid to the features of the second peak. Therefore we first introduced the second peak index representing the feature of the second peak of chickenpox epidemic pattern.

The purpose of this study was to analyse the

* Author for correspondence.

features of the second peak and especially to investigate whether there was a correlation between the second peak index and any meteorological factors.

METHODS

Data

The data to be analysed were collected in the following way. Chickenpox incidence data were obtained from the surveillance system of infectious diseases in Japan. The data reported in 1993–7 were utilized. However, in the case of Hyogo Prefecture, the Great Hanshin-Awaji Earthquake made the data in 1995 unavailable.

Definition of the second peak index

We first introduced the second peak index. The second peak index was calculated as the following equation:

$$\text{Second peak index} = \left(\begin{matrix}\text{incidence at point}\\ \text{of 2nd peak}\end{matrix} - \begin{matrix}\text{minimum incidence between}\\ \text{1st and 2nd peaks}\end{matrix}\right) \div \left(\begin{matrix}\text{incidence at point}\\ \text{of 2nd peak}\end{matrix} - \begin{matrix}\text{minimum incidence}\\ \text{in the year}\end{matrix}\right).$$

We calculated the values of the second peak index of every prefecture and every year through 1993–7. Moreover, we figured out the averages of the second peak indexes from 1993–7.

Analysis of correlation between the second peak index and the difference of temperature in a year

We paid attention to the variation of temperature within a year. We utilized meteorological data from 1993–7 observed at the weather observatories, belonging to the Meteorological Agency, located in the prefectural capitals. We attempted to calculate the correlations between the second peak index and the variation in temperature, namely the average of Δhighest temperature ($\Delta T_{\text{highest}}$), Δaverage temperature ($\Delta T_{\text{average}}$), and Δlowest temperature (ΔT_{lowest}) across 1993–7. The definitions of these meteorological factors are as follows: $\Delta T_{\text{highest}}$ is the difference between the maximum of the monthly average of the highest daily temperature and the minimum of the monthly average of the highest daily temperature. $\Delta T_{\text{average}}$ is the difference between the maximum of the monthly average of the average daily temperature and the minimum of the monthly average of the average daily temperature. ΔT_{lowest} is the difference between the maximum of the monthly average of the lowest daily temperature and the minimum of the monthly average of the lowest daily temperature. The student *t*-test was used to evaluate the correlation coefficients between the second peak index and the differences of temperature.

RESULTS

The epidemic pattern of chickenpox among 47 prefectures

The location of 47 prefectures is shown in Figure 1. In epidemic patterns of 47 prefectures, there were some common characteristics as well as some obvious differences (epidemic patterns of 47 prefectures cannot be shown here for lack of space). Figure 2 shows the epidemic patterns of three prefectures, namely Niigata, Nagano, and Shizuoka Prefectures. The reason why we have selected these three prefectures, being located in the approximately same longitude, is that they are typical examples showing two peaks with different size and shape in the epidemic patterns of chickenpox incidence. Many prefectures, especially those facing the Sea of Japan, show the pattern of Niigata Prefecture. Namely, the first peak was larger than the second peak, or the both peaks are almost equivalent. In case of Nagano Prefecture, it was found that the second peak was larger than the first peak every year in 1993–7. The same finding can be found for Nara Prefecture. There was the similarity between the case of Shizuoka Prefecture and the cases of the prefectures facing the Pacific Ocean. Namely, the minimum incidence between the first and second peaks was not very low. However, in case of Shizuoka Prefecture in 1994, the small second peak just like an upheaval was recognized. This pattern was quite similar to that of Okinawa Prefecture. Table 1 summarizes the key time of chickenpox incidence, namely the time of the first peak, the time of the minimum incidence between the first and second peaks, the time of the second peak, and the time of nadir in year with the range across 5 years. The first peaks appeared from the end of the previous year to the beginning of a year, but except a few cases, the occurrence points of the first peak were within narrow range. However, the occurrence points of the second peaks appeared with wide range among 47 prefectures. The points of the minimum incidence between two peaks in 1993–7 were diverse among 47 prefectures, and even in an identical prefecture. In every pre-

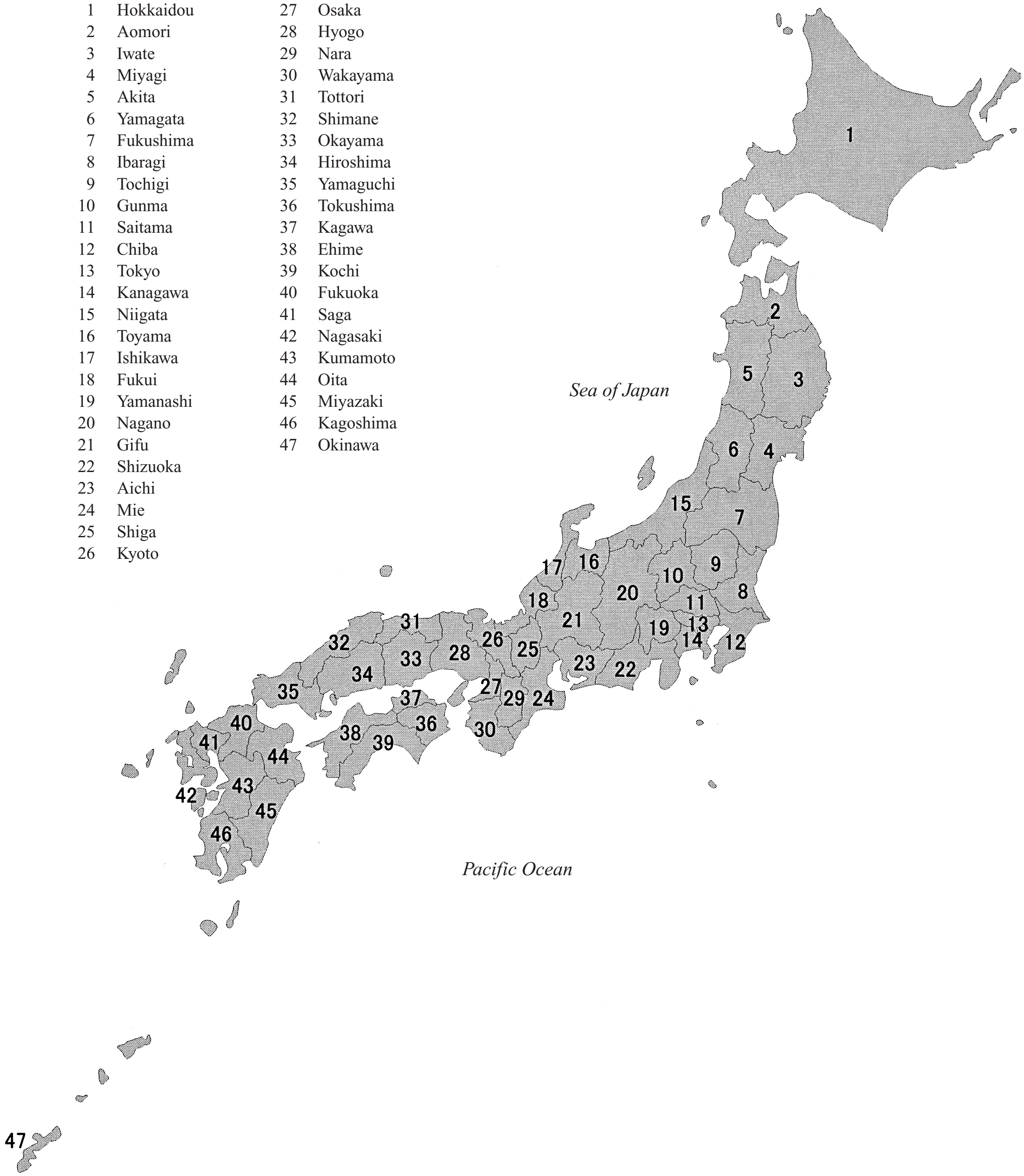

Fig. 1. Distribution of 47 prefectures in Japan.

fecture, the yearly minimum incidence appeared in September.

The feature of the second peak by utilizing the second peak index

The extreme right column of Table 1 shows the average of second peak index, with the range, of each prefecture in 1993–7. The second peak indexes ranged from 0·244–0·808 with 0·636 ± 0·115 of mean ± S.D. The highest average of the second peak index could be found in Nagano Prefecture. The average of the second peak index was remarkably higher in Nara Prefecture than in neighbouring prefectures, namely

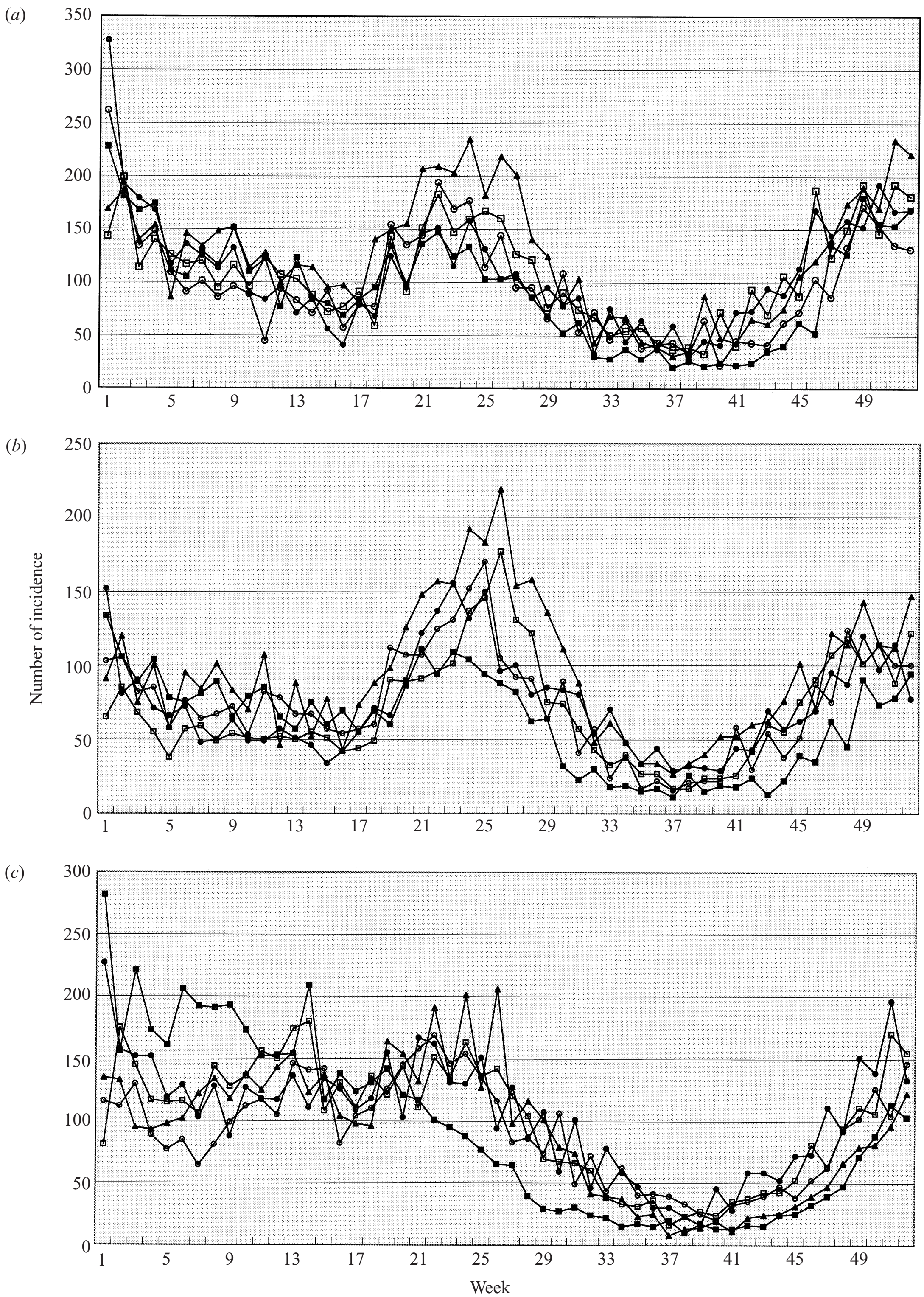

Fig. 2. Three prefectural epidemic patterns of chickenpox incidence in 1993–7 (*a*) Niigata Prefecture (No. 15), (*b*) Nagano Prefecture (No. 20), (*c*) Shizuoka Prefecture (No. 22). (●) the incidence in each week of 1993, (■) that of 1994, (▲) that of 1995, (○) that of 1996, and (□) that of 1997.

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Table 1. *Summary table of the epidemic pattern of the chickenpox incidence in 47 prefectures*

No.	Time of the first peak	Time of the minimum incidence between two peaks	Time of the second peak	Time of the nadir	Average of the second peak index with the range in 1993–7
1	py51–2	14–18	24–25	36–39	0·734 (0·667–0·859)
2	py50–1	14–18	21–28	34–39	0·700 (0·630–0·827)
3	py49–1	13–23	24–31	34–38	0·787 (0·746–0·844)
4	py51–2	14–19	24–31	36–41	0·751 (0·682–0·833)
5	py49–1	16–17	22–27	36–41	0·779 (0·712–0·806)
6	py50–1	11–19	22–27	33–41	0·775 (0·525–0·953)
7	py48–2	15–18	24–31	37–40	0·701 (0·518–0·930)
8	1–4	10–18	11–27	36–41	0·527 (0·424–0·673)
9	py50–1	6–21	12–26	36–39	0·592 (0·481–0·645)
10	py51–1	5–16	19–26	35–41	0·669 (0·400–0·873)
11	py52–2	5–18	19–26	37–38	0·568 (0·466–0·676)
12	py52–9	5–17	14–23	33–39	0·602 (0·505–0·703)
13	1–2	5–16	14–23	33–39	0·585 (0·407–0·597)
14	py52–2	7–18	19–26	37–39	0·553 (0·368–0·713)
15	1–2	11–17	22–24	37–40	0·779 (0·614–0·914)
16	py49–10	5–15	19–24	33–43	0·694 (0·569–0·818)
17	py51–7	5–16	21–24	34–38	0·617 (0·487–0·724)
18	py61–4	11–15	19–24	36–41	0·756 (0·605–0·955)
19	py50–4	5–20	21–26	35–41	0·739 (0·529–0·880)
20	py48–2	10–17	21–26	37–37	0·808 (0·560–0·961)
21	py49–6	5–14	17–24	36–38	0·768 (0·487–0·913)
22	1–3	7–18	14–26	34–41	0·506 (0·294–0·705)
23	py50–2	1–18	19–24	36–38	0·607 (0·339–0·725)
24	py50–1	5–16	19–26	35–39	0·663 (0·463–0·742)
25	py51–2	5–19	19–26	38–40	0·754 (0·607–0·906)
26	py50–2	10–18	19–24	37–39	0·652 (0·455–0·752)
27	2–2	6–18	10–25	36–40	0·616 (0·515–0·700)
28	py52–2	5–18	21–24	37–39	0·562 (0·394–0·659)
29	py50–3	5–9	22–26	33–39	0·798 (0·589–0·990)
30	py50–9	12–18	19–26	35–41	0·670 (0·578–0·944)
31	py51–3	9–17	24–31	33–38	0·720 (0·659–0·955)
32	py50–2	5–22	19–25	29–39	0·734 (0·536–0·920)
33	py50–4	9–13	19–22	35–37	0·716 (0·528–0·856)
34	py52–2	3–15	14–24	35–41	0·569 (0·381–0·808)
35	1–2	5–18	19–26	33–38	0·532 (0·476–0·605)
36	1–5	7–18	12–22	32–38	0·665 (0·512–0·778)
37	py50–2	15–18	19–25	32–41	0·662 (0·459–0·778)
38	py52–1	5–17	19–25	35–40	0·638 (0·379–0·785)
39	1–2	5–20	15–22	36–40	0·482 (0·373–0·780)
40	1–1	5–7	9–19	37–38	0·512 (0·437–0·659)
41	py52–4	9–16	14–24	34–40	0·550 (0·410–0·659)
42	py52–7	6–15	11–24	11–24	0·596 (0·500–0·700)
43	py52–2	6–16	7–21	36–41	0·553 (0·453–0·678)
44	py51–2	5–21	18–24	37–39	0·521 (0·385–0·707)
45	py51–2	8–15	11–19	37–40	0·423 (0·261–0·551)
46	1–7	3–14	9–20	35–38	0·499 (0·205–0·807)
47	10–12	12–17	15–19	30–44	0·244 (0·189–0·314)

No. shows the prefectural number in Fig. 1.
The figures in each column except extreme right column mean the order of weeks in a year and py is an abbreviation for the previous year.
The numbers in Table 1 depict the earliest week and the latest week during 1993–7.

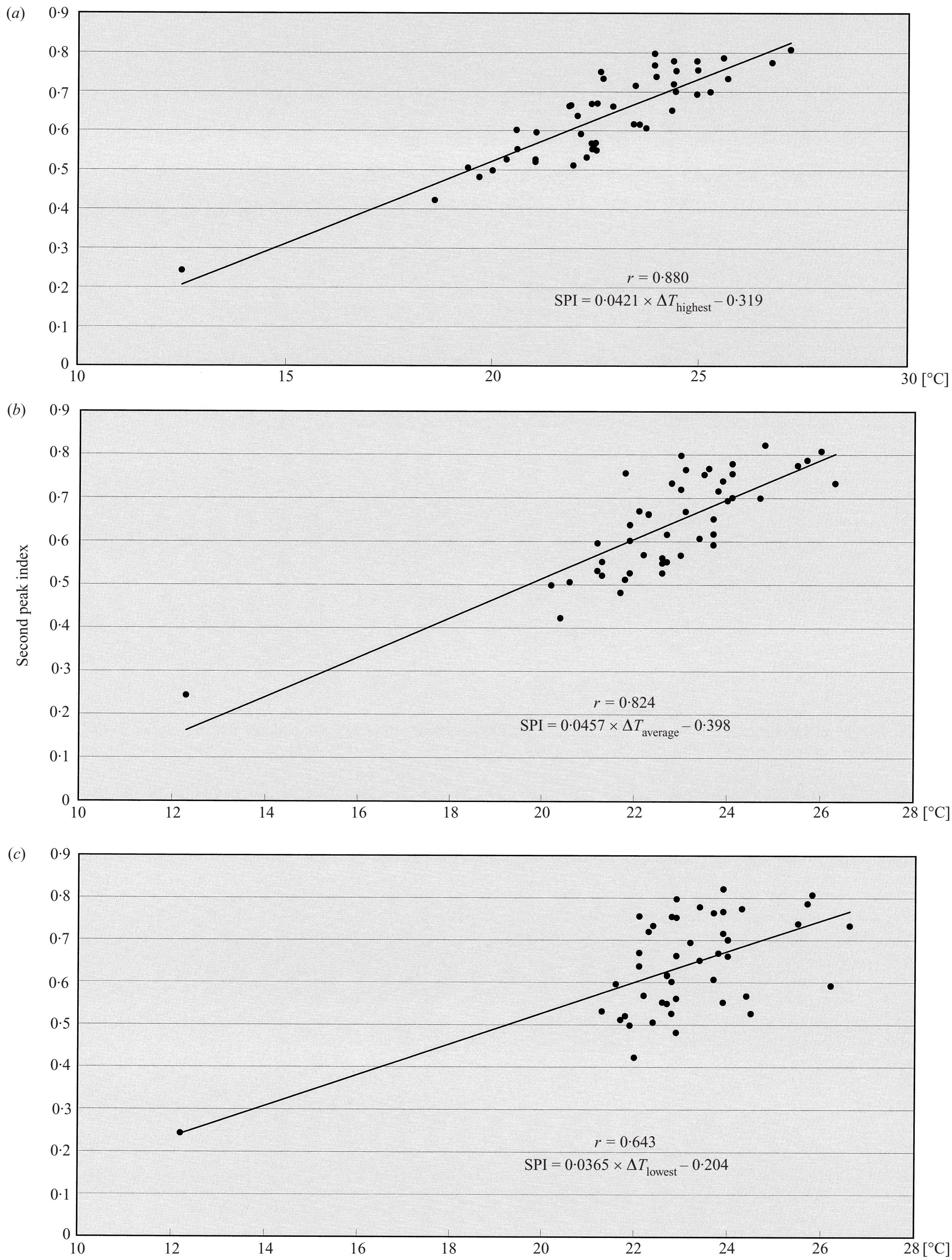

Fig. 3. Correlation between the second peak index (SPI) and meteorological factors (*a*) Δhighest temperature ($\Delta T_{highest}$), (*b*) Δaverage temperature ($\Delta T_{average}$), and (*c*) Δlowest temperature (ΔT_{lowest}). The lines in the graphs show the approximate linear lines. In each figure the correlation coefficient and the regression equation are shown. The *F*-test was used to evaluate the slope and intercept in regression analysis. Statistical significances were found in all regression analysis using the *F*-test.

Osaka, Kyoto, and Wakayama Prefecture. The average of the second peak index of Okinawa Prefecture, located at the southernmost of Japan, was the lowest value. The relative high values of the average of the second peak index were found in Hokkaido and Tohoku district (prefectural numbers 1–7 shown in Fig. 1), located in the north part of Japan. On the other hand, the relative low values of the average of the second peak index was noted in the prefectures facing the Pacific Ocean.

The correlation between the second peak index values and meteorological factors

The scattergrams for the second peak index value and the average levels of $\Delta T_{\text{highest}}$, $\Delta T_{\text{average}}$, and ΔT_{lowest} are shown in Figure 3(*a–c*). The correlation coefficients were calculated as 0·880 ($P < 0{\cdot}0001$), 0·824 ($P < 0{\cdot}0001$), and 0·643 ($P < 0{\cdot}0001$), respectively. Since the data from Okinawa Prefecture contributed to the elevation of the correlation coefficients, the correlation coefficients were calculated after the data from Okinawa Prefecture were excluded. These coefficients for 46 prefectures were 0·838 ($P < 0{\cdot}0001$), 0·778 ($P < 0{\cdot}0001$), and 0·464 ($P < 0{\cdot}005$), respectively. Significant differences were found in between these three correlation coefficients using the student *t*-test. In any case, it is appropriate to suppose that there is a close correlation between the value of the second peak index and $\Delta T_{\text{highest}}$.

DISCUSSION

Many studies on the relationship between climate and epidemics of infectious disease have been performed in order to disclose the reason why some epidemic diseases show their seasonality. For example, it is well known that influenza is prevalent in winter and polio is common in summer, and these seasonal variations can be explicable by the optimal temperature and humidity [6].

Chickenpox is a ubiquitous, highly contagious, generalized exanthema that spreads rapidly in a susceptible population and displays marked seasonality, at least in temperate climates [1]. In the United States, the nadir of incidence occurs in September, with the peak in March and April [7]. The incidence increases more than 10-fold during the winter [8]. These relative differences occur in every year regardless of the prevalence level, although the winter epidemic tends to persist into late spring. In Japan, it can be concisely pointed out that chickenpox is prevalent in winter and spring. However, there were some differences in the epidemic patterns of chickenpox incidence among 47 prefectures from our results. The first peaks of epidemic pattern in 47 prefectures occurred at almost the same point of a year. Likewise, in all prefectures, the nadirs were recognized in September with some exceptions. Regarding the nadir, the occurrences nearly coincide in both United States and Japan [7]. On the other hand, there were some differences in the time, size and shape of the second peak of chickenpox incidence among 47 prefectures, as stated in results. Therefore, in the case of chickenpox, the feature of the second peak might characterize the epidemic pattern of each prefecture.

The occurrence point of the second peaks differed among 47 prefectures. These findings could be explained by the variation in monthly changes in the average daily temperature in Japan. Shoji and Ishida analysed the relationship between the incidence of chickenpox and meterological factors [3]. In their study, the epidemic of chickenpox incidence was considered to begin after approximately 2 weeks, the incubation period of chickenpox, from the point that the average daily temperature reached to 5 °C, and end after 2 weeks from the point that the average daily temperature reached beyond 20 °C. It restarted, reversely, after the incubation period from the point that the average daily temperature was measured below 20 °C, and it came to an end after the incubation period from the point that the average daily temperature went down below 5 °C. The fluctuations in the chickenpox incidence were likely to be mostly explained by their consideration.

From our results, it was found that the average of the second peak index of Nagano Prefecture was highest, and that of Nara Prefecture was much higher than those of neighbouring prefectures. Neither Nagano nor Nara Prefecture faces the sea. Moreover, many cities in both prefectures are located in natural basins. From a viewpoint of geography and meteorology, the basin shows remarkable variability of temperature within a day and within a year. Okinawa Prefecture is famous for a warm temperature. The temperature of Okinawa Prefecture slightly varies within a year. From our results, we framed a hypothesis that there might be a correlation between the second peak index and the variation in temperature within a year. Therefore three meteorological factors, representing the magnitude of the difference in temperature in a year, namely the average of

$\Delta T_{\text{highest}}$, $\Delta T_{\text{average}}$, and ΔT_{lowest}, across 5 years were examined. Each correlation coefficient shows a close correlation between the second peak index and each factor, especially the average of $\Delta T_{\text{highest}}$. We do not know why the second peak of the chickenpox incidence is associated with the difference between the maximum and the minimum of the monthly average of the highest daily temperature. One possible inference is that the variation in temperature influences on the infectivity of VZV. VZV is moderately temperature sensitive. A couple of previous papers reported that *in vitro* the VZV yield and point of maximum titre were variable and depended on the temperature of incubation [9–12]. *In vivo*, or in the natural course of chickenpox infection, the variability of temperature may affect the VZV titre or the other factors.

There are six or more points to be considered in explanation for our results. The first is the effect of varicella vaccine, and the second is the accuracy of the infectious disease surveillance system in Japan. The incidence of other infectious diseases such as measles and pertussis is strongly influenced by the vaccination. It was reported that the rate of varicella vaccination was very low [13]. Moreover, Takayama et al. showed high incidence of chickenpox among Japanese children vaccinated with varicella vaccine [14]. Thus the execution of varicella vaccine might not have serious influence on the incidence of chickenpox at present. As regards the infectious diseases surveillance system, there have been the medical institutes that correspond to the monitor stations for selected infectious diseases throughout Japan. The directors of medical institutes have a duty to report the number of patients with the objective infectious diseases to the surveillance center of the Ministry of Health and Welfare through prefectual government. However, since there are substantial differences in the number of monitor stations *per capita* among 47 prefectures, the distribution of monitor stations is not proportional across the prefectures. Therefore, focusing on the second peak, the accuracy of the number of patients suffering from chickenpox may be diverse among the prefectures. Accordingly, we introduced the second peak index showing the proportion of increase before and decrease after the second peak in each prefecture in order to cancel the effects of the measurement error. The third point is the difference in infectivity among VZV isolates. VZV was considered to be genetically stable and not highly diversified [15–17]. Takayama et al. reported that nucleotide sequence variation among VZV isolates in Japan was estimated less than 0·05% [18]. Therefore, the difference in infectivity might be negligible. The fourth point to be considered is the inclusion of herpes zoster. The chickenpox data should be considered to include a large amount of noise due to an accidental counting of herpes zoster [8]. The incidence of herpes zoster in infancy and children has increased in Japan [19, 20]. There is room for reconsidering this matter. The fifth is other confounders including the interaction with other seasonal diseases, the seasonal changes of the host immune system, and so on. They remain matters to be debated. Finally, the second peak index ranged widely even in an identical prefecture. The correlation coefficient between the second peak index and $\Delta T_{\text{highest}}$ for all the prefecture and year-specific data, was only 0·375 (details not shown). It reveals that there remain issues to be investigated further. Although we showed that the variation in temperature in a year may have effect on the seasonal variations of chickenpox incidence in Japan, it is still unclear whether there are similar effects also for other infectious diseases.

The epidemic pattern of chickenpox incidence in Japan has been interpreted in some ways, namely nationwide outbreak of long duration [4], noisy limit cycle [5], and so on. Although it is difficult to estimate the incidence of chickenpox, from our results we might go on to the possibility of prediction of chickenpox incidence based on the meteorological data. However, further studies are necessary to utilize the correlation between epidemic pattern and meteorological factors for the prediction of chickenpox incidence.

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