in the number of wide-area epidemic weeks varied among diseases with increasing trends for pharyngoconjunctival fever and group A streptococcal pharyngitis; a decreasing trend for measles; and fluctuations for hand-foot-mouth disease, erythema infectiosum, and mumps. The proportion of wide-area epidemics in epidemic weeks was 40.7% for herpangina, 28.3-29.1% for infectious gastroenteritis and hand-foot-mouth disease, and less than 20.0% for other diseases.

DISCUSSION

Using the infectious disease surveillance data of 1999-2005, we investigated epidemics and wide-area epidemics of influenza and pediatric diseases in various prefectures in Japan. Epidemics and wide-area epidemics of influenza occurred for an average of 7.0 and 4.3 weeks, respectively in a year in a given prefecture. The occurrence of wide-area epidemics in prefectures was not expected to be frequent when compared with epidemics in PHC areas.[9,13] The proportion of wide-area epidemics in epidemic weeks was 62%. This implied that when the number of influenza cases increased and an epidemic started in a certain PHC area, the disease was likely to spread over a prefecture.[1,3]

Few epidemics of pertussis, rubella, and measles were observed during the 7-year period. Hence, very few wide-area epidemics occurred. These results were mainly attributed to the vaccination program against pertussis, rubella, and measles in Japan.[14-16] Wide-area epidemics of other diseases were observed among many epidemics. The proportion of wide-area epidemics in epidemic weeks was 41% for herpangina, suggesting that the epidemic in small areas was likely to spread over wide areas, similar to influenza. With many other diseases, the proportion of wide-area epidemics was less than 20%. These findings would be useful for public health practices against these diseases in the prefectures.

A previously reported method for detecting epidemics in small areas was used in this analysis. This method has been used as a part of the epidemic alert system in the NESID in Japan.[6,9] It would be reasonable to assume that most wide-area epidemics of infectious diseases start from aberrations of cases in small PHC areas. Based on this rationale, epidemic information for PHC areas was used in our analysis during the detection of epidemics or wide-area epidemics in a prefecture.

The method for early detection of epidemics in PHC areas has been established and is in operation in the infectious surveillance system in Japan.[6,9] Thus, although there are several approaches to define a wide-area epidemic based on infectious disease surveillance data, it is practical to utilize this resource for the detection of wide-area epidemics.

Our study has several limitations. A wide-area epidemic was defined to occur when the proportion of people living in PHC areas with epidemics in a prefecture exceeded 30% of the prefectural population. The number of PHCs in a prefecture ranged from 3 to 30. In some prefectures with small number of PHCs, only one PHC dominated more than 30 % population in a prefecture (Table 2). If the number of PHCs was small and/or one PHC dominated over half population in a prefecture, an epidemic in only one PHC would greatly affect the issue of wide-area epidemics. When we interpret a wide-area epidemic in a given prefecture, we must check the PHC distribution in a prefecture. The criterion for a wide-area epidemic was fixed at 30% for all diseases. Although this criterion worked well for influenza and some other pediatric diseases, as there were a fair number of wide-area epidemics of influenza that occurred each year, a more apt criterion may be needed for improvement for those diseases with relatively few cases. In our definition of a wide-area epidemic, the prefecture is the unit of a wide-area epidemic. When an epidemic occurred in-between prefectures, we can not detect this epidemic from the proposed method.

As a countermeasure against epidemics of infectious diseases, an alert for wide-area epidemics is an important issue in public health practice. Although some difficulties exist with respect to the alert issue, such as the purpose for an alert, the definition of an epidemic, and countermeasures for control, the development of an alert system is necessary.[7,8,10] We believe that this study will help to promote further discussion on this important issue.

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Annual and Weekly Incidence Rates of Influenza and Pediatric Diseases Estimated from Infectious Disease Surveillance Data in Japan, 2002-2005

Miyuki Kawado,[1] Shuji Hashimoto,[1] Yoshitaka Murakami,[2] Michiko Izumida,[3] Akiko Ohta,[3] Yuki Tada,[4] Mika Shigematsu,[4] Yoshinori Yasui,[4] Kiyosu Taniguchi,[4] and Masaki Nagai.[3]

BACKGROUND: The method for estimating incidence of infectious diseases from sentinel surveillance data has been proposed. In Japan, although the annual incidence rates of influenza and pediatric diseases estimated using the method were reported, their weekly incidence rates have not.
METHODS: The weekly sex- and age-specific numbers of cases in the sentinel medical institutions in the National Epidemiological Surveillance of Infectious Diseases in Japan in 2002-2005 were used. Annual and weekly incidence rates of influenza and 12 pediatric diseases were estimated by the above-mentioned method, under the assumption that sentinels are randomly selected from all medical institutions.
RESULTS: The annual incidence rate of influenza in 2002-2005 was 57.7-142.6 per 1,000 population. The highest weekly incidence rate was 7.4 at week 8 in 2002, 14.9 at week 4 in 2003, 14.1 at week 5 in 2004, and 21.2 at week 9 in 2005. The annual incidence rate per 1,000 population of 0-14 years old in 2002-2005 was less than 5.0 for pertussis, rubella and measles, 293.2-320.8 for infectious gastroenteritis, and 5.3-89.6 for 8 other diseases. The highest weekly incidence rate was less than 1.0 for exanthem subitum, and was more than 5.0 for infectious gastroenteritis, hand-foot-mouth disease and herpangina.
CONCLUSION: We estimated annual and weekly incidence rates of influenza and pediatric diseases in Japan in 2002-2005, and described their temporal variation.
J Epidemiol 2007; 17: S32-S41.

Key words Sentinel Surveillance; Incidence; Influenza, Human

In infectious diseases with large seasonal variation, such as influenza or measles, the annual and monthly or weekly incidence rate is essential for public health practice. The magnitude and temporal accumulation of such disease epidemics in a population, which would be important for planning control of epidemics, were observed in annual and monthly/weekly incidence rates. National infectious disease surveillance has been established in many countries.[1-8] The incidence rate of a targeted disease is obtained directly from the surveillance data completely covering its occurrence, but it is not calculated directly from the data of sentinel surveillance. A method for estimating incidence rate of infectious disease from sentinel surveillance data has been proposed.[9-12]

In Japan, sentinel surveillance for influenza and pediatric diseases is conducted as a part of the National Epidemiological Surveillance of Infectious Diseases (NESID).[13-15] The annual incidence rates of these diseases in 2002-2004 estimated from the sentinel surveillance data using the proposed method were reported,[16] but the weekly incidence rates are not yet clear.

In the present study, we estimated annual and weekly incidence rates of influenza and pediatric diseases from the NESID data in Japan in 2002-2005, using the proposed method.

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[1] Department of Hygiene, Fujita Health University School of Medicine.
[2] Department of Health Science, Shiga University of Medical Science.
[3] Department of Public Health, Saitama Medical University Faculty of Medicine.
[4] Infectious Disease Surveillance Center, National Institute of Infectious Diseases.
Address for correspondence: Miyuki Kawado, Department of Hygiene, Fujita Health University School of Medicine, 1-98, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. (e-mail: kawado@fujita-hu.ac.jp)

METHODS

Surveillance of Infectious Diseases in Japan

General outline of the NESID in Japan has been described elsewhere.[13-15] Since 1999, the NESID has targeted influenza and 12 pediatric diseases (shown in Table 3) for sentinel surveillance. Local governments (prefectures) select sentinel medical institutions for influenza and pediatric diseases according to the NESID guidelines. The numbers of sentinels in the areas covered by public health centers are approximately proportional to their population sizes. Each sentinel reports to a local public health center weekly. The report includes the sex- and age-specific numbers of cases newly diagnosed during a given week.

Surveillance Data and Method for Estimating Incidence

The data of sentinels' report of influenza and pediatric diseases from week 1 of 2002 through week 52 of 2005 in the NESID in Japan were used. The numbers of all medical institutions were obtained from the National Survey of Medical Care Institutions conducted by the Ministry of Health, Labour and Welfare in October 2002.[17]

The annual and weekly incidence was estimated using the method proposed by Hashimoto et al.[12] For each disease, prefecture and type of medical institution, the incidences in sentinels follow a multi-hypergeometric distribution under the fixed condition of the total number of sentinels under the assumption that sentinels are randomly selected from all medical institutions. The total incidence in each prefecture and type of medical institution were estimated as the total incidence in sentinels divided by the proportion of sentinels to all medical institutions. The total incidence in all medical institutions was estimated to be the total of those in all prefectures and types of medical institution. The approximate confidence interval for the incidence was given based on the distribution. The appendix shows the method for estimating incidences in detail.

Types of medical institutions were classified using the information from the National Survey of Medical Care Institutions as follows; three types for pediatric diseases: "pediatric department in hospital," "clinic with pediatric department as its main department" and "clinic with pediatric department not as its main department." For influenza, the three types above were used plus "department of internal medicine in hospital, and clinic with inter-

Table 1. The number of all and sentinel medical institutions by type of medical institution, Japan, 2002-2005.

	No. of all medical institutions	No. of sentinel medical institutions (%)			
		2002	2003	2004	2005
Influenza					
Total	66,014	4,659 (7.1)	4,672 (7.1)	4,679 (7.1)	4,693 (7.1)
Pediatric department in hospital	2,859	643 (22.5)	656 (22.9)	597 (20.9)	592 (20.7)
Clinic with pediatric department as its main department	5,483	1,816 (33.1)	1,831 (33.4)	1,838 (33.5)	1,844 (33.6)
Clinic with pediatric department not as its main department	18,156	1,093 (6.0)	1,108 (6.1)	1,103 (6.1)	1,093 (6.0)
Department of internal medicine in hospital, and clinic with internal medicine but without pediatric department	39,516	1,107 (2.8)	1,077 (2.7)	1,141 (2.9)	1,164 (2.9)
Pediatric diseases					
Total	26,498	3,057 (11.5)	3,077 (11.6)	3,062 (11.6)	3,086 (11.6)
Pediatric department in hospital	2,859	737 (25.8)	734 (25.7)	733 (25.6)	732 (25.6)
Clinic with pediatric department as its main department	5,483	1,779 (32.4)	1,804 (32.9)	1,806 (32.9)	1,810 (33.0)
Clinic with pediatric department not as its main department	18,156	541 (3.0)	539 (3.0)	523 (2.9)	544 (3.0)

The number of all medical institutions was obtained from the National Survey of Medical Care Institutions in 2002.
Proportion of sentinel medical institutions in all medical institutions in parentheses.

Table 2. Estimated incidence rates of influenza by sex and age, Japan, 2002-2005.

Year	Sex	Age (years)	Estimated incidence	Incidence rate (per 1,000 population)	
				Estimate	95% confidence interval
2002	Total	Total	7,360,000	57.7	54.5 - 60.7
	Male	Total	3,740,000	60.0	56.8 - 63.2
		0-14	2,190,000	238.7	221.2 - 256.1
		15-60	1,420,000	36.6	34.8 - 38.4
		60 and over	130,000	9.1	8.4 - 9.8
	Female	Total	3,620,000	55.4	52.4 - 58.5
		0-14	1,950,000	223.4	206.2 - 239.4
		15-60	1,510,000	39.5	37.6 - 41.6
		60 and over	160,000	8.7	7.6 - 9.3
2003	Total	Total	11,560,000	90.6	86.7 - 94.4
	Male	Total	5,800,000	93.1	89.1 - 97.1
		0-14	3,160,000	344.4	324.8 - 364.0
		15-60	2,330,000	60.0	56.9 - 63.1
		60 and over	310,000	21.7	21.0 - 23.1
	Female	Total	5,760,000	88.2	84.5 - 91.9
		0-14	2,820,000	323.1	304.7 - 341.4
		15-60	2,560,000	66.9	63.8 - 70.0
		60 and over	380,000	20.7	19.6 - 21.8
2004	Total	Total	8,950,000	70.1	67.2 - 73.1
	Male	Total	4,500,000	72.2	69.2 - 75.4
		0-14	2,220,000	241.9	229.9 - 252.8
		15-60	2,040,000	52.5	49.7 - 55.3
		60 and over	250,000	17.5	16.1 - 18.9
	Female	Total	4,450,000	68.1	65.2 - 70.9
		0-14	1,970,000	225.7	214.2 - 237.1
		15-60	2,160,000	56.5	53.8 - 59.3
		60 and over	310,000	16.9	15.8 - 18.0
2005	Total	Total	18,200,000	142.6	135.6 - 149.6
	Male	Total	9,020,000	144.8	137.2 - 152.2
		0-14	4,500,000	490.4	465.3 - 516.6
		15-60	3,790,000	97.6	90.1 - 105.0
		60 and over	730,000	51.1	46.2 - 56.0
	Female	Total	9,180,000	140.5	134.0 - 147.1
		0-14	4,030,000	461.7	437.6 - 484.6
		15-60	4,260,000	111.3	104.6 - 117.9
		60 and over	890,000	48.6	44.2 - 52.9

nal medicine but without pediatric department."

Table 1 shows the numbers of all and sentinel medical institutions by type of medical institution. The number of sentinels in 2002-2005 was about 4,700 for influenza and 3,100 for pediatric diseases. The proportion of sentinels in all medical institutions was 7.1% for influenza and 11.5-11.6% for pediatric diseases.

Method of Analysis

Incidence rate per population was calculated using the incidence estimated above and the 2003 population in Japan. For influenza, the sex- and age-specific annual and weekly incidence rates were calculated. The proportion of weekly incidence to each influenza season's total incidence was presented by age group. Age groups were the following three; 0-14, 15-59, and 60 years old or over. In pediatric diseases, annual and weekly incidence rates were calculated for population aged 0-14 years.

RESULTS

Influenza

Table 2 shows the annual incidence rates of influenza by sex and age. The annual incidence rate per 1,000 population was 57.7 (95% confidence interval [CI]: 54.5-60.7) in 2002, 90.6 (95% CI: 86.7-94.4) in 2003, 70.1 (95% CI: 67.2-73.1) in 2004, and 142.6

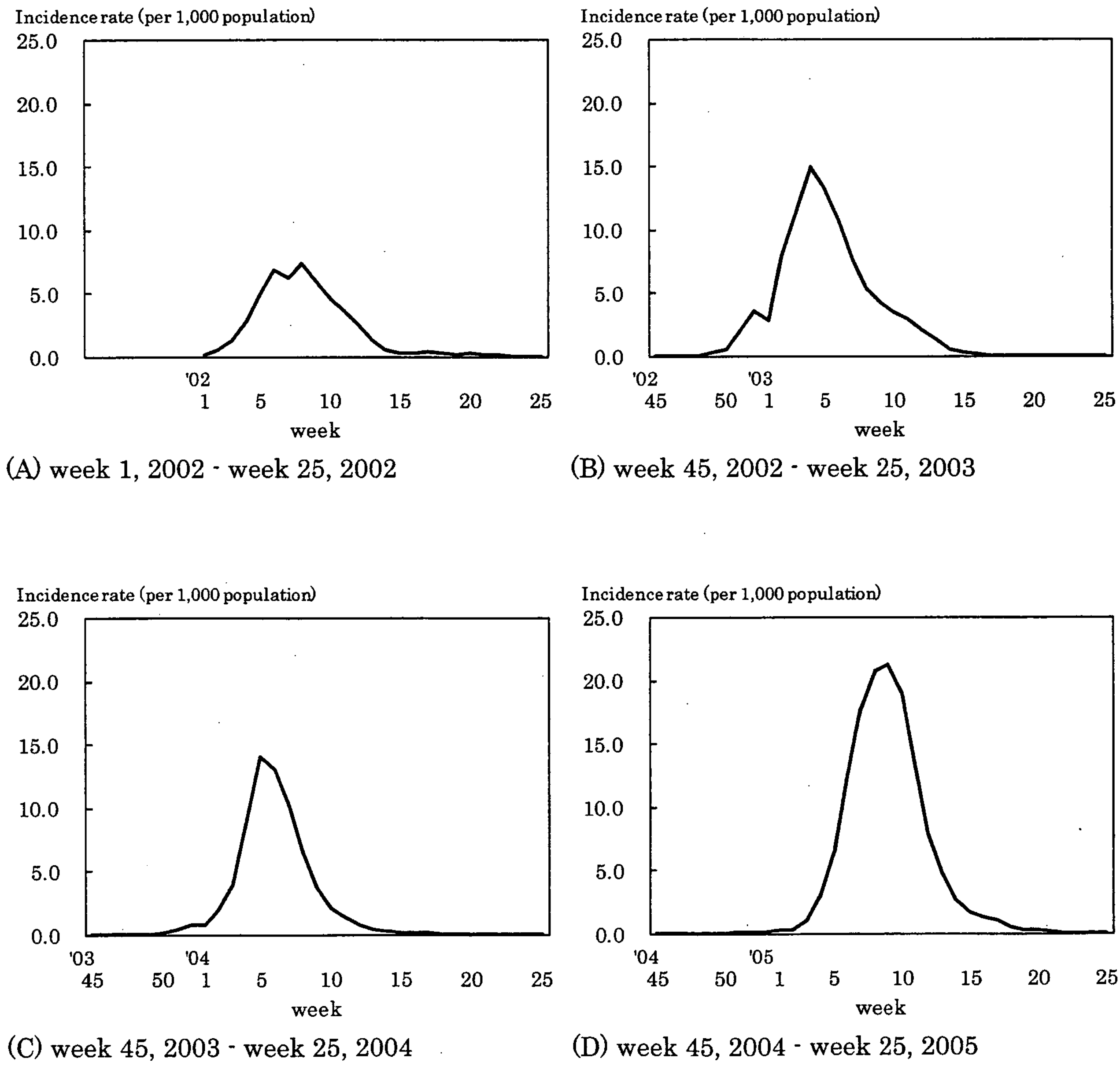

Figure 1. Estimated incidence rates of influenza by week, Japan, 2002-2005.

(95% CI: 135.6-149.6) in 2005. The difference in incidence rates between male and female was not so large. The incidence rate in the 0-14 years age group was higher than in other age groups.

Figure 1 shows the weekly incidence rates of influenza. The highest weekly incidence rate per 1,000 population was 7.4 in week 8 of 2002, 14.9 in week 4 of 2003, 14.1 in week 5 of 2004, and 21.2 in week 9 of 2005. The period with an incidence rate of 1.0 or more was as follows: from week 3 to week 13 of 2002, from week 51 of 2002 to week 13 of 2003, from week 2 to week 11 of 2004, and from week 3 to week 17 of 2005.

Figure 2 shows the proportion of weekly incidence in relation to each influenza season's total incidence by age. The peak week in the proportions in every age group was week 8 of 2002 in the 2001/2002 season and week 4 of 2003 in the 2002/2003 season. In the 2003/2004 season, the peak week was week 5 of 2004 in the aged 0-14 and 15-59 groups, and week 6-7 of 2004 in those aged 60 and over. In the 2004/2005 season, the peak week was week 8 in those aged 0-14, week 9 in those aged 15-59 and week 9-10 in those aged 60 and over.

Pediatric Diseases

Table 3 shows the incidence rates of pediatric diseases per 1,000 population among persons aged 0-14 years. The incidence rate in 2002-2005 was less than 5.0 for pertussis, rubella, and measles, 293.2-320.8 for infectious gastroenteritis, and 5.3-89.6 for other 8 diseases.

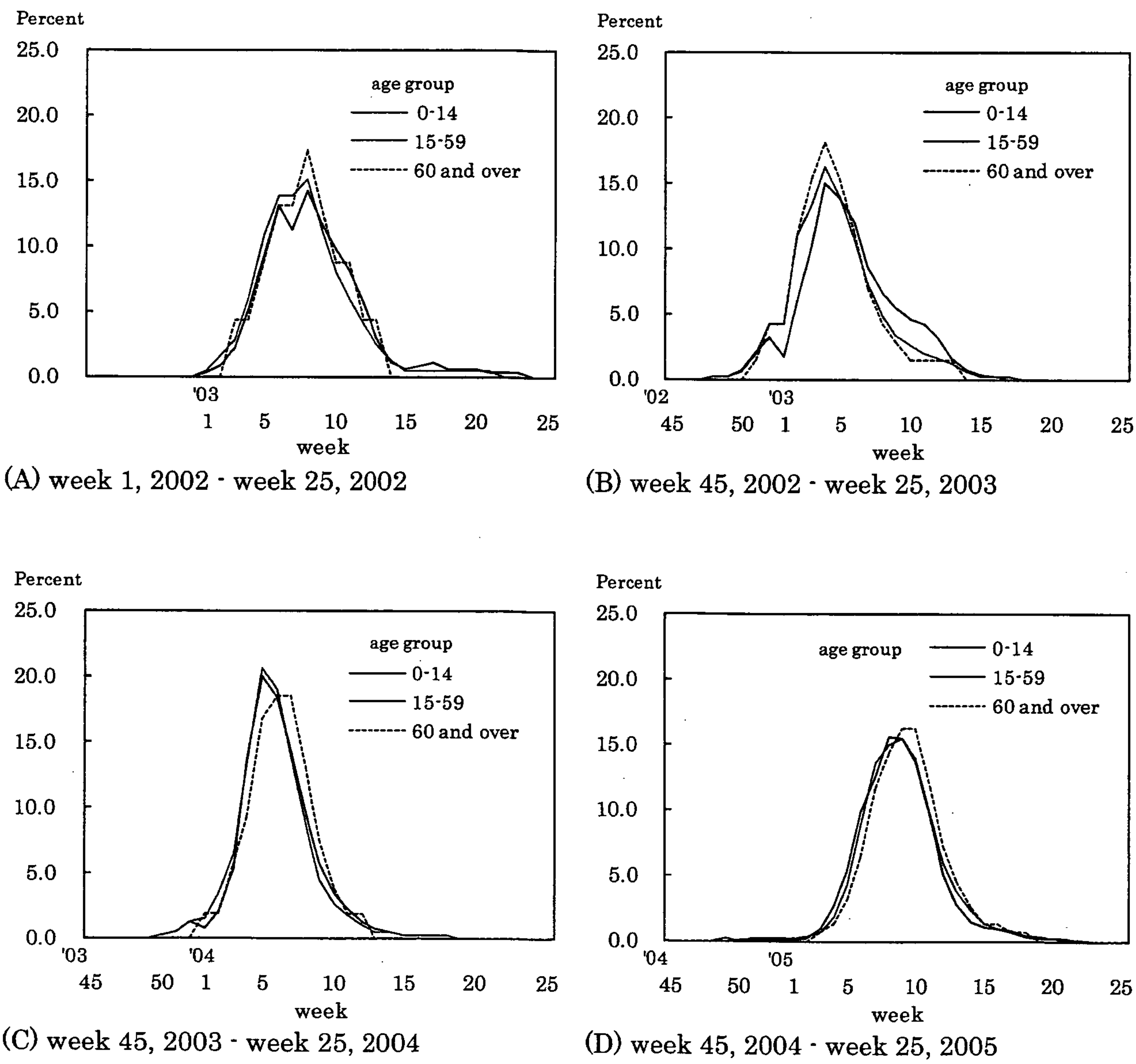

Figure 2. Proportion of weekly incidence in relation to each influenza season's total incidence by age group, Japan, 2002-2005.

Table 3. Estimated incidence rates of pediatric diseases in population aged 0-14 years, Japan, 2002-2005.

Disease	Year	Estimated incidence	Incidence rate (per 1,000 population aged 0-14 years)	
			Estimate	95% confidence interval
Pharygoconjunctival fever	2002	99,000	5.5	4.6 - 6.5
	2003	256,000	14.3	12.3 - 16.4
	2004	383,000	21.4	18.6 - 24.1
	2005	397,000	22.2	18.4 - 26.0
Group A streptococcal pharyngitis	2002	929,000	51.9	47.2 - 56.5
	2003	995,000	55.6	51.0 - 60.1
	2004	1,244,000	69.5	62.3 - 76.6
	2005	1,192,000	66.6	60.5 - 72.6
Infectious gastroenteritis	2002	5,249,000	293.1	273.3 - 313.0
	2003	5,405,000	301.9	280.1 - 323.6
	2004	5,744,000	320.8	296.8 - 344.8
	2005	5,639,000	314.9	293.7 - 336.2
Chickenpox	2002	1,605,000	89.6	85.1 - 94.2
	2003	1,481,000	82.7	78.1 - 87.3
	2004	1,474,000	82.3	77.9 - 86.7
	2005	1,542,000	86.1	81.8 - 90.4
Hand-foot-mouth disease	2002	570,000	31.8	29.9 - 33.8
	2003	1,027,000	57.4	54.2 - 60.5
	2004	527,000	29.4	27.3 - 31.6
	2005	657,000	36.7	34.1 - 39.3
Erythema infectiosum	2002	369,000	20.6	19.2 - 22.1
	2003	205,000	11.4	10.6 - 12.3
	2004	308,000	17.2	15.8 - 18.5
	2005	272,000	15.2	13.9 - 16.6
Exanthem subitum	2002	687,000	38.4	36.0 - 40.7
	2003	682,000	38.1	35.6 - 40.5
	2004	685,000	38.3	35.4 - 41.1
	2005	689,000	38.5	36.0 - 41.0
Pertussis	2002	9,000	0.5	0.4 - 0.6
	2003	8,000	0.4	0.4 - 0.6
	2004	12,000	0.7	0.6 - 0.8
	2005	9,000	0.5	0.4 - 0.6
Rubella	2002	18,000	1.0	0.8 - 1.3
	2003	17,000	0.9	0.7 - 1.1
	2004	30,000	1.7	1.2 - 2.2
	2005	10,000	0.6	0.4 - 0.7
Herpangina	2002	695,000	38.8	36.0 - 41.7
	2003	912,000	50.9	47.3 - 54.5
	2004	659,000	36.8	33.7 - 39.9
	2005	926,000	51.7	47.8 - 55.6
Measles	2002	72,000	4.0	3.6 - 4.4
	2003	48,000	2.7	2.3 - 3.0
	2004	10,000	0.6	0.4 - 0.7
	2005	6,000	0.3	0.3 - 0.4
Mumps	2002	1,045,000	58.4	54.9 - 61.8
	2003	492,000	27.5	25.6 - 29.4
	2004	789,000	44.1	40.2 - 47.9
	2005	1,308,000	73.0	68.5 - 77.6

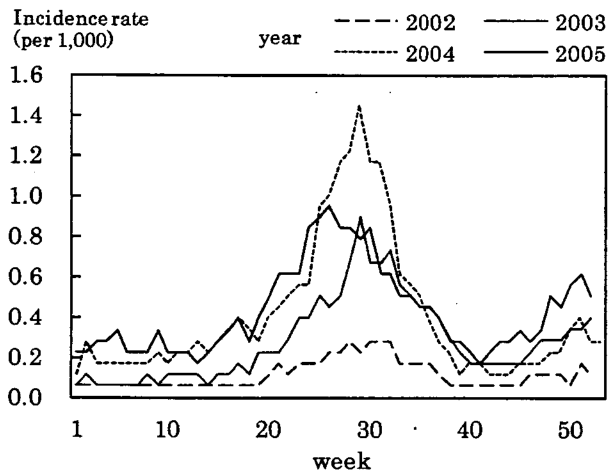

Figure 3. Estimated incidence rates of pharygoconjunctival fever by week, Japan, 2002-2005.

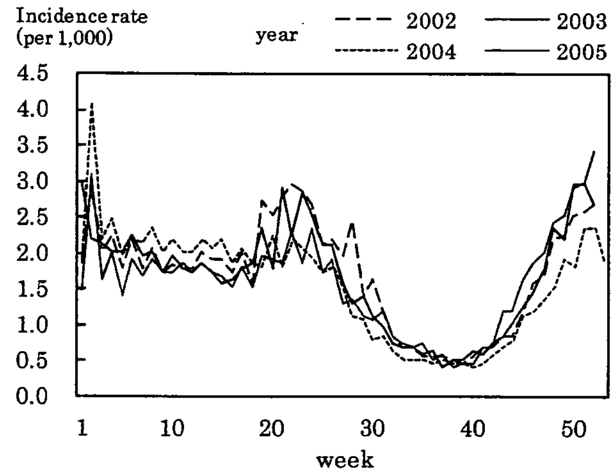

Figure 6. Estimated incidence rates of chickenpox by week, Japan, 2002-2005.

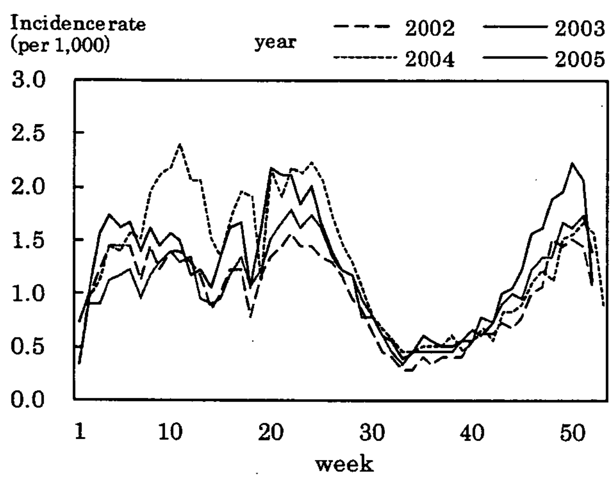

Figure 4. Estimated incidence rates of group A streptococcal pharyngitis by week, Japan, 2002-2005.

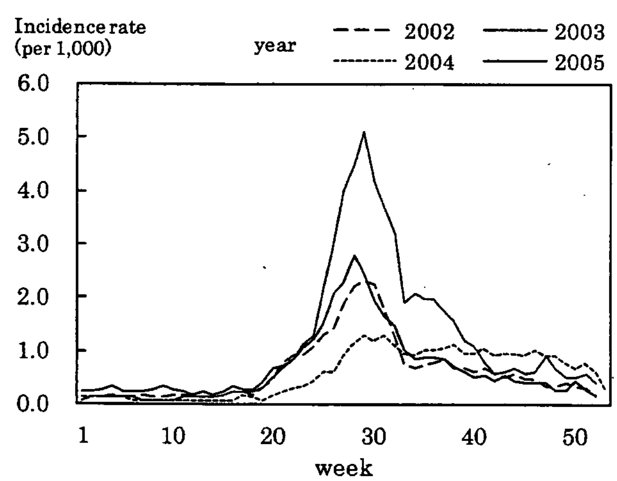

Figure 7. Estimated incidence rates of hand-foot-mouth disease by week, Japan, 2002-2005.

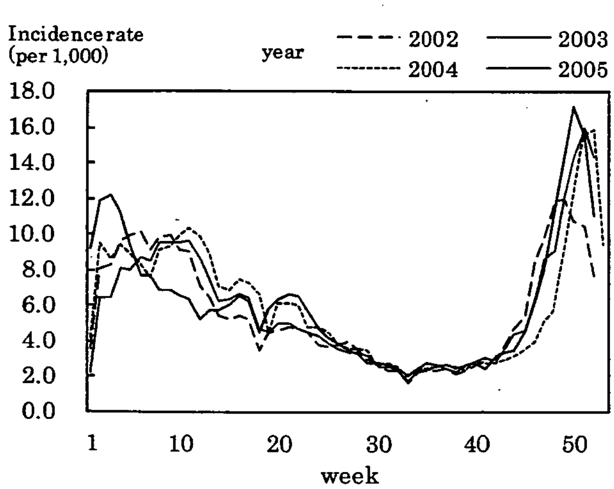

Figure 5. Estimated incidence rates of infectious gastroenteritis by week, Japan, 2002-2005.

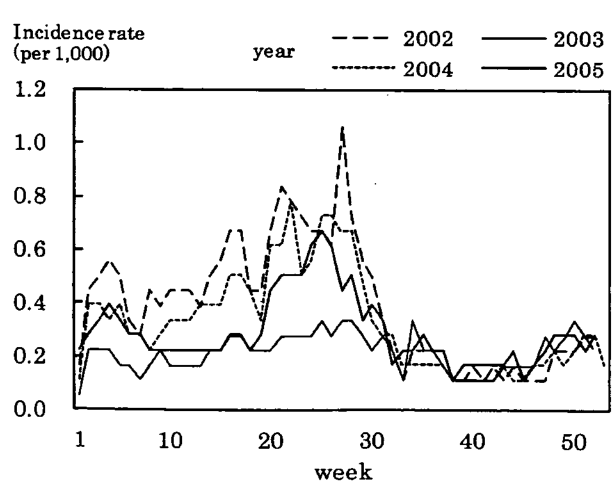

Figure 8. Estimated incidence rates of erythema infectiosum by week, Japan, 2002-2005.

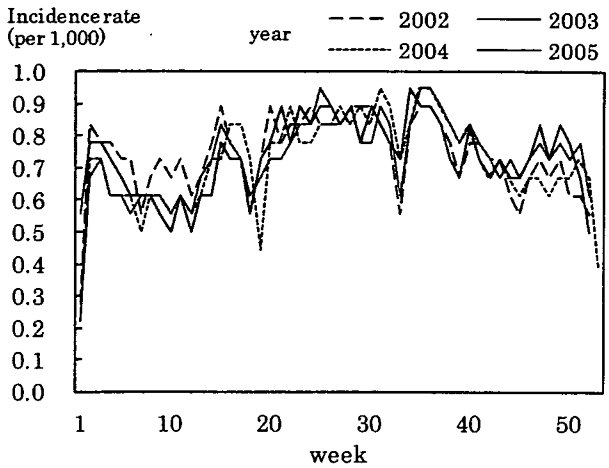

Figure 9. Estimated incidence rates of exanthem subitum by week, Japan, 2002-2005.

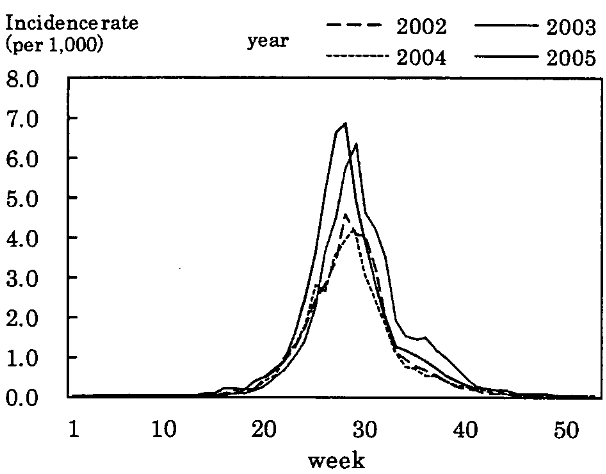

Figure 10. Estimated incidence rates of herpangina by week, Japan, 2002-2005.

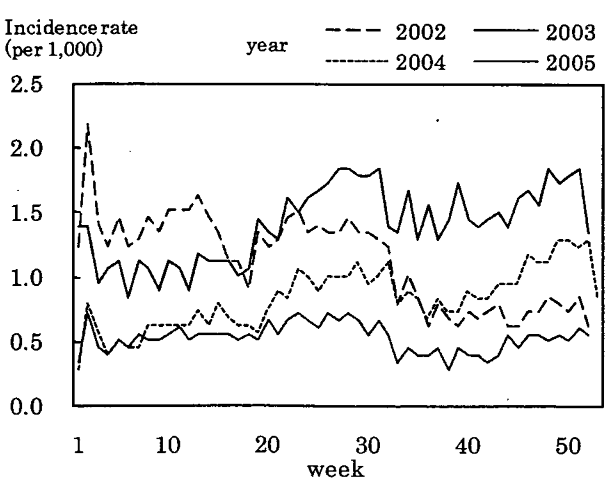

Figure 11. Estimated incidence rates of mumps by week, Japan, 2002-2005.

Figures 3 to 11 shows the weekly incidence rates of 9 pediatric diseases per 1,000 population among those 0-14 years old, respectively. For pertussis, rubella, and measles, they were not shown because of their low annual incidence rates. The seasonal pattern was observed each year in many diseases. The highest weekly incidence rate in the four years was less than 1.0 for exanthem subitum (Figure 9), more than 5.0 for infectious gastroenteritis (Figure 5), hand-foot-mouth disease (Figure 7) and herpangina (Figure 10), and 1.0-5.0 in the other five diseases.

DISCUSSION

Large yearly and seasonal variation, small sex difference and age distribution with higher incidence rate in younger population were observed in the incidence rates of influenza. These results were similar to those in previous studies.[1-3] The highest weekly incidence rate in 2002-2005 was 7.4-21.2 per 1,000 population. This would provide useful information for preventive countermeasures against the epidemic spread of influenza. The week with the highest weekly incidence rate in the over-sixties bracket was later than that in the 0-14 years of age bracket in 2004 and 2005, while such a phenomenon was not observed in 2002 and 2003. This finding would be related to several factors such as combination of epidemics of different virus types, its difference between years, proportion of persons with susceptibility to the virus, its difference between younger and older population.[18]

The incidence rate in the population aged 0-14 years in 2002-2005 was low in pertussis, rubella, and measles, presumably due to the association with the vaccination program against these diseases in Japan.[19,20] Some seasonal patterns were observed in many pediatric diseases as shown in Figures 3 to 11. These results were obtained in other previous reports.[4-6] The highest weekly incidence rate per 1,000 population aged 0-14 years in 2002-2005 was less than 1.0 for exanthem subitum. It is related to little seasonal variation. The rate was more than 5.0 for infectious gastroenteritis, hand-foot-mouth disease and herpangina. This is related to the high incidence rate of infectious gastroenteritis, and the large seasonal variation in hand-foot-mouth disease and herpangina. This finding means that the epidemic of these three diseases spread rapidly, and would be important for planning control of their epidemics.

There are some limitations and problems in the present study. The main problems would be in the data and method for estimating the incidence. Problems with the data in the reports to the NESID in Japan include the inaccuracy of disease diagnosis and incompleteness of reporting.[13] Those in the method have been already discussed in the previous reports in detail.[12,16] The assumption in the method that sentinels are randomly selected from all medical institutions is critical. Although the NESID guidelines in Japan calls for the sentinels to be selected from all medical institutions in public health areas as randomly and as representatively as possible, sentinels seem to be recruited on a voluntary basis to some extent. It was reported that the mean size of the underlying population was larger in sentinels than in all medical institutions, that the incidence was overestimated because the assumption was failing, and that the ratio of the estimated to the actual incidence of influenza and pediatric diseases based on the sentinel surveillance data in the NESID in Japan would be 1.06-1.26.[12]

In conclusion, we estimated the annual and weekly incidence rates of influenza and pediatric diseases in Japan in 2002-2005, and described their temporal variation.

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APPENDIX

Consider the distribution of incidences in medical institutions. Let m be an integer greater than the largest incidence among medical institutions, n be the number of all medical institutions, and n_i be the number of medical institutions with the incidence of i for $i = 0, 1, \cdots, m$. Let N be the number of sentinels, and N_i be the number of sentinels with the incidence of i for $i = 0, 1, \cdots, m$. The constants of n and N are known, and those of $\{n_i\}$ are unknown. $\{N_i\}$ are obtained from the sentinel surveillance, and follow a multi-hypergeometric distribution under the condition of N fixed under the assumption that sentinels are randomly selected in all medical institutions.

Let α be the total incidence in all medical institutions, and note that $\alpha = \sum i \times n_i$. The estimate of α is given to be $\alpha = \sum i \times N_i \times n / N$, i.e., the incidence is estimated as the total incidence in sentinels ($\sum i \times N_i$) divided by the proportion of sentinels among all medical institutions (N / n).

The approximate confidence interval for α is given to be $(\hat{\alpha} - 1.96 \times s, \hat{\alpha} + 1.96 \times s)$, where s^2 is an estimate of variance of α and is given to be:

$$\left[\sum i^2 \times N_i / N - \left(\sum i \times N_i / N\right)^2\right] \times n^3 (1 / N - 1/n) / (n - 1) .$$

Consider that the incidences in some strata such as prefectures and types of medical institution are estimated using the above-explained method. Let k be the number of strata, $\hat{\alpha}_1$, $\hat{\alpha}_2$, $\cdots$, α_k, the estimated incidences in the strata, and s_1^2, s_2^2, $\cdots$, s_k^2, their estimated variances. The approximate confidence interval for the total incidence is given as $(\hat{\alpha}_t - 1.96 \times s_t,\ \hat{\alpha}_t + 1.96 \times s_t)$, where $\hat{\alpha}_t = \hat{\alpha}_1 +, \hat{\alpha}_2 + \cdots + \alpha_k$ and $s_t^2 = s_1^2 + s_2^2 + \cdots + s_k^2$.

Epidemics of Drug-Resistant Bacterial Infections Observed in Infectious Disease Surveillance in Japan, 2001-2005

Michiko Izumida,[1] Masaki Nagai,[1] Akiko Ohta,[1] Shuji Hashimoto,[2] Miyuki Kawado,[2] Yoshitaka Murakami,[3] Yuki Tada,[4] Mika Shigematsu,[4] Yoshinori Yasui,[4] and Kiyosu Taniguchi.[4]

BACKGROUND: Drug-resistant bacteria have been increasing together with advancement of antimicrobial chemotherapy in recent years. In Japan, the target diseases in the National Epidemiological Surveillance of Infectious Diseases (NESID) include some drug-resistant bacterial infections.
METHODS: We used the data in the NESID in Japan, 2001-2005. Target diseases were methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and multi-drug-resistant *Pseudomonas aeruginosa* (MDRPA) infections. The numbers of patients reported by sentinel hospitals (about 500) on a monthly basis were observed.
RESULTS: The numbers of patients per month per sentinel hospital of 2001-2005 were 3.37-3.98 in MRSA, 0.96-1.19 in PRSP, and 0.11-0.13 in MDRPA infections. The sex ratios (male / female) of patients were 1.69-1.82, 1.34-1.43, and 1.71-2.52, respectively. More than 50% of all patients were adults aged 70 years or older in MRSA and MDRPA infections, but more than 60% were children under 10 years in PRSP infections. The number of patients per sentinel hospital in MRSA infections showed little variation between months, but evidenced a large variation in PRSP and MDRPA infections. The annual trend in the number of patients per sentinel hospital was increasing significantly for the 5-year period in MRSA and PRSP infections, but not in MDRPA infections.
CONCLUSIONS: We revealed sex-age distributions of the patients reported to NESID in Japan, 2001-2005. An increasing incidence of MRSA and PRSP infections and monthly variation in PRSP and MDRPA infections were observed for the 5-year period. Extended observation would be necessary to confirm these trends and variations.
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Key words: Drug-resistant Bacterial Infections, Methicillin-resistant *Staphylococcus aureus* (MRSA), Multi-drug-resistant *Pseudomonas Aeruginosa* (MDRPA), Penicillin-resistant *Streptococcus Pneumoniae* (PRSP), Sentinel Surveillance.

Drug-resistant bacteria have been increasing together with advancement of antimicrobial chemotherapy in recent years.[1] The emergence of drug-resistant bacteria will make these infections more difficult to treat.[1-5] Observing the epidemics of drug-resistant bacterial infections is necessary and important.[1] In Japan, the target diseases in the National Epidemiological Surveillance of Infectious Diseases (NESID) include methicillin-resistant *Staphylococcus aureus* (MRSA) infections, penicillin-resistant *Streptococcus pneumoniae* (PRSP) infections, and multi-drug-resistant *Pseudomonas aeruginosa* (MDRPA) infections.[6] According to a current report in Japan, 57.1% (70.9% of inpatients, 31.2% of outpatients) of *S. aureus* isolated are resistant to methicillin, and 62.4% (61.5% of inpatients, 63.8% of outpatients) of *S. pneumoniae* isolated are resistant to penicillin.[7] In *P. aeruginosa*, about 80% of these isolated bacteria are susceptible to imipenem or ciprofloxacin, and 90% are susceptible to amikacin.[7] There are few reports about the epidemiologic features and changes of incidence in these infections nationwide in Japan.

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[1] Department of Public Health, Saitama Medical University Faculty of Medicine.
[2] Department of Hygiene, Fujita Health University School of Medicine.
[3] Department of Health Science, Shiga University of Medical Science.
[4] Infectious Disease Surveillance Center, National Institute of Infectious Diseases.
Address for correspondence: Michiko Izumida, Department of Public Health, Saitama Medical University Faculty of Medicine, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan. (e-mail: kidomi@saitama-med.ac.jp)

In the present study, we observed the number of patients reported to NESID in Japan, 2001-2005, and revealed sex-age distributions of the patients and temporal changes in the number of patients of these three drug-resistant bacterial infections.

METHODS

Surveillance of Infectious Diseases in Japan

The NESID in Japan has been described elsewhere.[6,8-9] The number of drug-resistant bacterial infections at sentinel hospitals is reported every month to public health centers.[6,8-9] The sentinel hospitals (about 500 hospitals with more than 300 beds providing medical care in pediatrics and internal medicine across Japan) primarily target inpatients.[6,8] The information reported includes sex and age.[6]

Reporting criteria of bacteriological examinations of these infections were *S. aureus* resistant to oxacillin [minimal inhibitory concentration (MIC)≧4μg/mL] for MRSA, *S. pneumoniae* resistant to penicillin [MIC≧0.125μg/mL] for PRSP, and *P. aeruginosa* resistant to imipenem [MIC≧16μg/mL], amikacin [MIC≧32μg/mL] and ciprofloxacin [MIC≧4μg/mL] for MDRPA.[6]

Surveillance Data and Method of Analysis

We used the data in the NESID in Japan, 2001-2005. Target diseases are three infections, MRSA, PRSP and MDRPA.

Annual trend and monthly variation in the number of patients per sentinel hospital were evaluated using a Poisson regression with that as a dependent variable, and a year (as a continuous variable) and a month (as dummy variables) as independent variables. The SAS® (SAS Institute, Cary, North Carolina, USA) GENMOD procedure was used for the analysis.

RESULTS

Table 1 shows the numbers of patients with drug-resistant bacterial infections reported by sentinel hospitals in 2001-2005. The total numbers of patients (per month per sentinel hospital) were 18,257-22,454 (3.37-3.98) in MRSA infections, 5,202-6,700 (0.96-1.19) in PRSP infections, and 608-747 (0.11-0.13) in MDRPA infections. The sex ratios (male / female) of patients were 1.69-1.82, 1.34-1.43, and 1.71-2.52, respectively.

Figure 1 shows the age distributions of drug-resistant bacterial infections by sex. More than 50% of all patients were adults aged 70 years or older in MRSA and MDRPA infections, but more than 60% of them were children under 10 years in PRSP infections.

Figures 2, 3, and 4 show the number of patients per sentinel hospital of MRSA, PRSP and MDRPA infections by month, respectively. Table 2 shows the adjusted ratios of the number of patients per sentinel hospital by year and month in Japan, 2001-2005. The number of patients per sentinel hospital of MRSA infections showed little variation between months (adjusted ratio: 0.96-1.07 compared with the annual mean value), but the annual trend in the number of patinets per sentinel hospital was increasing significantly (adjusted ratio: 1.04 for 1 year, that is equal to

Table 1. Numbers of patients with drug-resistant bacterial infections reported by sentinel hospitals in 2001-2005.

Diseases	patients	Year				
		2001	2002	2003	2004	2005
MRSA infections	Total	18,257	19,904	21,117	21,835	22,454
	Male	11,482	12,638	13,637	13,828	14,215
	Female	6,775	7,266	7,480	8,007	8,239
	Male/Female	1.69	1.74	1.82	1.73	1.73
	Number of patients per month per sentinel hospital	3.37	3.59	3.77	3.87	3.98
PRSP infections	Total	5,202	6,071	6,400	6,700	6,217
	Male	3,043	3,497	3,660	3,893	3,660
	Female	2,159	2,574	2,740	2,807	2,557
	Male/Female	1.41	1.36	1.34	1.39	1.43
	Number of patients per month per sentinel hospital	0.96	1.09	1.14	1.19	1.10
MDRPA infections	Total	608	715	747	669	692
	Male	398	496	535	422	452
	Female	210	219	212	247	240
	Male/Female	1.90	2.26	2.52	1.71	1.88
	Number of patients per month per sentinel hospital	0.11	0.13	0.13	0.12	0.12

MRSA: methicillin-resistant *Staphylococcus aureus*.
PRSP: penicillin-resistant *Streptococcus pneumoniae*.
MDRPA: multi-drug-resistant *Pseudomonas aeruginosa*.

1.23 for 5 years) (Figure 2 and Table 2). The number of those PRSP infections showed a large variation between months (adjusted ratio: 0.55-1.40 compared with the annual mean value), and their annual trend was increasing significantly (adjusted ratio: 1.03 for 1 year, that is equal to 1.19 for 5 years). The month with the least number of patients was September, and the month with the largest number was December, followed by May (Figure 3 and Table 2). In MDRPA infections, the number of patients per sentinel hospital showed a large variation between months (adjusted ratio: 0.77-1.40 compared with the annual mean value), and it was higher during the latter than the former half of the year. However, their annual trend was not increasing significantly (adjusted ratio: 1.01 for 1 year, that is equal to 1.05 for 5 years) (Figure 4 and Table 2).

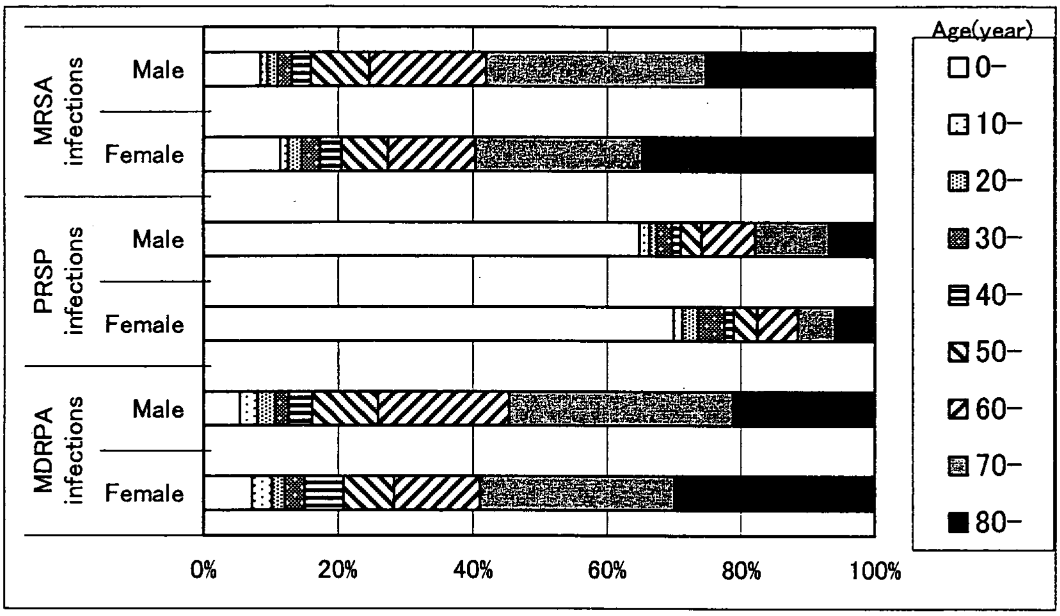

Figure 1. Age distributions of drug-resistant bacterial infections by sex.
MRSA: methicillin-resistant *Staphylococcus aureus.*
PRSP: penicillin-resistant *Streptococcus pneumoniae.*
MDRPA: multi-drug-resistant *Pseudomonas aeruginosa.*

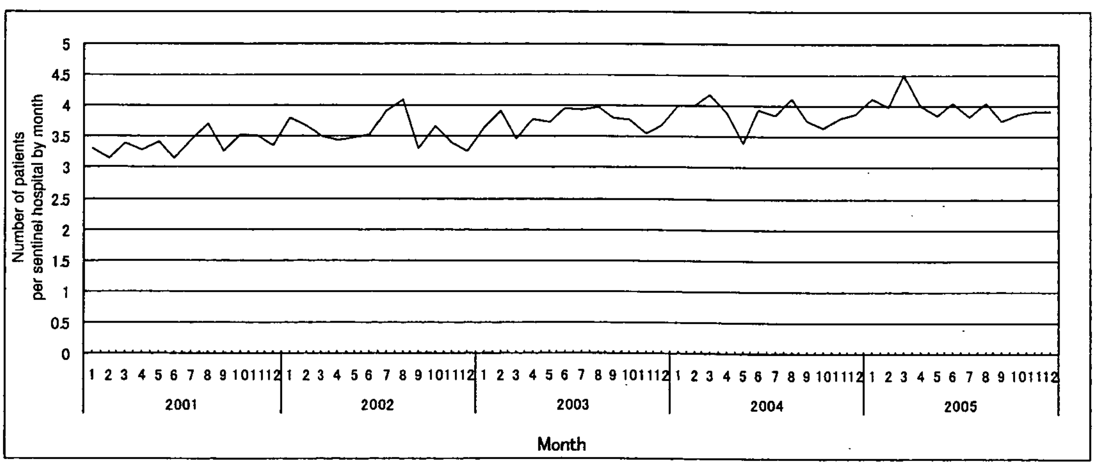

Figure 2. Number of patients per sentinel hospital of methicillin-resistant *Staphylococcus aureus* infections by month (2001-2005).

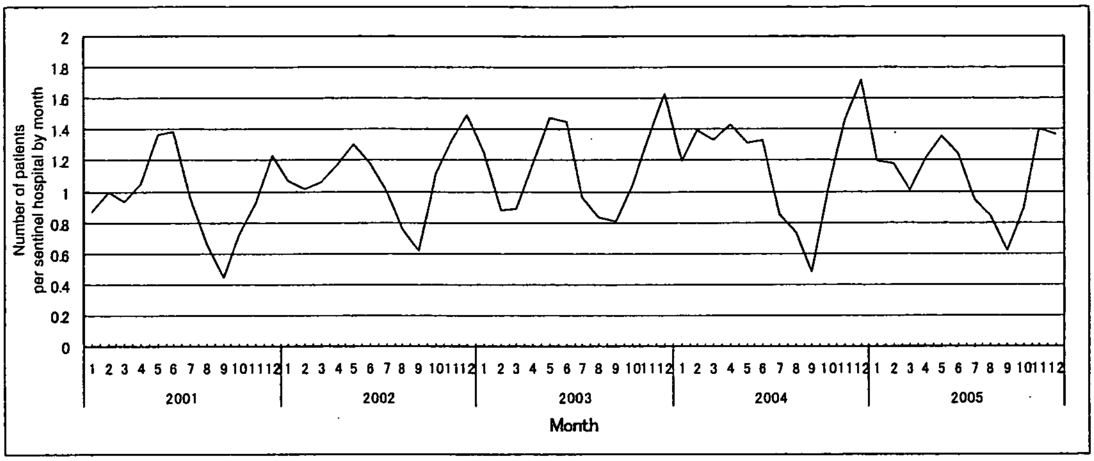

Figure 3. Number of patients per sentinel hospital of penicillin-resistant *Streptococcus pneumoniae* infections by month (2001-2005).

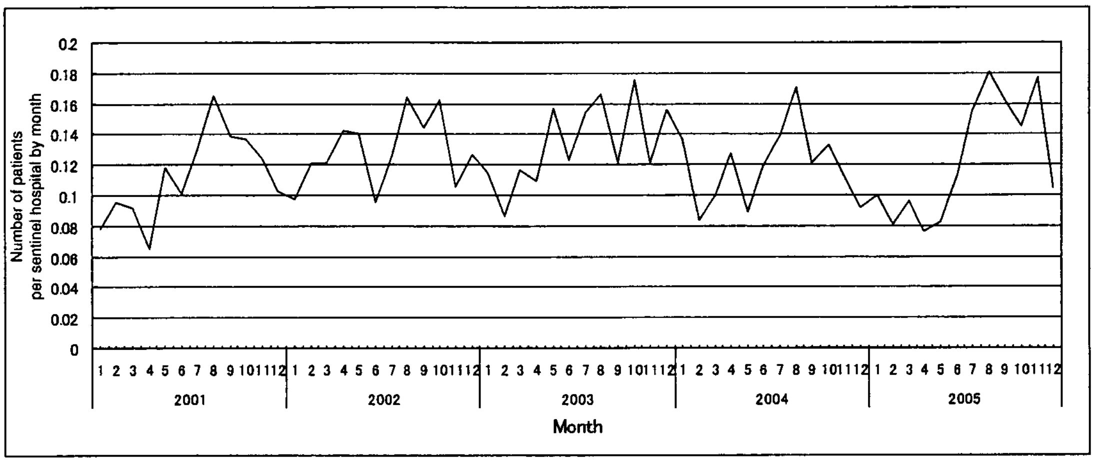

Figure 4. Number of patients per sentinel hospital of multi-drug-resistant *Pseudomonas aeruginosa* infections by month (2001-2005).

Table 2. Adjusted ratios of the number of patients per sentinel hospital by year and month in 2001-2005.

Parameter	MRSA infections		PRSP infections		MDRPA infections	
	Adjusted ratio* of number of patients per sentinel hospital	p-value	Adjusted ratio* of number of patients per sentinel hospital	p-value	Adjusted ratio* of number of patients per sentinel hospital	p-value
Year	1.04	< 0.001	1.03	< 0.001	1.01	0.483
January	1.02	0.124	1.05	0.017	0.87	0.022
February	1.01	0.463	1.02	0.237	0.77	< 0.001
March	1.03	0.010	0.98	0.266	0.87	0.018
April	0.99	0.298	1.13	< 0.001	0.86	0.014
May	0.96	< 0.001	1.28	< 0.001	0.97	0.546
June	1.00	0.661	1.23	< 0.001	0.91	0.116
July	1.02	0.041	0.88	< 0.001	1.16	0.006
August	1.07	< 0.001	0.72	< 0.001	1.40	< 0.001
September	0.96	< 0.001	0.55	< 0.001	1.13	0.022
October	0.99	0.498	0.90	< 0.001	1.24	< 0.001
November	0.98	0.028	1.21	< 0.001	1.05	0.346
December	0.97	0.011	1.40	< 0.001	0.96	0.452

MRSA: methicillin-resistant *Staphylococcus aureus*.

PRSP: penicillin-resistant *Streptococcus pneumoniae*.

MDRPA: multi-drug-resistant *Pseudomonas aeruginosa*.

* Adjusted ratio was estimated by Poisson regression analysis.

The ratio for the year indicates the difference in one year. The ratio for month is the ratio to the annual mean value.

DISCUSSION

We could observe representative cases of three major drug-resistant bacterial infections throughout Japan because we used the data from the sentinel hospitals in the NESID. But the patients in the present study might be more serious than all patients with these infections because these hospitals primarily target inpatients.

Half or more of the MRSA and MDRPA patients in our study were elderly. The two bacteria are basically opportunistic and hospital pathogens.[10-11] Besides, the elderly generally visit hospitals more than other adults, and they may easily become compromised hosts. On the other hand, more than 60% of all patients of PRSP infections involved children under 10 years. *S. pneumoniae* colonizes in the nasopharynx of healthy children more than healthy adults, and causes infections of the middle ear, sinuses, trachea, bronchi, and lungs.[12] Infants may have an increased risk of viral (upper respiratory tract) infections (which triggered *S. pneumoniae* infections) compared to adults. We consider these to be why most patients of PRSP infections are in children.

In Japan, although there are many reports about annual changes in the susceptibilities of bacteria isolated from patients,[1,13-18] only a few concern annual changes in the incidence of infections due to drug-resistant bacteria, and even fewer with monthly variations in incidence.

In the present study, the annual trend in the number of patients per sentinel hospital was found to be increasing significantly in MRSA and PRSP infections, but not in MDRPA infection for the 5-year period between 2001 and 2005. A past report showed that a proportion of PRSP in *S. pneumoniae* which was isolated from patients (with lower respiratory infectious diseases) was increasing in recent years.[15] The increasing trend of PRSP infections might reflect an increasing proportion of PRSP in *S. pneumoniae*. However, one should recall that the number of reported patients in sentinel hospitals might increase if the number of population covered by the sentinel hospitals increased. In addition, if the clinical abilities of pediatrics departments in the sentinel hospitals were improved, the number of patients might increase because many patients with PRSP infections are children. On the other hand, the above-mentioned report showed that a proportion of MRSA in *S. aureus* which was isolated from patients was not increasing in recent years.[15] We thought one of the reasons for the increasing trend of MRSA infections was that the number of compromised hosts who would easily become MRSA-infected was increasing for the observed period, but we did not know the details. In MDRPA infections, because the number of patients per sentinel hospital was very few, it is important to observe the longer period trend.

In addition, in the present study, the numbers of patients per sentinel hospital showed a large monthly variation in PRSP and MDRPA infections, possibly reflecting differences in their monthly incidence. PRSP is frequently isolated from children who have acute otitis media. There was a report that the number of children who were receiving treatment in a hospital as inpatients for acute otitis media peaked in December and May, and was lowest in September.[19] The monthly variation of PRSP infections in our study agrees with this variation. On the other hand, we could not find previous reports that the incidence of MRSA infections showed a large monthly variation, and our result was consistent with this. There was no report that the incidence of MDRPA infections showed a large monthly variation, and the reasons for the large monthly variation in our study remain unknown. Because the number of patients was very few in MDRPA infections, the longer period data might be effective to observe a clear monthly variation in incidence.

In conclusion, in the present study we revealed the sex-age distributions of the patients reported to NESID in Japan, 2001-2005. An increasing incidence of MRSA and PRSP infections and monthly variation in PRSP and MDRPA infections were observed for the 5-year period. Extended observation would be necessary to confirm these trends and variations.

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Epidemics of Vector-borne Diseases Observed in Infectious Disease Surveillance in Japan, 2000-2005

Shuji Hashimoto,[1] Miyuki Kawado,[1] Yoshitaka Murakami,[2] Michiko Izumida,[3] Akiko Ohta,[3] Yuki Tada,[4] Mika Shigematsu,[4] Yoshinori Yasui,[4] Kiyosu Taniguchi,[4] and Masaki Nagai.[3]

BACKGROUND: Observing the epidemics of vector-borne diseases is important. One or more cases of 6 vector-borne diseases were reported to the National Epidemiological Surveillance of Infectious Diseases in Japan in 2000-2005.

METHODS: The reports of those cases were available. The incidence was observed by region of acquired infection, prefecture reporting, and week and year of diagnosis.

RESULTS: The incidence rate per year per 1,000,000 population was 0.36 for dengue fever, 0.04 for Japanese encephalitis, 0.38 for Japanese spotted fever, 0.08 for Lyme disease, 0.74 for malaria, and 3.50 for scrub typhus. There were no cases of dengue fever or malaria derived from domestic infections. The yearly incidence rate increased for dengue fever and Japanese spotted fever, and declined for malaria and scrub typhus. The proportion of cases reported in Tokyo was 44% for dengue fever and 37% for malaria. The number of prefectures reporting one or more cases of Japanese spotted fever increased in western Japan. The cases of scrub typhus increased in autumn-winter in prefectures of eastern Japan, and increased both in autumn-winter and spring in western prefectures.

CONCLUSIONS: The study reveals the epidemiologic features of both temporal and geographic distributions of cases of 6 vector-borne diseases in Japan, 2000-2005.

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Key words: Disease Vectors, Disease Notification, Dengue, Japanese Spotted Fever, Scrub Typhus.

Vector-borne diseases, such as dengue fever and malaria, have a major impact on public health all over the world.[1] There are disease-specific characteristics in geographic distribution, temporal trends and seasonality of such cases because their transmission is dependent on the spread and density of appropriate vectors (mosquito, tick, etc).[2] In many countries, the surveillance of various vector-borne diseases has been conducted with the aim of detecting, controlling and preventing their epidemics.[3-6] The epidemiologic characteristics of those diseases have been described from the surveillance data.[3,4]

In Japan, the National Epidemiological Surveillance of Infectious Diseases (NESID) has targeted specific vector-borne diseases.[6,7] Those with one or more cases reported in 2000-2005 include 6 diseases: dengue fever, Japanese encephalitis, Japanese spotted fever, Lyme disease, malaria and scrub typhus (tsutsugamushi disease).[7] The epidemiologic features of these diseases have been described,[8-12] but have not be sufficiently evaluated from the viewpoint of geographic and temporal clustering.

In the present study, the geographic and temporal distributions of cases of the above 6 vector-borne diseases were analyzed from the NESID data in Japan, 2000-2005.

METHODS

Surveillance of infectious diseases in Japan

NESID in Japan has been described elsewhere.[6,7,13] Any physician who has diagnosed a notifiable disease must report the patient information to local public health center. Notification by public

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[1] Department of Hygiene, Fujita Health University School of Medicine.

[2] Department of Health Science, Shiga University of Medical Science.

[3] Department of Public Health, Saitama Medical University Faculty of Medicine.

[4] Infectious Disease Surveillance Center, National Institute of Infectious Diseases.

Address for correspondence: Shuji Hashimoto, Department of Hygiene, Fujita Health University School of Medicine, 1-98, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. (e- mail: hasimoto@fujita-hu.ac.jp)

health centers to the local government (prefecture) and the Ministry of Health, Labour and Welfare of Japan is made through an on-line computer network.

A total of 11 vector-borne diseases are notifiable: the above 6 as well as relapsing fever, yellow fever, Crimean-Congo hemorrhagic fever, epidemic typhus, and plague.[6,7] The information reported includes sex, age, date of diagnosis, and region where infection was acquired.

Surveillance data and method of analysis

The reports involving the above 6 vector-borne diseases diagnosed in 2000-2005 to the NESID in Japan were available. The data we used were the week and year of diagnosis, prefecture reporting, and region of acquired infection (Japan, others, and unknown).

The incidence of 6 vector-borne diseases was observed by region acquired, prefecture reporting, and week and year of diagnosis. The incidence rate per population by prefecture reporting was calculated using the 2000 census population data, and was compared with that nationwide. The exact test under the assumption that the number of cases follows a Poisson distribution was used for the comparison.

RESULTS

Table 1 shows the incidence of vector-borne diseases in 2000-2005. The total incidence and the incidence rate per year per 1,000,000 population were, respectively, 275 and 0.36 for dengue fever, 33 and 0.04 for Japanese encephalitis, 294 and 0.38 for Japanese spotted fever, 60 and 0.08 for Lyme disease, 566 and 0.74 for malaria, and 2,680 and 0.35 for scrub typhus. The yearly incidence rate rose for dengue fever and Japanese spotted fever, and declined for malaria and scrub typhus.

Table 2 shows the incidence of vector-borne diseases by region of acquired infection in 2000-2005. While nobody acquired the infection of dengue fever or malaria in Japan, the proportion of infection for the other 4 diseases was 86.7-100.0%.

Figure 1 shows the incidence of vector-borne diseases by week and year of diagnosis in 2000-2005. Some seasonal patterns of incidence were observed for Japanese spotted fever and scrub typhus, but none for dengue fever and malaria.

Table 3 shows the incidence of vector-borne diseases by prefecture reporting in 2000-2005. The dengue fever cases reported in Tokyo were 43.6% of the national total. The incidence of Japanese encephalitis by prefecture was 4 cases or less. The incidence rate ratio of Japanese spotted fever compared with the national rate was over 3 in several prefectures of western Japan: Wakayama, Shimane, Tokushima, Ehime, Kochi, Miyazaki, and Kagoshima. Those ratios being higher than one were statistically significant. The cases of Lyme disease reported in Hokkaido, Japan's northernmost island, were 45.0% of the national total, while malaria cases reported in Tokyo were 37.2%. The incidence rate ratio of scrub typhus was over 3 in several prefectures in eastern and western Japan: Akita, Fukushima, Oita, Miyazaki, and Kagoshima. Those ratios being higher than one were statistically significant.

Figures 2 and 3 show the distribution of cases of Japanese spotted fever and scrub typhus by prefecture reporting, and week and year of diagnosis in 2000-2005, respectively. Distributions of other diseases were not shown since the cases of Japanese encephalitis by prefecture were too few and the proportion of cases of dengue fever, Lyme diseases and malaria reported only in one prefecture was high, as shown in Table 3.

Table 1. Incidence of vector-borne diseases, Japan, 2000-2005.

Vector-borne diseases	Year						Total
	2000	2001	2002	2003	2004	2005	
Dengue fever	18	50	52	32	49	74	275 (0.36)
Japanese encephalitis	7	5	8	1	5	7	33 (0.04)
Japanese spotted fever	38	40	36	52	66	62	294 (0.38)
Lyme disease	12	15	15	5	5	8	60 (0.08)
Malaria	154	109	83	78	75	67	566 (0.74)
Scrub typhus	791	491	338	402	313	345	2,680 (3.50)

Incidence rates per year per 1,000,000 population in parentheses.

Table 2. Incidence of vector-borne diseases by region of acquired infection, Japan, 2000-2005.

Vector-borne diseases	Region of acquired infection			Total
	Japan	Others	Unknown	
Dengue fever	0 (0.0)	275 (100.0)	0 (0.0)	275 (100)
Japanese encephalitis	33 (100.0)	0 (0.0)	0 (0.0)	33 (100)
Japanese spotted fever	294 (100.0)	0 (0.0)	0 (0.0)	294 (100)
Lyme disease	52 (86.7)	8 (13.3)	0 (0.0)	60 (100)
Malaria	0 (0.0)	557 (98.4)	9 (1.6)	566 (100)
Scrub typhus	2,669 (99.6)	6 (0.2)	5 (0.2)	2,680 (100)

Percentages in parentheses.