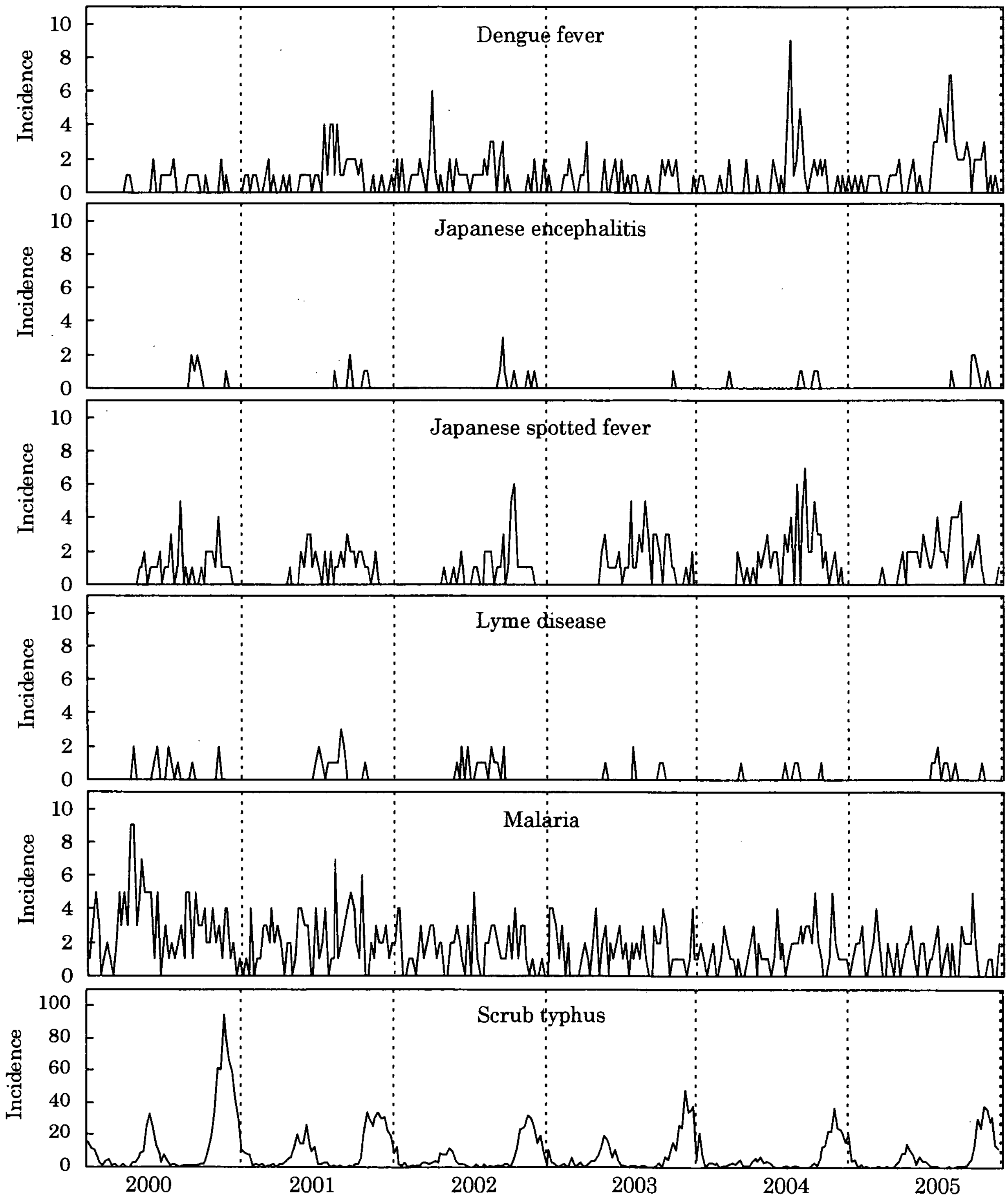

Figure 1. Incidence of vector-borne diseases by week and year of diagnosis, Japan, 2000-2005.

Table 3. Incidence of vector-borne diseases by prefecture reporting, Japan, 2000-2005.

Prefecture reporting	Dengue fever	Japanese encephalitis	Japanese spotted fever	Lyme disease	Malaria	Scrub typhus
Hokkaido	4 (0.33)	0 (0.00)	0 (0.00)	27 (10.09) *	14 (0.55)	0 (0.00)
Aomori	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.44)	1 (0.15)	78 (2.51) *
Iwate	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	41 (1.38)
Miyagi	6 (1.17)	0 (0.00)	0 (0.00)	1 (0.89)	6 (0.57)	30 (0.60)
Akita	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	160 (6.42) *
Yamagata	1 (0.37)	0 (0.00)	0 (0.00)	1 (1.71)	2 (0.36)	55 (2.11) *
Fukushima	1 (0.22)	0 (0.00)	0 (0.00)	2 (2.00)	3 (0.32)	220 (4.92) *
Ibaraki	3 (0.46)	0 (0.00)	0 (0.00)	0 (0.00)	10 (0.75)	13 (0.21)
Tochigi	3 (0.69)	0 (0.00)	0 (0.00)	0 (0.00)	12 (1.34)	17 (0.40)
Gunma	3 (0.68)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	67 (1.57) *
Saitama	8 (0.53)	0 (0.00)	0 (0.00)	1 (0.30)	20 (0.64)	5 (0.03)
Chiba	23 (1.78) *	0 (0.00)	13 (0.94)	0 (0.00)	18 (0.68)	172 (1.37) *
Tokyo	120 (4.58) *	0 (0.00)	0 (0.00)	9 (1.57)	211 (3.91) *	50 (0.20)
Kanagawa	29 (1.57) *	0 (0.00)	0 (0.00)	4 (0.99)	65 (1.71) *	110 (0.61)
Niigata	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.86)	7 (0.64)	113 (2.17) *
Toyama	3 (1.24)	0 (0.00)	0 (0.00)	1 (1.89)	1 (0.20)	16 (0.68)
Ishikawa	1 (0.39)	1 (3.26)	0 (0.00)	0 (0.00)	1 (0.19)	6 (0.24)
Fukui	1 (0.56)	0 (0.00)	1 (0.52)	0 (0.00)	3 (0.81)	3 (0.17)
Yamanashi	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.21)
Nagano	3 (0.62)	0 (0.00)	1 (0.19)	2 (1.91)	1 (0.10)	43 (0.92)
Gifu	1 (0.22)	0 (0.00)	0 (0.00)	1 (1.01)	2 (0.21)	107 (2.41) *
Shizuoka	5 (0.61)	1 (1.02)	1 (0.11)	0 (0.00)	9 (0.54)	58 (0.73)
Aichi	13 (0.85)	0 (0.00)	0 (0.00)	1 (0.30)	30 (0.95)	19 (0.13)
Mie	2 (0.50)	1 (2.07)	2 (0.47)	0 (0.00)	5 (0.60)	19 (0.49)
Shiga	4 (1.37)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.33)	3 (0.11)
Kyoto	4 (0.70)	0 (0.00)	0 (0.00)	0 (0.00)	13 (1.11)	3 (0.05)
Osaka	16 (0.84)	1 (0.44)	1 (0.05)	1 (0.24)	49 (1.25)	5 (0.03)
Hyogo	5 (0.42)	0 (0.00)	18 (1.40)	2 (0.76)	18 (0.73)	31 (0.26)
Nara	5 (1.61)	1 (2.68)	0 (0.00)	0 (0.00)	2 (0.31)	0 (0.00)
Wakayama	1 (0.43)	1 (3.62)	13 (5.28) *	0 (0.00)	2 (0.42)	33 (1.47)
Tottori	0 (0.00)	1 (6.29)	1 (0.71)	1 (3.46)	3 (1.10)	19 (1.47)
Shimane	0 (0.00)	2 (10.14)	66 (37.55) *	0 (0.00)	4 (1.18)	35 (2.18) *
Okayama	0 (0.00)	4 (7.90) *	0 (0.00)	0 (0.00)	3 (0.35)	16 (0.39)
Hiroshima	1 (0.16)	4 (5.36) *	2 (0.30)	1 (0.74)	7 (0.55)	90 (1.48) *
Yamaguchi	0 (0.00)	2 (5.06)	0 (0.00)	1 (1.39)	2 (0.30)	5 (0.16)
Tokushima	1 (0.56)	0 (0.00)	21 (11.06) *	0 (0.00)	1 (0.27)	11 (0.64)
Kagawa	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.22)	1 (0.05)
Ehime	0 (0.00)	1 (2.59)	12 (3.48) *	0 (0.00)	8 (1.21)	1 (0.03)
Kochi	0 (0.00)	2 (9.49)	61 (32.49) *	0 (0.00)	0 (0.00)	32 (1.87) *
Fukuoka	3 (0.28)	3 (2.30)	1 (0.09)	1 (0.42)	12 (0.54)	15 (0.14)
Saga	0 (0.00)	3 (13.21) *	0 (0.00)	0 (0.00)	0 (0.00)	21 (1.14)
Nagasaki	1 (0.31)	2 (5.10)	0 (0.00)	0 (0.00)	3 (0.45)	68 (2.13) *
Kumamoto	1 (0.25)	2 (4.15)	1 (0.23)	0 (0.00)	3 (0.36)	61 (1.56) *
Oita	0 (0.00)	1 (3.16)	1 (0.35)	0 (0.00)	0 (0.00)	117 (4.55) *
Miyazaki	0 (0.00)	0 (0.00)	17 (6.30) *	0 (0.00)	2 (0.38)	234 (9.51) *
Kagoshima	0 (0.00)	0 (0.00)	61 (14.81) *	1 (1.19)	4 (0.50)	472 (12.57) *
Okinawa	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)	6 (1.02)	1 (0.04)

Ratios of incidence rate to that in whole of Japan in parentheses.
* p<0.01 by exact test for comparing with incidence rate in the whole of Japan.

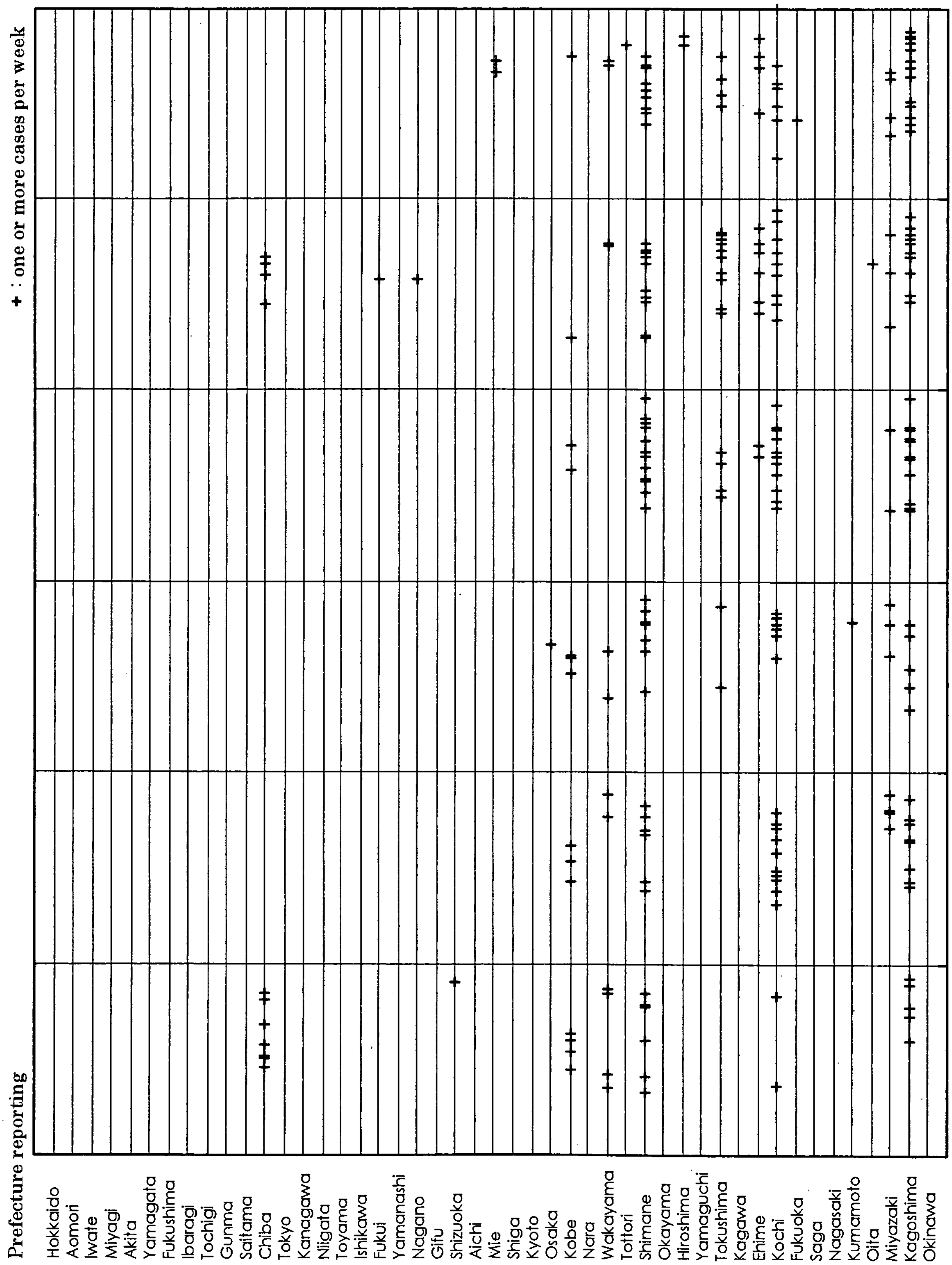

Figure 2. Distribution of cases of Japanese spotted fever by prefecture reporting, week and year of diagnosis, Japan, 2000-2005.

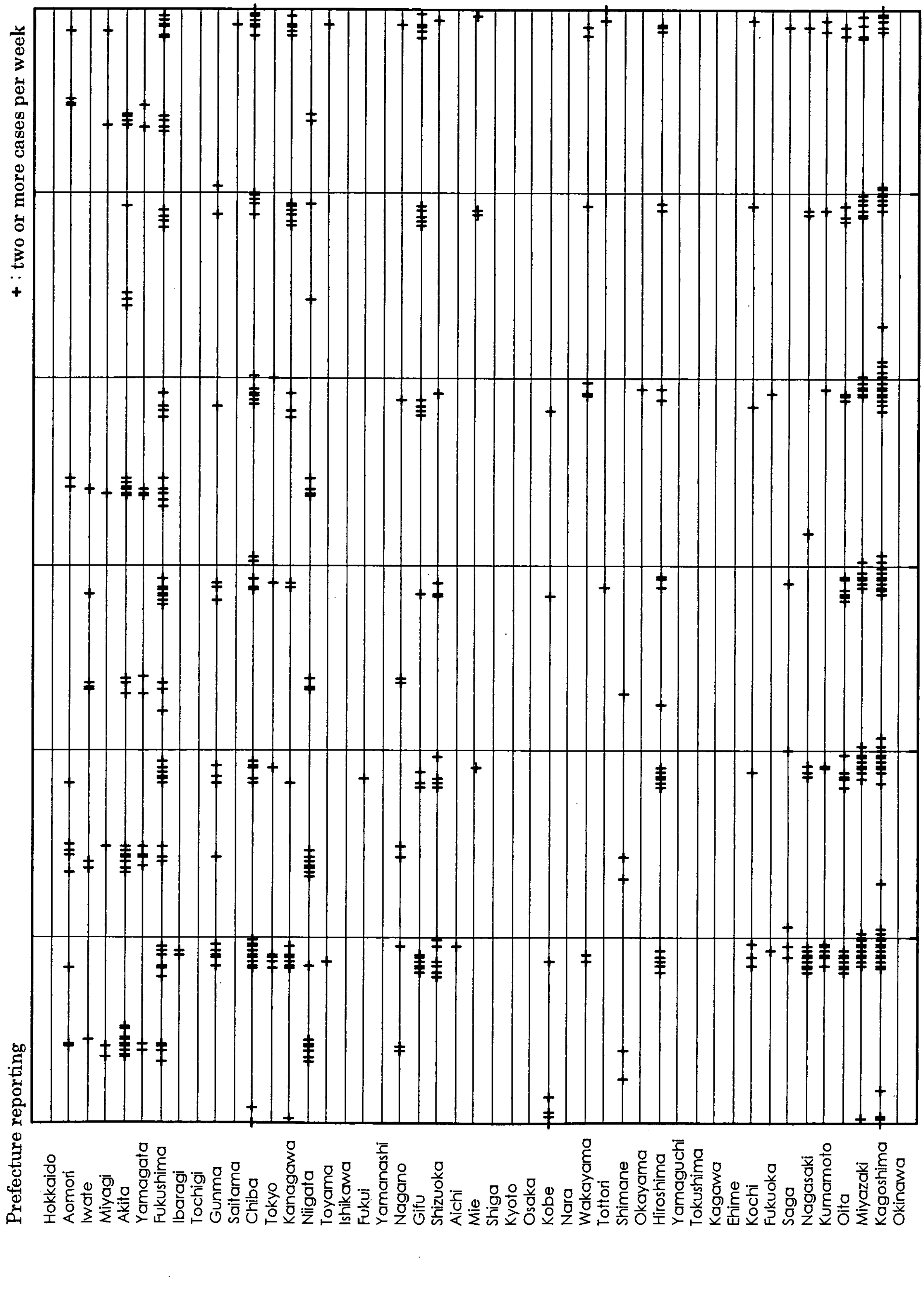

Figure 3. Distribution of cases of scrub typhus by prefecture reporting, week and year of diagnosis, Japan, 2000-2005.

Cases of Japanese spotted fever (one or more cases in a week denoted as '+' in Figure 2) in Shimane, Kochi and Kagoshima were reported annually in 2000-2005. The reporting of cases in Miyazaki, Tokushima and Ehime started from 2001, 2002 and 2003, respectively. The number of prefectures reporting one or more cases increased from 6-9 in 2000-2003 to 12 in 2004 and 2005. Cases of scrub typhus (two or more cases in a week denoted as '+' in Figure 3) were reported in most prefectures in 2000-2005. Reported cases in several prefectures in eastern Japan increased in autumn-winter, while those in the west increased in both autumn-winter and spring.

DISCUSSION

Dengue fever and malaria are transmitted by the bite of infected mosquitoes.[2] No cases of anyone in Japan acquiring these infections were reported in 2000-2005, suggesting that domestic infections were highly unlikely to occur during this period, and that most cases encountered were almost certainly acquired while traveling in endemic areas and developing symptoms after returning home.[8,11] Most cases of dengue fever and malaria observed in this study were reported in Tokyo, a finding that reflects the many travelers returning home through airports and seaports. The incidence of dengue fever increased in this period, while that of malaria decreased. The rise in dengue fever might be associated with the increased opportunities for infection due to the spread of endemic areas worldwide and with the rising coverage of diagnosis due to the enhanced awareness of physicians to this disease.[8,14] The decrease in malaria might be attributable to more widespread prevention measures using several methods, such as chemoprophylaxis.[11,15]

Japanese encephalitis is a mosquito-borne disease, with many cases occurring in Japan during the 1950s, but falling dramatically to several dozen by the 1980s.[2,9] In this study, it was observed that the incidence rate was stable at under 0.1 per year per 1,000,000 population in 2000-2005. The leading reason for such dramatic improvement was that most children acquired protective immunity to the Japanese encephalitis virus through an increase in vaccination programs.[9,16]

Lyme disease is a tick-borne infection endemic to the United States, and eastern and central Europe.[2,17] The tick mainly transmitting Lyme disease infection in Japan is most prevalent in Japan's northernmost island of Hokkaido and in the mountains of central and northern Japan.[18] The high proportion of cases reported in Hokkaido would be associated with the distribution pattern of those ticks.

Japanese spotted fever as a tick-borne disease was first reported in Japan in 1984.[10] In this study, we observed the spread of temporal and geographic distributions of cases in 2000-2005. Our results were similar to those reported in previous studies.[10,19] One reason for the spread of cases might be that the distribution of infected vector ticks spread during this period.

Scrub typhus is transmitted by the attaching of infective trombiculid mites, and has been endemic all over Japan except for a few prefectures.[10,12] The incidence of cases was observed to fall from 791 in 2000 to 345 in 2005. Though the reason for the decrease is unknown, some interesting seasonal and geographic patterns of infections were reported in previous studies.[10,20] Such pattern have been related to the activities of two different species of trombiculid mites, insofar as the high incidences in autumn-winter in many areas were mainly due to one species of mite, while those in spring in western Japan were mainly due to the other.

In conclusion, although there were some limitations and problems in the present study, based as it was only on reports to the NESID, some meaningful epidemiologic features in the temporal and geographic distributions of cases of 6 vector-borne diseases in Japan, 2000-2005, were revealed.

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Measles outbreaks in high schools closely associated with sporting events in Niigata, Japan

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KEYWORDS
Measles outbreak;
Sporting event;
High school;
Measles vaccination

Summary *Objectives:* Due to high vaccine coverage in Niigata, we had no outbreaks of measles from 1997 to 2003 but an opportunity to study the role of sporting events in the propagation of an epidemic was experienced in the spring of the latter year.
Methods: Mandatory measles case reports were requested from all high schools in Niigata, which covered a school year, date of onset, club activity, vaccination status, and hospitalization.
Results: With national marathon and kendo (Japanese fencing) meetings for high school students, measles outbreaks occurred at 27 high schools with 192 patients (186 students and 6 teachers) in Niigata. Of 64 unvaccinated patients, 14 (21.9%) were hospitalized and 6 (6.2%) of 97 vaccinated patients. Mostly single cases were encountered at high schools in which index cases had a vaccination history, whereas at a high school in which index cases had no vaccination history, the total number of cases per school increased, mostly within more than 3 cases ($p < 0.05$).
Conclusion: We conclude that sporting events, even if outdoors, might be a risk factor for measles infections. Appropriate actions to control outbreaks should be performed promptly in collaboration with related personnel and institutions.

Introduction

Measles is highly infectious with airborne transmission, and with close contact such as in the home, 75–90% of individuals would develop the disease.[1,2] Measles outbreaks due to sporting events are potentially serious because of the danger of transmission to susceptible persons in large

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groups gathered in a relatively confined environment.[3] High schools and universities may also play major roles in measles transmission, since they contain unusual concentrations of susceptible individuals.[2,4]

Measles is the greatest vaccine-preventable disease,[5–7] and routine immunization with a single dose of measles vaccine has been conducted in Japan since 1978. However, measles epidemics still occurs, and cases of measles in unvaccinated young adults have increased in number.[8,9] Measles vaccination coverage in Niigata Prefecture is generally over 90% and there had been no major outbreak of measles from 1997 to 2003.[10,11]

In spring of the latter year, a measles outbreak occurred in high school students in Niigata, and we had the opportunity to study the role of sporting events in its propagation as a retrospective study.

Materials and methods

Niigata Prefecture is located in the middle of Honshu Island and has a population of approximately 2.5 million (in the 2000 census) with the land area is 1,250,000 km^2.

To clarify measles outbreaks in high schools in Niigata Prefecture, mandatory measles case reports were requested from all high schools in Niigata, covering a school year, date of onset, and club activity. Measles was defined as a body temperature over 38.5 °C, maculopapular rashes lasting more than 3 days and one of following signs: coughing; conjunctivitis; or Koplik's spots. Date of onset was defined as the day when body temperature increased over 38.0 °C. This information was reported by telephone or fax to the prefectural office during the outbreak. Subsequently, we asked all high schools to submit background information of patients, such as vaccination status and hospitalization.

Statistical analysis

Comparison of proportions was accomplished with a $2 \times m$ table. Numbers of measles cases in different groups were compared with the Mann–Whitney U-test. Statistical significance was concluded at $p < 0.05$.

Results

Measles outbreaks occurred from April 5 (week 14) to June 16 (week 25) in 2003, and showed double peaks (Fig. 1). A total of 192 patients were reported from 27 high schools in Niigata Prefecture. Among measles cases, 186 cases were students and 6 cases were teachers (Table 1). Among the 186 students, 97 (52.2%) had been vaccinated, 64 (34.4%) unvaccinated, and 25 (13.4%) were unknown. The hospitalization rate was 6.2% (6 patients) for the vaccinated and 21.9% (14) for the unvaccinated cases, and deaths were not reported. Among the 6 teachers, 1 (16.7%) had been vaccinated, 3 (50.0%) unvaccinated, and 2 (33.3%) were unknown. Only one unvaccinated was hospitalized, and deaths were not reported.

From April 5 to April 16, 20 measles patients were reported from 13 high schools (school a–m) (Figs. 2 and 3).

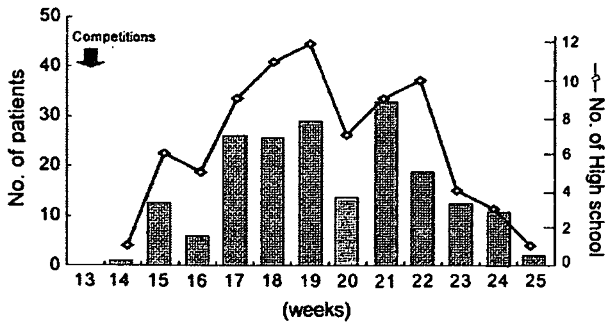

Figure 1 Surveillance based on high school reports, measles cases of teachers or students, and school numbers by week from April 5 to June 16, 2003.

Eleven of them from 8 schools (school a, c, d, e, i, j, k, m) participated in one or two national high school kendo (Japanese fencing) meetings, in Akita Prefecture on March 29 and 30, and in Nagaoka city in Niigata Prefecture on April 2–4. Furthermore, the remaining nine of them from 5 schools (school b, d, f, g, h, l) participated in a national high school marathon meeting in Yahiko village, Niigata Prefecture on March 29 and 30. From April 17 to 20, there was no measles report from high school but from April 21, the patient number increased with almost no member of athlete or kendo.

We analyzed the relation between vaccination history of the index case in 27 high schools and total number of patients in each school (Fig. 4). With high schools in which index cases had a vaccination history, one case per school was found in 8 schools, two in 3 schools, and more than three in one school. With no vaccination history, one case per school was found in 2, two in one, and more than three in 6 schools. With an unknown vaccination history, two cases per school were found in one and more than three in one school. High schools where index cases had mixed vaccination histories were four, each with more than three cases. The total number (classified by one, two, or more than three cases per school) was relevant to the vaccination status (vaccinated or unvaccinated) for the index cases ($p < 0.05$).

Discussion

With the measles outbreaks in high schools observed in Niigata Prefecture in 2003, all cases in the first three weeks

Table 1 Measles cases and hospitalization by vaccination status

	Vaccination	Patients (%)	Hospitalization (%)
Students ($n = 186$)	Vaccinated	97 (52.2)	6 (6.2)*
	Non-vaccinated	64 (34.4)	14 (21.9)*
	Unknown	25 (13.4)	6 (24.0)
Teachers ($n = 6$)	Vaccinated	1 (16.7)	0 (0)*
	Non-vaccinated	3 (50.0)	1 (33.3)*
	Unknown	2 (33.3)	2 (100)
Total		192	29 (15.3)

*$p < 0.01$ (Mantel-Haenszel).

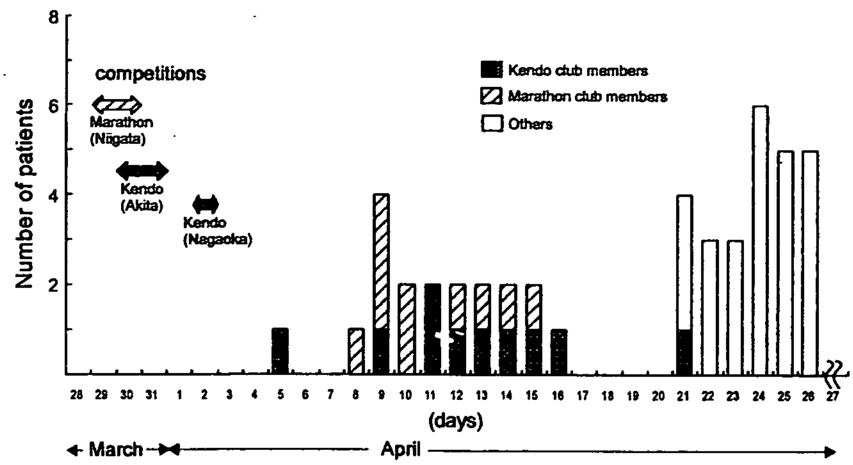

Figure 2 The relation between kendo and marathon competitions and measles patients. Measles patients have participated in any of kendo and marathon competitions.

were members of kendo or athletic clubs, who had participated in national kendo meeting in Akita Prefecture. It was confirmed that some participating teams came from measles reporting Prefectures and some members of them were diagnosed as measles. With this as a start, measles outbreaks spread out in all area of Niigata Prefecture and finally occurred at 27 high schools with 192 cases. Furthermore, in relation to the two meetings in Niigata Prefecture, measles

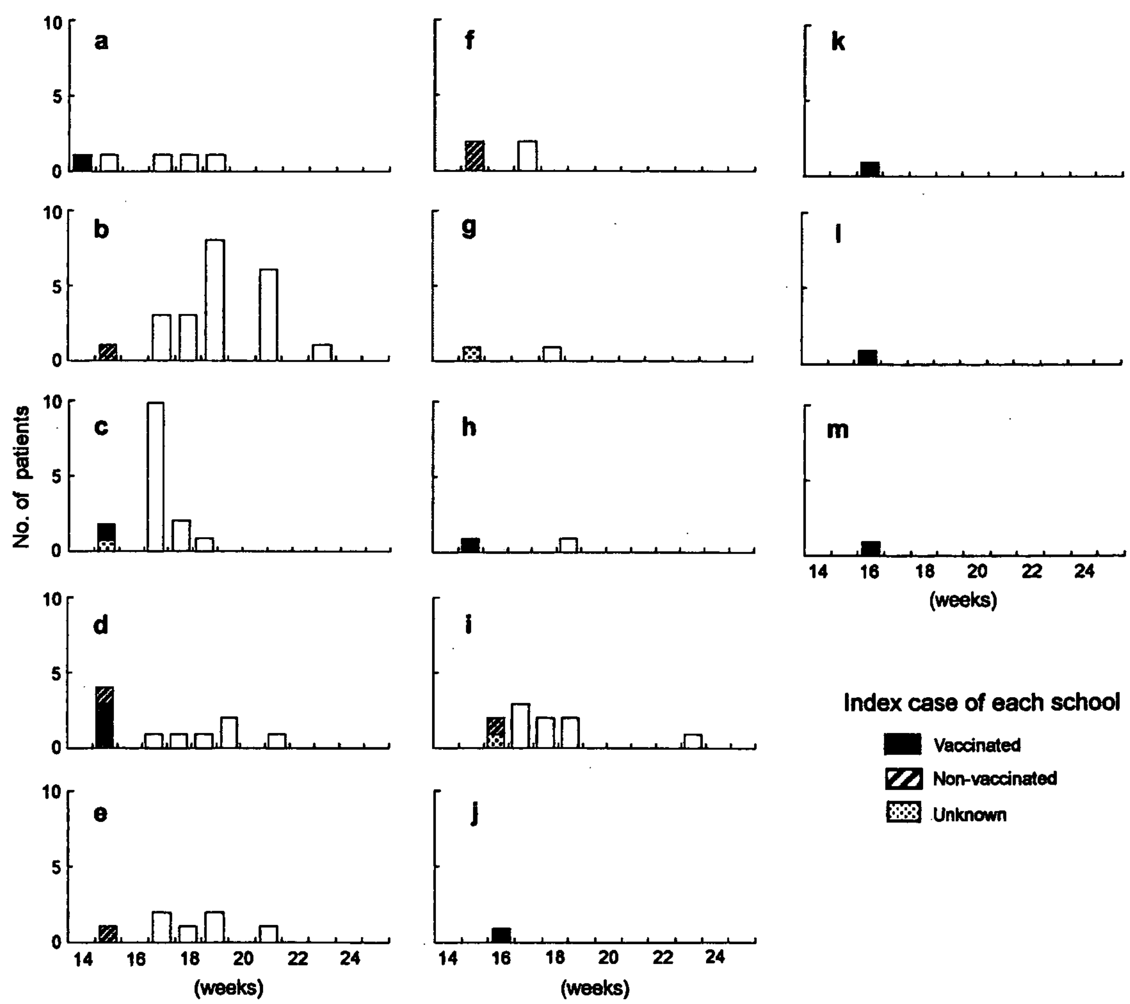

Figure 3 The relation between the first measles cases vaccination status and measles cases in each school.

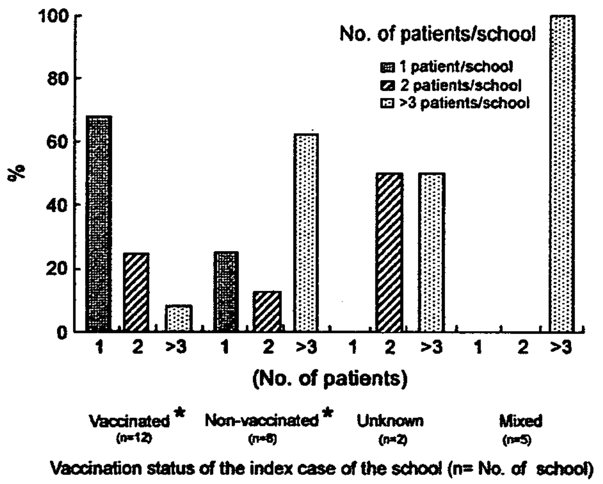

Figure 4 The relation between vaccination status of index cases and the total number of measles cases in each school. * Mixed: vaccination statuses of index cases in a school were mixed with vaccinated, unvaccinated, and unknown.

outbreaks also spread to other high schools in two neighboring Prefectures, Gunma, and Ishikawa, and these epidemiological information were informed to all Prefectures participated.[12] As measles is an airborne and readily transmissible infection, sporting meetings are risk activities.[13–15] While marathon is an outdoor sport, participants have several chances to make contact with other people, such as at opening ceremonies in the halls, in the locker rooms, or in hotels. Thus, we conclude that indoor as well as outdoor sporting meetings may be high-risk factor for measles infections.

The measles outbreaks in high schools in this study were unpredictable and the first school infections in Niigata for many years. Staff of the high schools and prefectural office did not recognize these outbreaks as serious incidents, and did not take proper actions at an early stage. After 3 and 6 weeks, the prefectural office provided guidelines for measles outbreaks to all schools: (1) Submitting case reports to the prefecture office; (2) Students with fever should not attend school; (3) Notification of a measles outbreak to parents; and (4) If measles occurs in any kind of club, the club should stop its activity. The epidemic curve for the outbreak showed an M pattern with two peaks. Numbers of cases decreased after the first peak, in week 20, probably due to distribution of the guideline as well as many national holidays in weeks 18 and 19. However, measles cases increased again in week 21 due to participation in a basketball meeting and incomplete implementation of the guideline in some high schools. Fortunately after this week, the number of cases decreased and tailed off. Thus, appropriate actions to control outbreak should be undertaken promptly in collaboration with several related personnel and institutions for control of measles outbreaks. Vaccination to unvaccinated students is also effective way to control outbreak, but this strategy has not yet been comprehensively adopted in Japan.

It is well documented from outbreak investigations that current measles vaccines protect between 90 and 95 percent of people from typical measles. Evidence is accumulating which suggests that vaccine-derived immunity might be less protective the previously assumed, as waning occurs. In our study, clinical and epidemiological outcomes of vaccinated cases showed different conditions from these of unvaccinated cases. First, the hospitalized rate of vaccinated cases was lower than that of unvaccinated patients, indicating milder clinical manifestations in vaccinated individuals, as in other reports.[16–18] Second, total numbers of measles cases per school were strongly related to the vaccination status of index cases in a school. Our observations support an earlier report that vaccinated patients have weaker infectivity than unvaccinated patients.[18,19] It is also said that vaccinated incubation time of measles is longer than the unvaccinated,[1] but further studies are clearly warranted.

Measles occurred mainly in high school students, but did not spread to junior high school and elementary school students, and other family members including infants and children as a high-risk population during that period of time. Routine immunization coverage has been more than 90% by age of 48 months since 1989, and measles have been decreasing in number since 1995 due to high coverage of more than 60% by the age of 24 months in Niigata.[10,11] We assume that the high vaccine coverage in children contributed to suppression of measles infections, and small numbers of siblings in families in present day Japan reduces the risk of household exposure. Thus, we should maintain and strengthen our routine immunization program with high vaccination coverage. As a new strategy for measles in Japan, a two-dose vaccination schedules started from 2006. This new strategy is as an essential part of the measles elimination strategy for young people and adults.

Disease surveillance is one of the most important activities for prevention and control of infectious diseases.[20,21] The National Epidemiological Surveillance of Infectious Diseases program of the Ministry of Health, Labor and Welfare in Japan is numbers of patients clinically diagnosed with measles have been reported on a weekly basis from 3000 sentinel pediatricians/general physicians throughout Japan. In the present comparison of Infectious Disease Surveillance data and mandatory measles case reports from high schools, the former did not reflect the actual epidemiological conditions, such as patient numbers and duration of the outbreak. Therefore, we need to make surveillance system based on all the measles cases.

In conclusion, our findings indicate that indoor as well as outdoor sports meetings may be a risk factor for measles infections. Efforts to ensure high immunization coverage are needed to reduce the risk of infection at sports meetings. Furthermore, educational institutions and athletic organizing officials should recognize the risk of infection at sports meetings, and consult public health officials in advance of such meetings, especially in epidemic seasons.

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薬剤耐性インフルエンザウイルス

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鈴木康司* 李 丹娟*

要旨

インフルエンザへの抗ウイルス薬による治療効果と相まって，日常診療での高頻度の使用による薬剤耐性株発生が心配となっている．高率なアマンタジン耐性 A/H 3 N 2 発生が最近日本を含むアジア地区と米国でみられ，この株は，M 2 遺伝子の 31 番目が変異し，HA 遺伝子でも 2 カ所の多重変異をもつ株（Clade N）であり，容易に伝播する特異な株である．一方，本邦での世界に類をみないほどのタミフル® 処方による耐性株発生がある．これらの状況から，抗ウイルス薬使用法の再検討と，耐性株発生を常にモニタリングする必要性は大きくなっている．しかし，大切な耐性株の臨床への影響に関する研究が，手つかずである問題は依然として残る．

はじめに

薬剤投与により耐性微生物が出現することは，細菌においては日常的に議論され，一方ウイルス疾患でも HIV においては，耐性株発生から治療継続に多くの困難に直面している．インフルエンザウイルス感染についても，抗ウイルス薬が日常の治療において用いられるようになり，耐性株出現にどう対処したらよいかの疑問が起きつつある．

インフルエンザは変異しやすいウイルスの代表である．実際，最近日本を含むアジア地区と米国での高率なアマンタジン耐性株発生がみられ，発生が少ないとされていたタミフル® にあっても耐性株発生が問題となっている[1)~7)]．しかも，単一の治療薬を大量に長期に使用すれば耐性株発生が起きやすくなることは明らかであり，パンデミック時にはなおさらである．このことから，臨床家として，患者からの要求のみで安易に本薬剤を投与してよいかを議論すべきとも思われる．

現在インフルエンザにおいて，耐性株を有する患者への当該薬剤による治療は無効であるとし，対策をたてている現状である．しかし，耐性株の判定はあくまでも *in vitro* の話であり，臨床とは必ずしも一致しないのは細菌感染でも同様であり，今後抗ウイルス薬の感受性試験結果と臨床での効果を密に検討する必要がある．

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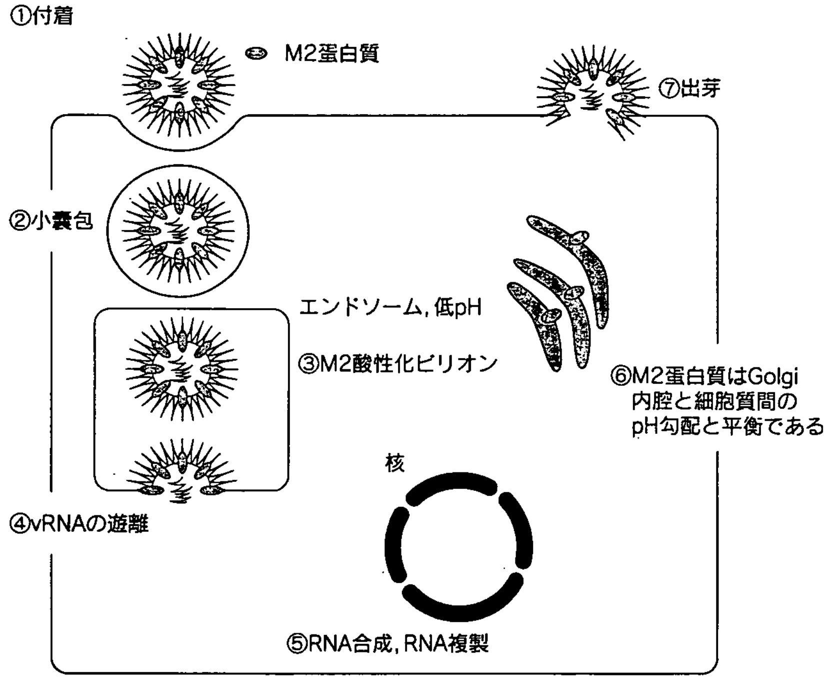

図1 インフルエンザウイルスの成熟機序 (Pinto LH et al, 2006[10])
② の部位はアマンタジンが関与し，⑦ はノイラミニダーゼ (NA) を阻害する.

I. 抗ウイルス薬

インフルエンザウイルスには A, B, C の 3 型がある. 抗ウイルス薬にはインフルエンザ A 型のみに効果なアマンタジン (シンメトリル®) とリマンタジン(本邦未承認), そして A 型と B 型インフルエンザの両者に有効なノイラミニダーゼ (NA) 阻害薬として，リレンザ®，タミフル® がある[1]. 歴史的には，アマンタジンは 1964 年に米国で抗 A インフルエンザ薬として開発され，本邦では 1998 年にアマンタジンのみ使用認可を受けた. NA 阻害薬はリレンザ® に次いでタミフル® が開発され，本邦での市販認可はそれぞれ 2000 年, 2001 年からである. 新型インフルエンザは A 型であり，上記 3 剤のいずれもが有効と思われるが，現在の使用状況，服薬のしやすさ，薬剤耐性からタミフル® が備蓄の第 1 対象薬剤として推奨されている[8]. 一方，予防としてワクチンの重要性はあるが絶対的ではなく，ワクチン接種であっても発症するハイリスク患者の場合，パンデミックではワクチン製造・供給までの期間，例年のインフルエンザにおいても流行株とワクチン株が合致しない場合など，抗ウイルス薬の出番は多い.

1. アマンタジン (シンメトリル®)

a) 作用機序

M 2 膜蛋白質は 97 個のアミノ酸からなる膜貫通蛋白質であり，ウイルス粒子の外に N 末端の 24 残基，ウイルス粒子内に C 末端の 54 残基，そして膜貫通部位に 19 残基の疎水性領域によりアルファフェリックスを形成し，H^+イオンチャンネルとなっている[5)9)10)]. アマンタジンは M 2 イオンチャンネルの H^+流入部位を阻害し，ウイルス粒子内の酸性化を妨げ，ウイルス増殖時の脱核抑制作用を示す (図 1).

b) 耐性株発生頻度

アマンタジン耐性化は M 2 蛋白質の膜貫通

部位の26, 27, 30, 31, 34番目の1個ないしは複数のアミノ酸変異により示される．自然界に感受性株と耐性株が1万：1との割合で存在しているとされる状態が，本剤投与により耐性株優位へと移行し，耐性株と判定される．通常，投与患者の1/3程度で投与48時間後から耐性株が容易に出現する．

薬剤投与前に判定される「市中耐性株」は，これまでの報告では世界各国で0.8〜1.54%ときわめて低く，本邦でも本剤承認前の0から1999年の213万人分(100 mg/日×5日)投与となっても耐性株は3.4%へと微増しただけであり，その後は0〜1.1%であった[5)11)〜13)]．しかし，2005年5月から突如37%から100%と地域別に差はあるものの，A/H3N2耐性株発生は高率になった．これは，米国，中国，香港と世界各地での動向と一致しており，耐性株の捉え方において新たな進展となった[1)〜6)]．

特に中国での耐性株の上昇は，SARS発生後のアマンタジンの大量使用が関与しているとされたが，日本，米国においては当薬剤の使用傾向とは一致せず，なぜに耐性株が流行株として市中に高頻度で存在するかの機序は不明とされた．われわれの研究から，A/H3N2耐性株の31番目がSerからAsn (S31N) へと変異しており，HA遺伝子系統樹解析から，この株はすべて193と225と多重変異をもつ株である特異な集積を示しClade Nと命名し，これまでの耐性株の状況とは異なっていたことが明らかになった(**図2**)[6)]．特に193番目はレセプターと関連しており，この変異が感受性株と同等あるいはそれ以上の伝播力を獲得し，伝播を容易にした可能性が示唆されるが，2カ所の関与も含め今後の検討が必要である．このClade N株と感受性株を検出した患者の病像はほぼ同程度であり，この株の病原性に変化がない可能性も示唆された．これまで，米国，オセアニア，アジア各国でClade Nに属するウイルスが確認された．

同様な状況がA/H5N1でもみられる．ベトナム，タイ，カンボジアから得られた株のほとんどは26番目と31番目の多重変異がみられるアマンタジン耐性であるが，別の系統に属する中国，インドネシアの株は感受性株が混在している[14)]．このように，アマンタジン耐性株の発生について，時期ごと，地域ごとの調査が必要と思われる．

2006-2007年シーズンに，A/H3N2と同様にA/H1N1でも高率にアマンタジン耐性株が発生し[15)]，この発生機序は現在検討中である．

c）耐性株の臨床への影響

アマンタジン投与後耐性株の排出が確認された小児例において，投与5日目にいったん解熱した状態から再度熱発する2峰性熱型を示した(**図3**)．一方，最初から耐性株を呈した小児においては，きわめて少数ではあるが，感受性株の治療と同様に解熱したことを経験している．これに関しては，年齢，ワクチン接種歴，A型ウイルス亜型，HA遺伝子の違いなどを加味した多数の症例を対象とした今後の研究は不可欠と思われる．

2．ノイラミニダーゼ(NA)阻害薬(リレンザ®，タミフル®)

リレンザ®は噴霧により口から投与され，その10〜20%はウイルスの感染，増殖部位である肺や気道に高濃度に分布し，吸入直後十数秒と短時間で効果を示す即効性がある(**表**)．この作用機序から耐性株発生を抑制する働きをしていると思われ．また，guranido基をもつことより経口吸収が悪いことから吸入薬となっているが，静注薬として有効との結果もあり，市販を検討中ともいわれる．一方，タミフル®は経口投与され，消化管より吸収され，肝臓で代謝されて活性型に変化して効果を示し，服用後3〜4時間で血中濃度が最高に達する(表)．

予防・治療効果がみられ，ワクチンによる抗体獲得には何らの害を及ぼさず，効果はアマンタジンと比較し100倍以上であり，アマンタジン耐性株にも有効である．

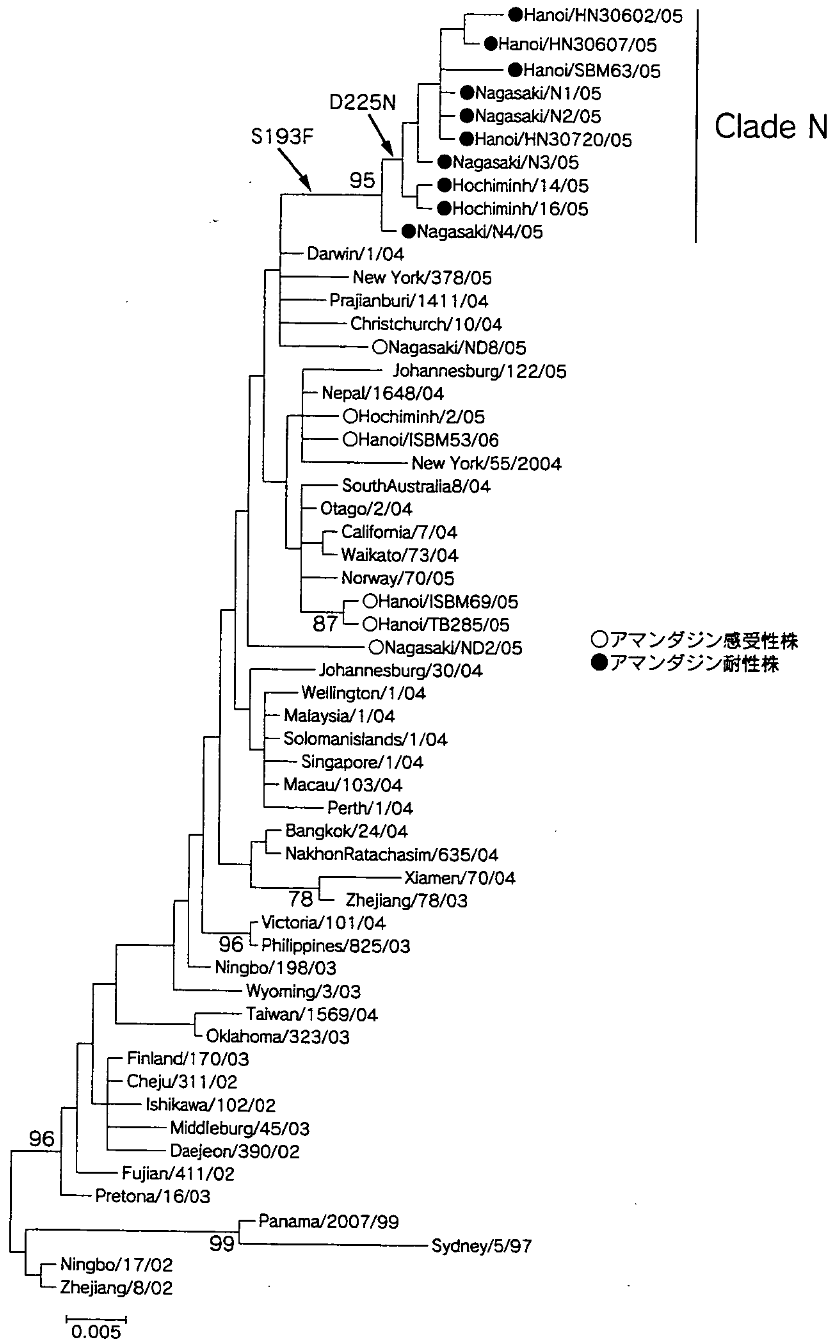

図 2　長崎県で検出された A/H 3 N 2 アマンタジン耐性株の HA 遺伝子の系統樹解析 (Saito R et al, 2006[6])

31 番目が Ser から Asn (S 31 N) へと変異しており，HA 遺伝子解析から，この株はすべて 193 と 225 と多重変異をもつ株 (Clade N) である特異な集積を示していた.

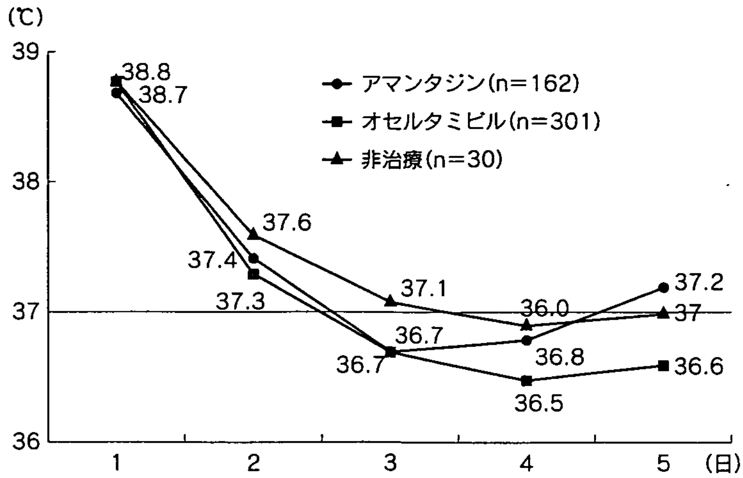

図3　2000/01〜2004/05 年シーズン新潟市内小児科（よいこの小児科さとう）にて A 型インフルエンザ患児にアマンタジン，およびオセルタミビルを投与した際の熱経過

A 型インフルエンザに対しアマンタジン，オセルタミビル投与群とも非投与群に比して約 1〜1.5 日速く解熱する．アマンタジン投与群は第 5 病日に熱の再上昇傾向を認める．

アマンタジン：A 型インフルエンザアマンタジン治療群，オセルタミビル：A 型インフルエンザオセルタミビル治療群，非治療：A 型非治療群

（当教室データ）

表　2 種類のノイラミニダーゼ阻害薬の比較

	ザナミビル（リレンザ®）		オセルタミビル（タミフル®）
有効ウイルス	A 型，B 型		A 型，B 型
剤　型	吸入（口から）薬 （直接作用）		経口薬 （消化管から吸収後，肝臓で活性型へ）
作用機序	シアル酸の水酸基をグアニジン基に置換し，NA 活性部位底面の負に荷電したアミノ酸部分と電気的に強力に結合し，酵素活性部位を阻害する		NA 活性部位に新たな疎水性の窪みを作り，疎水基同士の誘因力でさらに強く結合し，酵素活性部位を阻害する
効　果	（即効性）	>	服用後 3〜4 時間で血中濃度が最高 （1.3 μmol/l）
気道局所濃度	非常に高い（10 μmol/l）	≫	?
排　泄	大半は気道分泌物		腎排泄
副作用	ほとんどない	≪	消化器系（10〜14%）
耐性株 （臨床株）	B 型で 1 例のみ 増殖力と病原性は弱い	≪	小数発生 （13 歳以上；1.3%，1〜2 歳；8.6%） 増殖力と病原性は弱い
供給量	少量	≪	大量
使用量	少量	≪	大量 本邦は世界一

NA：ノイラミニダーゼ

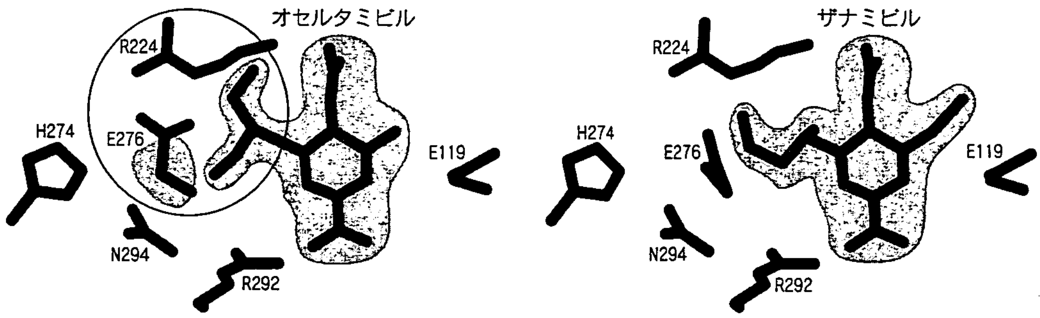

図4　ノイラミニダーゼ（NA）阻害薬耐性株発生機序（Moscona A, 2005[7]）
オセルタミビル（タミフル®）の効果はＥ276が回転しＲ224と結合してポケットが作られて起こるが，Ｒ292Ｋ，Ｎ294Ｓ，Ｈ274Ｙの変異をもつ株においてはこの回転が阻害されて耐性となる．

a）作用機序

ノイラミニダーゼ(NA)はインフルエンザ粒子の表面にあり，感染細胞からのウイルス粒子の遊離に関連する[1)15)]．このことより，NA阻害薬は粒子の遊離阻害と，細胞外ウイルス粒子の凝集塊形成促進をもたらし，ウイルスの新たな細胞への感染を阻止する（図1）．

NA活性部位はインフルエンザウイルスA型とB型でNA部位のアミノ酸配列の相同性は高くないが，活性部位のアミノ酸はよく保存されており，NAの3次元構造を基にしてその部分に結合するようにNA阻害薬は作られている．この活性部位のアミノ酸はA型の亜型(N 1〜N 9)，B型では保存されており，全A亜型，B型に有効であるとされる．しかし，最近の報告では，有熱期間を指標とするとB型に罹患した小児へのタミフル®の効果がA型と比較して低いとされている[16)]．

b）耐性株発生頻度

NA阻害薬は十数代近くで耐性株になり，NAのアミノ酸変異による機序が示されている．臨床症例からの耐性株発生とし，リレンザ®ではB型からの1例のみであるが，これは投薬されても構造的に何ら変化ないことに因る．一方，タミフル®では耐性株発生が小数ながら発生する[1)]．この原因は，タミフル®では，投与後に肝臓で活性化され，NA活性部位がポケットを新たに作って効果を発する機序に因る[7)]．分子レベルの解析では，E 276が回転しR 224と結合してポケットが作られるが，R 292 K，N 294 S，H 274 Yの変異をもつ株においては，この回転が阻害されて耐性となる(図4)．E 119 Vの変異でもタミフル®が活性部位と結合できず効果を失うが，活性部位にあるバリンの間に水分子が介在し，タミフル®の結合が阻止されるためである．

ヒトから分離された耐性株では，タミフル®，リレンザ®のいずれにも耐性をもつ例と，他方に影響しないなどさまざまである．

WHOの調査により，2003-2004年シーズンでの世界から得られたH 3 N 2の1,180株中4株（0.4%）が耐性株であった[17)]．しかし，日本はタミフル®を世界で一番使用して耐性株発生が危惧され，投与された小児50人中9人(18%)と高率に耐性株発生がみられた[1)18)]．この原因として，小児への投与時に体重当たりの投与量が不十分なことと，5日間から3日間に短縮された投与日数が関連するともされる．子どもでは初感染で免疫がなく，ウイルス産生とウイルス排出が大量で長期にみられたことが，耐性株発生を起こしやすくしたと思われる．これは，パンデミック時でもほとんどのヒトは初感染と上記と類似状況となり，耐性株発生が深刻な状況となることが懸念される．

c）耐性株の臨床への影響

耐性株が発生しても，臨床的な影響はないとされる．しかし，フェレットへの実験でタミフル® 耐性株はコントロールと比較し毒力と感染力は低下し，伝播力は弱いとされる．しかし，B型の家族内感染において，姉のタミフル® 耐性株が妹に関連した例も報告され，さらに市中でも伝播の可能性も指摘されているなど，伝播力を十分もっている可能性もある[19]．

3．併用療法

最近，ベトナムのヒトでの報告ではタミフル® 高度耐性H5N1がみられたが，この株はリレンザ® に感受性をもっており[20]，今後の複数薬剤使用の有用性が示唆された．複数の薬剤による相乗効果は，リマンタジンとリバビリン，アマンタジンとリバビリン，リレンザ® とリマンタジンないしはリバビリン，NA阻害薬とリマンタジンのいずれでも培養細胞や動物実験で示されている[21][22]．例えば，低濃度のタミフル® と通常濃度のアマンタジンの併用により，タミフル® とアマンタジン両者の耐性株発生が抑制された．これは，抗ウイルス薬の併用により，ウイルス増殖回数を減少させ，耐性株の選別や増殖を抑えたことに起因していると思われた．

現在，アマンタジンやNA阻害薬の耐性株発生が新たな問題ともなっており，これらの実験結果は今後のパンデミック対策に朗報であり，今後のヒトでも検討すべき課題と思われる．

おわりに

現在，通常のインフルエンザのみならずH5N1におけるアマンタジンやNA阻害薬の耐性株発生が問題となりつつあり，連続した疫学的調査に加え臨床面への影響を今後積極的に検討すべきであると思われる．その際には，人獣共通感染症としてヒトと獣の両者を視野に入れた対策が重要となるなど，きめ細いモニタリング活動が必要と思われる．特に最近のA/H1N1とH3N2における耐性頻度急増においては，倫理面を考慮しながら臨床への影響を検討することも必要と思われる．

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