TABLE 1. Distribution of RSV subgroups and genotypes and demographic details for patients infected with RSV over three epidemic seasons from November 2001 to July 2004

Subgroup and genotype	2001-2002 season[a]		2002-2003 season[b]		2003-2004 season[c]	
	n[d]/total[e] (%)	Age (yr [mean ± SD])	*n*/total (%)	Age (yr [mean ± SD])	*n*/total (%)	Age (yr [mean ± SD])
A	30/74 (40.5)	0.8 ± 0.6	9/187 (4.8)	1.6 ± 1.2	83/238 (34.9)	1.2 ± 0.8
GA2	0/74 (0.0)		0/187 (0.0)		1/238 (0.4)	1.1 ± 0.0
GA5	29/74 (39.2)	0.8 ± 0.6	6/187 (3.2)	1.3 ± 1.1	82/238 (34.5)	1.2 ± 0.8
GA7	1/74 (1.4)	0.3 ± 0.0	3/187 (1.6)	1.9 ± 1.4	0/238 (0.0)	
B	2/74 (2.7)	0.7 ± 0.5	45/187 (24.1)	1.0 ± 0.7	16/238 (6.7)	1.0 ± 0.9
GB3	0/74 (0.0)		4/187 (2.1)	1.0 ± 0.9	0/238 (0.0)	
SAB3	2/74 (2.7)	0.7 ± 0.5	0/187 (0.0)		0/238 (0.0)	
BA virus[f]	0/74 (0.0)		41/187 (21.9)	1.0 ± 0.7	16/238 (6.7)	1.0 ± 0.9
Total	32/74 (43.2)	0.8 ± 0.6	54/187 (28.9)	1.1 ± 0.8	99/238 (41.6)	1.1 ± 0.8

[a] The 2001-2002 season was from November 2001 to July 2002.
[b] The 2002-2003 season was from August 2002 to July 2003.
[c] The 2003-2004 season was from August 2003 to July 2004.
[d] *n*, number of confirmed cases.
[e] Total, number of suspected cases.
[f] BA viruses are strains with a 60-nucleotide insertion in the second variable region of G protein.

F1 (nucleotide positions 3 to 22) (22). The nucleotide positions were based on the sequences of prototype strains A2 and 18537 of subgroups A and B, respectively (14). We modified the heminested forward primers reported by Peret et al. (22), since both RSV-A and -B became positive by the heminested primer for RSV-A and the same misannealing happened to RSV-B due to the similar nucleic acid alignment of our strains of RSV-A and -B. Similar sequences between subtypes in the region of G protein were not found in prototype RSV strains. cDNA (1 to 3 μl) was added to 20 μl of the reaction mixtures, which contained optimized buffers, each deoxynucleoside triphosphate at a final concentration of 200 μM, 3.0 mM $MgCl_2$, 0.5 μM forward and reverse primers, and 0.5 U of *Taq* DNA polymerase (Promega, Madison, Wis.). Amplification was conducted for 2 min at 95°C, followed by 30 cycles of 94°C for 1 min, 50°C for 1 min, and 72°C for 2 min, with a final 7 min of extension at 72°C. Finally, the amplified product was analyzed by electrophoresis on a 3% agarose gel containing ethidium bromide, and the sizes of the amplicons were compared with those of standard molecular size markers. To validate the amplification process to exclude the presence of carryover contamination, positive and negative controls were run in each PCR.

Heminested PCR primers were used as the sequencing primers. Final PCR products were sequenced by using fluorescent dye-labeled terminators on an ABI 310 sequencer (Perkin-Elmer Applied Biosystems, Foster City, Calif.).

We did not isolate RSV by tissue culture, so we confirmed the presence of infection by an additional PCR with the same samples but with different primers, which targeted the N and P proteins of RSV (24), and the results were matched with those of the G protein.

Phylogenetic analysis. The nucleotide sequences of a 270-nucleotide segment of the G-protein gene second hypervariable region were aligned by using Genetyx-WIN software (version 5.1.1; Genetyx Co. Ltd., Tokyo, Japan). Unique sequences for both subgroup A and B viruses were included in the phylogenetic analysis. Phylogenetic trees were constructed by comparison of the sequences of strains from Niigata Rochester, N.Y.; Winnipeg, Manitoba, Canada; Houston, Tex.; St. Louis, Mo., with those in the GenBank database: Soweto, South Africa; Birmingham, Ala.; West Virginia; and Buenos Aires, Argentina.

Phylogenetic trees were computed and submitted to distance-based criterion analysis with ClustalW software (version 1.7; DDBJ). Trees were plotted with TreeView software (version 1.6.6). Bootstrap probabilities for 1,000 iterations were calculated to evaluate confidence estimates. Pairwise nucleotide distances within and between subgroups A and B were calculated as the numbers of pairwise nucleotide differences divided by the total number of nucleotides in the sequenced segment and were analyzed with ClustalW software (version 1.7; DDBJ).

Statistical analyses. Statistical analysis for comparison of mean values was performed by Scheffe's test. Comparison of the proportions was accomplished with 2-by-multiple tables. Statistical significance was concluded if the *P* value was <0.05.

***Nucleotide sequence* accession numbers.** The GenBank accession numbers of the nucleotide sequences obtained in the present study are AB175814 to AB175823.

RESULTS

Nasopharyngeal aspirate samples were obtained from 74 children from November 2001 to July 2002 (2001-2002 season), 187 children from August 2002 to July 2003 (2002-2003 season), and 238 children from August 2003 to July 2004 (2003-2004 season). The average age of the children with RSV infection was 0.93 ± 0.84 years. Thirty (40.5%) of the 74 children, 9 (4.8%) of the 187 children, and 83 (34.9%) of the 238 children were identified as having had subgroup A infections in the 2001-2002, 2002-2003, and 2003-2004 seasons, respectively, while 2 (2.7%), 45 (24.1%), and 16 (6.7%) of the children identified were as having subgroup B infections in the three seasons, respectively (Table 1).

Phylogenetic analysis revealed that 122 subgroup A strains clustered as three genotypes (117 strains in genotype GA5, 4 strains in genotype GA7, and 1 strain in genotype GA2) during the 2001-2002 to 2003-2004 seasons; the bootstrap values were 70 to 100% (Table 1 and Fig. 1). GA5 was the predominant genotype among subgroup A isolates during the three seasons, and the genetic distances (*p* distances) among the genotype GA5 strains ranged from 0.004 to 0.059. The number of genotype GA5 strains decreased in the 2002-2003 season but increased again in the 2003-2004 season (Table 1; Fig. 2). The 117 genotype GA5 isolates that caused infections could be classified into 28 distinct strains (Fig. 1). In the 2001-2002 season, 15 strains were genotype GA5 strains identical to strain NG-001-02. The numbers of strains identical to strain NG-065-02 were 1, 3, and 63 in the 2001-2002, 2002-2003, and 2003-2004 seasons, respectively. Genotype GA7 strains comprised one, three, and none of the strains in the 2001-2002, 2002-2003, and 2003-2004 seasons, respectively; and only one genotype GA2 strain was detected, which was in the 2003-2004 season (Table 1; Fig. 1 and 2).

Phylogenetic analysis also revealed that 63 subtype B strains were clustered in three genotypes (4 strains in genotype GB3, 2 strains in genotype SAB3, and 57 strains in a new genotype with a 60-nucleotide insertion in the second variable region of G protein) during the three seasons, with bootstrap values of

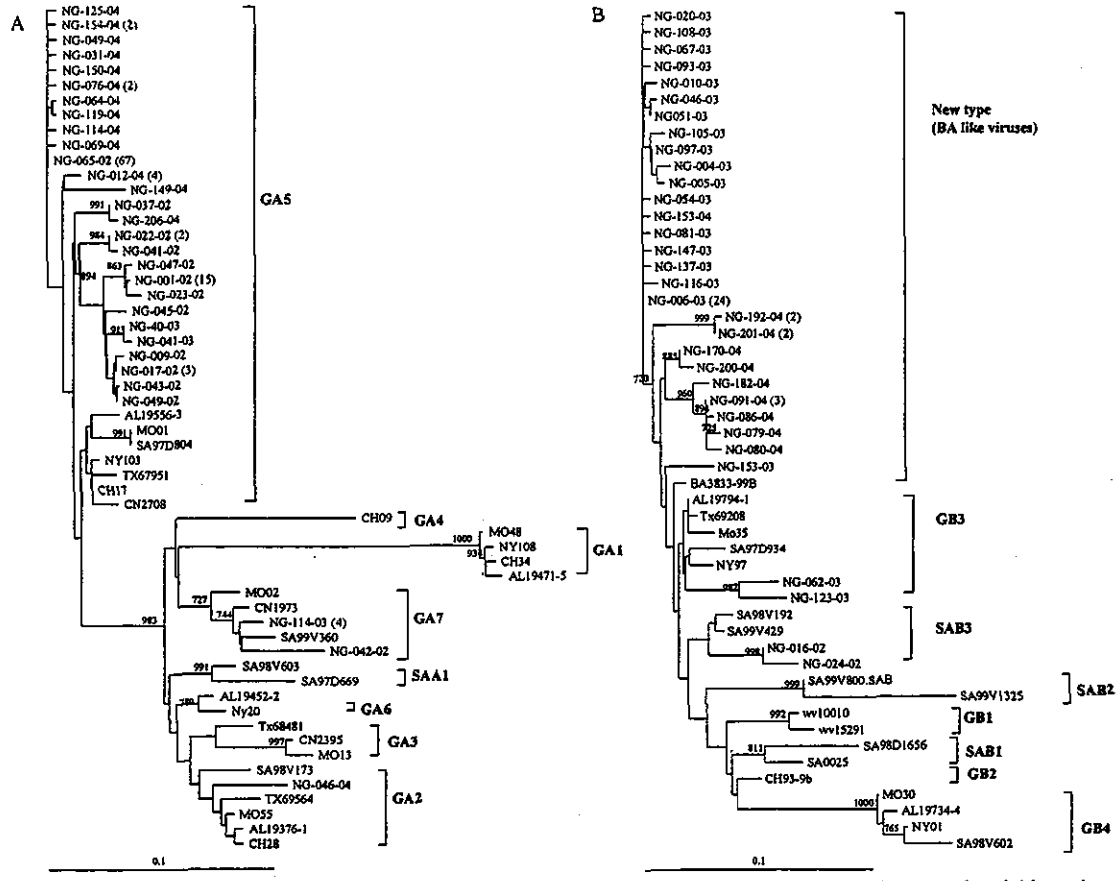

FIG. 1. Phylogenetic trees for RSV subgroup A (A) and subgroup B (B) nucleotide sequences based on the second variable region of G protein (270 bp). Genotypes were assigned by Peret et al. (21, 22) (genotypes GA1 to GA7 and GB1 to GB4) and Venter et al. (28) (genotypes SAA1 and SAB1 to SAB3). The new type, named BA virus, comprises strains with a 60-nucleotide insertion. The numbers of identical strains are indicated in parentheses. Reference GenBank sequences of strains from throughout the world were compared with strains in Niigata (NG); Rochester, N.Y. (CH) (22); Winnipeg, Manitoba, Canada (CN) (21); Houston, Tex. (TX) (21), Rochester, N.Y. (NY) (21); St. Louis, Mo. (MO) (21); Soweto, South Africa (SA) (28); Birmingham, Ala. (AL) (21); West Virginia (WV) (25); and Buenos Aires, Argentina (BA) (27). The scale bars show the proportions of nucleotide substitutions, and the numbers above the horizontal lines are bootstrap values determined for 1,000 iterations with the CLUSTALW program (DDBJ). Only bootstrap values greater than 700 are shown.

70 to 100% (Table 1; Fig. 1). Genotypes similar those of the strains of subgroup B of the new genotype with the 60-nucleotide insertion (named BA viruses) have been reported in Buenos Aires (Buenos Aires [BA] virus) in 1999 (27). All of our BA-like viruses demonstrated a Ser247Pro amino acid change compared with the sequence of BA virus in the region with the insert. Two genotype SAB3 strains of subgroup B were found only in the 2001-2002 season, 4 genotype GB3 strains were found only in the 2002-2003 season (Table 1, Fig. 1 and 2), 41 strains of the new genotype were found in the 2002-2003 season, and 16 strains of the new genotype were found in the 2003-2004 season. Genetic distances (p distances) among the strains of the new genotype ranged from 0.003 to 0.064, and 23 strains from the 2002-2003 season and 1 strain from the 2003-2004 season were identical to strain NG-006-03. Furthermore, strains in both subgroups A and B tended to cluster adjacently by year of collection by phylogenetic tree analysis.

RSV infections were detected from November 2001 to February 2002 and were detected again starting in September 2002 (Fig. 2A). The peak month for RSV infections was December in the 2001-2002 and 2002-2003 seasons and November in the 2003-2004 season. The predominant genotype shifted from genotype GA5 to BA viruses of subgroup B in the 2002-2003 season and returned to genotype GA5 in the 2003-2004 season (Table 1; Fig. 2B and C). The average age of the patients demonstrated no significant linkage with the subgroup or genotype infecting the patients in any of the 3 years (Table 1). The numbers of hospitalized patients infected with genotype GA5 were 3 (10.3%) of 29, 2 (20.0%) of 10, and 3 (3.7%) of 82 in the 2001-2002, 2002-2003, and 2003-2004 seasons, respectively. The values for BA viruses were 5 (12.5%) of 40 and 2 (12.5%) of 16 in the 2002-2003 and 2003-2004 seasons, respectively, and that for genotype GB3 was 1 (25.0%) of 4 in the 2002-2003 season.

Eight (4.3%) of 177 patients with RSV infections were reinfected over the study period. Two patients infected with genotype GA5 were reinfected with the same genotype over 2- to 24-month periods. One patient infected with genotype GA5 virus was reinfected with BA viruses after 1 year. Four patients infected with BA viruses in the 2002-2003 season were reinfected with genotype GA5 over 4- to 14-month periods.

DISCUSSION

The present investigation of the patterns of circulation of RSV infections in a community over three seasons by genotyping of the second hypervariable region of G protein (21, 22, 28) demonstrated that multiple genotypes cocirculate each year. In the present study RSV infections started in early winter, and the rates declined in the spring. The predominant subgroup changed from subgroup A to subgroup B over the three epidemic seasons, in line with the findings of earlier reports (4, 8, 15). In our study, we monitored patients over three seasons; however, the 2001-2002 season began in November 2001. The peak month for RSV infection was December 2001 in Niigata City, as was the case in a national survey of RSV infection (20), and we considered that our analysis may have been developed or implemented partially in the 2001-2002 season.

Our phylogenetic analysis revealed that genotype GA5 of subgroup A was predominant in the 2001-2002 and 2003-2004 seasons, while a new genotype of subgroup B, which featured a 60-nucleotide insertion in the second variable region of G protein (BA viruses), was predominant in the 2002-2003 season. Our observations indicate that multiple genotypes cocirculate in a single epidemic and that the genotypes in each epidemic may differ, as described previously (22, 28). Genotypes of both subgroups A and B showed temporal clustering by year of detection, which supported previous findings (6). Strains detected at the end of the previous season tended to be predominant in the next season, which might be associated with antigenic evasion from host immunity.

Viruses of genotypes similar to our BA viruses were also reported in Sapporo, Japan, in 2002 (GenBank accession number AB117522). The BA virus reported by Trento et al. (27) had an exact duplication of 60 nucleotides in the C-terminal one-third of the G-protein gene and illustrated a new type of drastic change introduced in G protein during the natural propagation of RSV. Our strains of the new genotype and strains from Sapporo were demonstrated to have 1 amino acid substitution in the insert region compared to the sequence of the BA strain. It is noted that the specific strains circulated in two countries, one in South America and another in Northeast Asia, after approximately 3 years with only a minor modification of the amino acid, which could support the robustness of the virus. The C terminus of the G-protein molecule has been shown to be immunologically relevant. Therefore, it is suggested that the 60-nucleotide insertion in the C-terminal one-third of the G-protein gene and the amino acid replacement compared with the amino acid in prototype BA strains change its antigenic structure, which confers an evolutionary advantage that allows reinfection of individuals previously exposed to the ancestor virus. However, as an emerging strain, our strain of the new genotype of subgroup B was not associated with new epidemiological or clinical features compared with those of the other clades during the three seasons that we studied. Further studies are required to determine the effect of the insertion on the immune response to RSV and susceptibility to infection and disease.

It has been reported that the severity of RSV infection may vary with the specific virus genotype (16); however, in the present study, no differences in the epidemiological or clinical manifestations, such as age or an illness that required hospitalization, were detected among these genotypes. Thus, we need continued observations to determine whether the greater severity of illness is associated with specific genotypes.

The variability of RSV strains may contribute to the cause of repeated infections, and children infected with subgroup A strains appear to be more likely to be reinfected than those

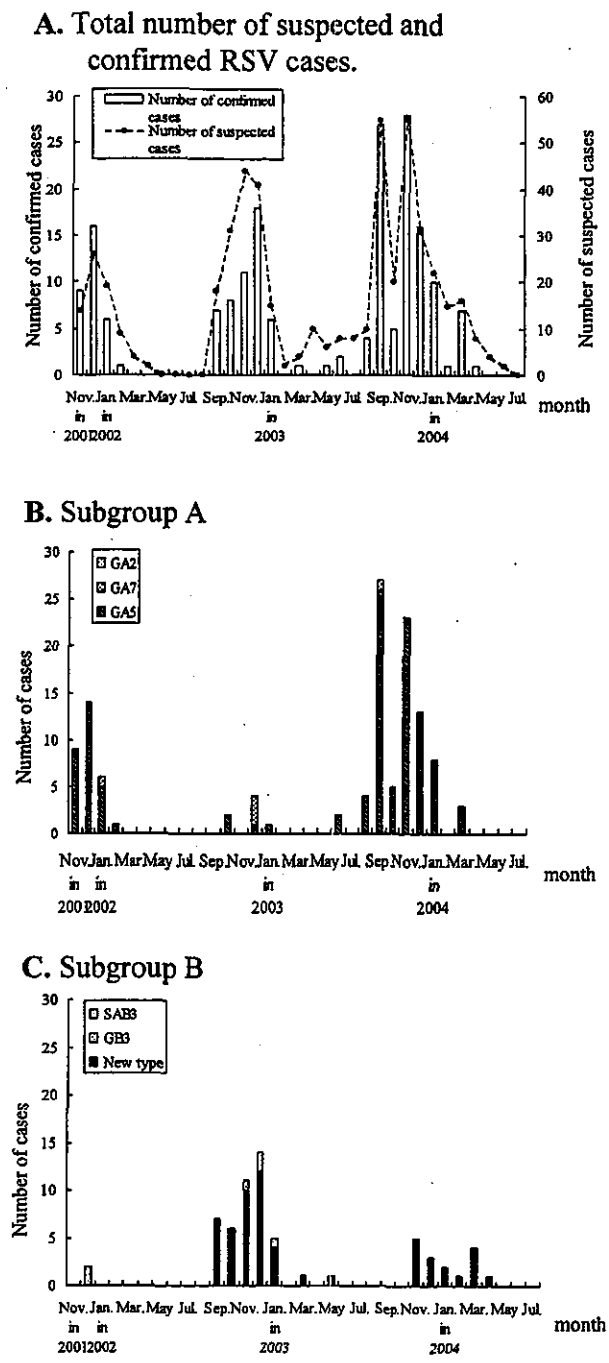

FIG. 2. Monthly distribution of 499 suspected and 185 confirmed cases of RSV infection (A), 122 cases of subgroup A RSV infection (B), and 63 cases of subgroup B RSV infection (C) from November 2001 to July 2004. Each subgroup is classified as genotype GA2, GA5, GA7, GB3, or SAB3 or the new genotype of subgroup B with a 60-nucleotide insertion.

infected with subgroup B strains (18). Only 8 (4.3%) of our 177 RSV patients became reinfected over the study period. With such a small number of patients, it is impossible to discuss the relationship between reinfection and genetic diversity, even with the new genotype of subgroup B strains. Furthermore, small numbers of reinfections may have been detected in our study because the patients visited other medical care facilities or the patients may have had mild symptoms during the second infections.

In conclusion, our molecular analysis of RSV in Niigata, Japan, confirmed that plural genotypes cocirculate each year and that the predominant genotype may shift with the season. A new genotype of subgroup B with a 60-nucleotide insertion, named BA-like virus, was found to be a predominant genotype, but it was not associated with new epidemiological or clinical features compared with those of the other genotypes that were present during the three seasons that we studied. Finally, our results provide support for genotype designation by RT-PCR methods as an effective tool for characterization of RSV circulation patterns in communities.

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Peak Rotavirus Activity Shifted From Winter to Early Spring in Japan

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

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

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

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

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

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

MATERIALS AND METHODS

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

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

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

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

RESULTS

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

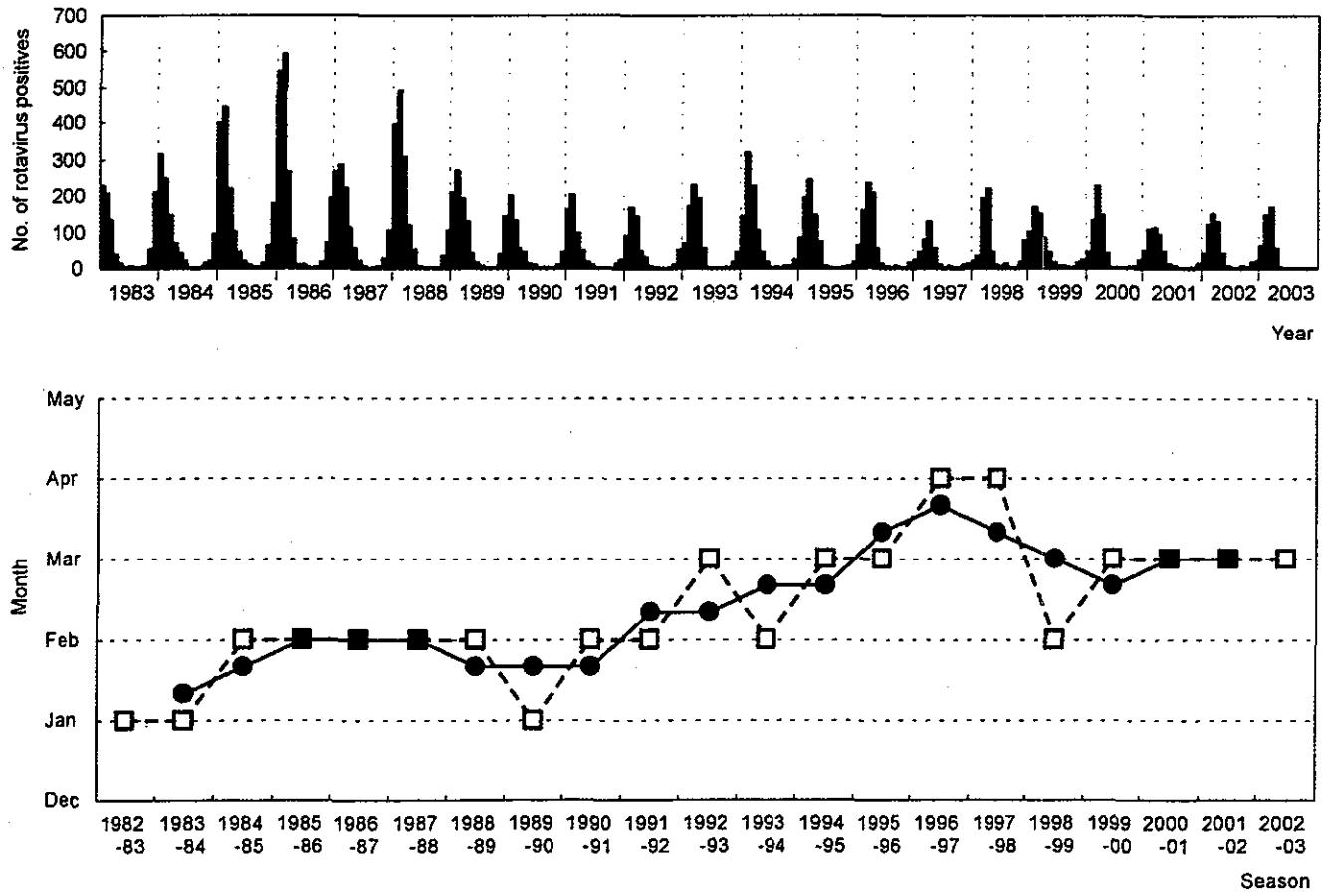

FIGURE 1. Data for rotavirus gastroenteritis in Japan from 1983–2003. Upper panel, monthly distribution based on laboratory data by 3-month unweighted moving average (mean). Lower panel, peak rotavirus activity, defined as the month during which the greatest numbers of rotavirus specimens were collected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

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

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

DISCUSSION

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

Seasonality in disease incidence often reflects associations with weather factors. Previously we reported that rotavirus infection frequently appeared related to temperature change, being found to appear abruptly when the mean temperature of 10-day period became <5°C (November or December), and reaching a peak when it was <0°C (January and February, the coolest months) in Yamagata, Japan.[8] The coolest months in winter have not changed, but annual average temperatures have increased gradually ~1.0°C during the past 100 years with global warming in Japan,[15] apparently coinciding with a temporal shift in the peak rotavirus activity, from November to March. Our observations suggest a determining role for a single climatic factor, temperature, to explain the temporal trend, but we could not find any evidence that infections with other viruses common in the cool season, such as the influenza and respiratory syncytial viruses, shifted from winter to spring in Japan. Furthermore the interrelationship of the start, peak of number of cases and alternating pattern of seasonal size of the respiratory syncytial virus epidemic reported in Stockholm[16] appears not to be a feature with our rotavirus infections.

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

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

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

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

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

†Mean ± SD.

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

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

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「定点サーベイランスの評価に関するグループ」
研究報告書

感染症発生動向調査に基づく
流行の警報・注意報および全国年間罹患数の推計
－ その５ －

平成17年３月

グループ長：永井正規

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目　次

Ⅰ. はじめに

本報告書は「感染症発生動向調査に基づく流行の警報・注意報および全国年間罹患数の推計」、その５である。「感染症の予防及び感染症の患者に対する医療に関する法律」（感染症法）が1999年４月１日に施行され、その２年後にあたる2001年３月以来毎年同名の報告書を発行して来た。今回は5年目、５回目である。各年の報告書は感染症法が新しくなるに伴い改変された感染症発生動向調査について、その時点で実績評価を行い、課題を指摘してきた。今回、本報告書の目的も大きく変わるものではなく、定点設定、警報･注意報発生、罹患数推定、情報の有効活用、情報システムの課題を対象としている。本報告は新しい感染症発生動向調査の実施後５年間、2003年度末までの資料を基に検討した結果を報告するものである。

本報告書では、第Ⅱ章で、1999年から2003年まで５年間の警報・注意報の発生状況を確認する。これによって、基準値の妥当性の影響を検討する。さらに、保健所単位でなく、より広域な都道府県レベルの警報（注意報）発生方法を提案するため、具体的な複数の方法を用いた発生状況を比較検討する。さらに、保健所別警報・注意報の発生基準値を地域(保健所・都道府県）別あるいは季節別に変更することの意義と問題点について検討する。第Ⅲ章は全国罹患数の推定であり、インフルエンザ、小児科定点対象疾患、眼科定点対象疾患について、これまでの2000年から2002年まで３年間の推計に2003年の推計値を加えるものである。全国の年間罹患数の性別、年齢階級別推計値ならびに全国週別罹患数についても推計する。さらに都道府県別罹患数の推計について検討するため、この場合は４年間平均罹患数の推計を検討する。第Ⅳ章では情報の更なる有効活用の一環として全数把握対象疾患の報告数を用い、有効活用方法を提案する。第Ⅴ章も有効活用の一環で、これまで検討してこなかった基幹定点対象疾患について、収集されている情報について基礎的な検討を加える。第Ⅵ章は情報システム:情報の収受方法の改善についての検討であり、今後の感染症サーベイランス情報システムの改善に関わる考え方を示す。

2003 年 11 月５日、感染症法の一部改正があり(10 月 16 日公布、11 月５日施行)、従来の１～４類感染症が１～５類感染症に再編成され、対象疾患の追加や一部疾患の分類や名称(表記法）の変更も行われた。昨年度までは前の分類に基づいた表現を用いて報告したが、本報告書では新しい表現（第５類までに分類された改正後の表現）を採用することにした。本研究で対象とする疾患、研究内容は法改正によって大きな影響を受けておらず、本報告書に示した知見や提言は、法改正の影響を受けることなく有効である。

Ⅱ. 流行の警報・注意報に関する検討—新基準値による発生状況、都道府県レベルの警報発生方法の提案、および基準値の個別化に関する検討—

インフルエンザをはじめとする定点把握対象疾患(週別報告 15 疾患)については感染症発生動向調査に基づいた警報・注意報の発生方法が提案され、地域の感染症流行の早期発見と対策を目的に保健所の入力システムに実装されている。インフルエンザについては国立感染症研究所感染症情報センターの Web ページ上(http://idsc.nih.go.jp/disease/influenza/inf-keiho/index.html)で公開され、一般の人々も含めた幅広い活用がなされている。

本報告では昨年度報告をふまえ、1999-2002 年度に 2003 年度のデータを追加した 5 年間のデータをもとに対象疾患における警報・注意報の発生状況を検討した。また本年度は都道府県など広域を対象にした警報のあり方を検討するため、広域における警報の目的と意義、都道府県における警報発生方法についてまとめ、3つの方法について具体的に 1999-2003 年度の保健所別定点あたり報告数データを使用し検討を行った。また一部から指摘されている季節・地域の要因を考慮した複数の基準値での対応について意義と問題点を整理し、1999-2003 年度の保健所別定点あたり報告数データにより都道府県間の感染症発生状況の差異を検討、都道府県別の基準値設定の可能性について考察した。

Ⅱ－1. 警報・注意報の発生方法の概要

データは 1999 年第 13 週から 2004 年第 13 週までの 5 年間(261 週)の感染症発生動向調査週報データにおける保健所別定点数、報告数を使用した。なお以下では 1999 年第 13 週から 2000 年第 13 週を 1999 年度、2000 年第 14 週から 2001 年第 13 週を 2000 年度、2001 年第 14 週から 2002 年第 13 週を 2001 年度、2002 年第 14 週から 2003 年第 13 週を 2002 年度、2003 年第 14 週から 2004 年第 13 週を 2003 年度と呼ぶ。対象とした疾患はインフルエンザ定点のインフルエンザ、小児科定点の対象疾患のうち突発性発疹を除いた 11、眼科定点の対象疾患 2 の計 14 疾患とした(疾患名は表 II-1 参照)。保健所の区分として 1999-2003 年度を通して途中分割された場合は分割前、併合された場合は併合後を採用、同期間を通して一定(568 保健所)のものを使用した。

警報・注意報の発生方法は警報については週ごとに保健所別定点あたり報告数が設定した基準値以上のとき、または前の週に警報が発生し定点あたり報告数が別の基準値(警報の終息基準値)以上の場合に発生する。注意報については週ごとに警報が発生していない週について、保健所別定点あたり報告数がある基準値(注意報基準値)以上の場合に発生する。警報の開始基準値、警報の終息基準値、注意報の基準値については平成 14 年度厚生科学研究費補助金(新興・再興感染症研究事業)による「効果的な感染症発生動向調査のための国及び県の発生動向調査の方法論の開発に関する研究」「定点サーベイランスの評価に関するグループ」研究報告書(グループ長:永井正規)で提案された値(表 II-1 参照)を使用した。警報の対象疾患はインフルエンザ定点のインフルエンザ、小児科定点のうち突発性発疹を除いた 11 疾患、眼科定点の 2 疾患の計 14 疾患、注意報の対象疾患はインフルエンザ定点のインフルエンザ、小児科定点の水痘、麻疹、流行性耳下腺炎の計 4 疾患である。

表 II-1　本グループ(平成 14 年度)で提案された警報・注意報の基準値
および旧基準値からの変更点の要約

	警報		注意報
	開始基準値	終息基準値	基準値
インフルエンザ定点			
インフルエンザ	30	10	10
小児科定点			
咽頭結膜熱	2.0	0.1	−
A群溶血性レンサ球菌咽頭炎	4	2	−
感染性胃腸炎	20	12	−
水痘	7	4	4
手足口病	5	2	−
伝染性紅斑	2	1	−
突発性発疹	−	−	−
百日咳	1.0	0.1	−
風疹	1.0	0.1	−
ヘルパンギーナ	6	2	−
麻疹	1.5	0.5	0.5
流行性耳下腺炎	6	2	3
眼科定点			
急性出血性結膜炎	1.0	0.1	−
流行性角結膜炎	8	4	−

−:警報・注意報の対象外
旧基準値からの変更部分は網掛で示した

旧基準値：平成１４年度以前の報告書で使用されていた基準値

旧基準値からの変更点(旧基準値→新基準値)：
咽頭結膜熱：　警報の開始基準値 1.0 → 2.0
風疹：　警報の開始基準値 3.0 → 1.0、警報の終息基準値 1.0 → 0.1
流行性耳下腺炎：警報の開始基準値 5.0 → 6.0
突発性発疹：　警報対象疾患から除外
風疹：　注意報対象疾患から除外

Ⅱ－2. 発生状況の推移(1999-2003年度)

1)検討方法

警報・注意報発生の有無については、定点あたり報告数に基づき各疾患で保健所、週ごとに定点あたり報告数を算定、決定した。なお警報の発生にあたっては、1999 年第 12 週までの状況を考慮しなかった。発生状況の推移については感染症法施行後の 1999-2003 年度の全国の定点あたり年間報告数および警報・注意報の発生状況を年度ごとに算定し、施行前の 1993-1997 年の全国の定点あたり年間報告数および警報・注意報の発生状況を比較した。

2)検討結果

(1)インフルエンザ

表 II-2-1 にインフルエンザの定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:5.5 %、2000 年度:0.4%、2001 年度:3.3 %、2002 年度:9.8%、2003 年度:5.6%と 2000 年度を除き 1993-1997 年の範囲内(0.7-10.9 %)であった。1999-2003 年度 5 年間における注意報あり延べ週数の割合は 1999 年度:4.6 %、2000 年度:2.7%、2001 年度:5.8 %、2002 年度:6.2%、2003 年度:4.4%と 1993-1997 年の範囲(1.9-4.5 %)を 2000、2003 年度以外で上回っていた。

(2)咽頭結膜熱

表 II-2-2 に咽頭結膜熱の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:0.9 %、2000 年度:3.0%、2001 年度:3.5 %、2002 年度:1.8%、2003 年度:7.2%と 1999,2003 年を除き 1993-1997 年の範囲内(1.8-5.0 %)であった。

(3)A群溶血性レンサ球菌咽頭炎

表 II-2-3 に A 群溶接性レンサ球菌咽頭炎の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:4.6 %、2000 年度:7.7%、2001 年度:6.5 %、2002 年度:5.3%、2003 年度:8.3%と 1999 年度のみ 1993-1997 年の範囲内(3.3-5.2 %)であった。

(4)感染性胃腸炎

表 II-2-4 に感染性胃腸炎の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:6.5 %、2000 年度:7.0%、2001 年度:6.1 %、2002 年度:5.5%、2003 年度:6.2%と 1993-1997 年の範囲内(3.6-7.3 %)であった。

(5)水痘

表 II-2-5 に水痘の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:2.8 %、2000 年度:4.3%、2001 年度:2.6%、2002 年度:2.9%、2003 年度:3.1%と 2000 年度のみ 1993-1997 年の範囲内(4.1-4.7 %)であった。1999-2003 年度 5 年間における注意報あり延べ週数の割合は 1999 年度:6.0 %、2000 年度:7.4%、2001 年度:5.8 %、2002 年度:6.0%、2003 年度:6.1%と全年度で 1993-1997 年の範囲(6.2-6.9 %)の範囲外であった。

(6)手足口病

表 II-2-6 に手足口病の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:1.6 %、2000 年度:10.5%、2001 年度:5.2 %、2002 年度:2.9%、2003 年度:8.1%と 1993-1997 年の範囲内(1.0-11.9 %)であった。

(7)伝染性紅斑

表 II-2-7 に伝染性紅斑の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:1.7 %、2000 年度:3.1%、2001 年度:6.5 %、2002 年度:4.3%、2003 年度:2.1%と 1993-1997 年の範囲内(1.2-8.9 %)であった。

(8)百日咳

表 II-2-8 に百日咳の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:0.3 %、2000 年度:0.4%、2001 年度 0.1 %、2002 年度:0.1%、2003 年度:0.1%と全年度で 1993-1997 年の範囲外(0.8-2.1 %)であった。

(9)風疹

表 II-2-9 に風疹の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:4.6 %、2000 年度:7.7%、2001 年度:6.5 %、2002 年度:5.3%、2003 年度:8.3%と 1999 年度を除き 1993-1997 年の範囲内(5.1-29.1 %)であった。

(10)ヘルパンギーナ

表 II-2-10 にヘルパンギーナの定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:7.8 %、2000 年度:6.2%、2001 年度:6.6 %、2002 年度:4.3%、2003 年度:7.3%と 2002 年度を除く全年度で 1993-1997 年(3.3-5.2 %)を上回っていた。

(11)麻疹

表 II-2-11 に麻疹の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:1.2 %、2000 年度:3.8%、2001 年度:4.6 %、2002 年度:1.3%、2003 年度:0.5%と 2001 年度を除き 1993-1997 年(4.2-8.2 %)を下回っていた。1999-2003 年度 5 年間における注意報あり延べ週数の割合は 1999 年度:2.2%、2000 年度:6.1%、2001 年度:5.9 %、2002 年度:2.9%、2003 年度:1.8%と 2000,2001 年度を除き、1993-1997 年の範囲(5.2-8.5 %)を下回っていた。

(12)流行性耳下腺炎

表 II-2-12 に流行性耳下腺炎の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:1.5 %、2000 年度:4.3%、2001 年度:8.9 %、2002 年度:4.2%、2003 年度:1.1%と 1999, 2003 年度を除き 1993-1997 年の範囲内(3.4-9.5 %)であった。1999-2003 年度 5 年間における注意報あり延べ週数の割合は 1999 年度:2.2 %、2000 年度:5.2%、2001 年度:8.0 %、2002 年度:4.1%、2003 年度:1.6%と 1999,2002 年度は 1993-1997 年の範囲内(2.1-4.7 %)であった。

(13)急性出血性結膜炎

表 II-2-13 に急性出血性結膜炎の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:2.5 %、2000 年度:2.3%、2001 年度:1.7 %、2002 年度:1.6%、2003 年度:1.7%と 2002 年度以外は 1993-1997 年の範囲内(1.7-3.0 %)であった。

(14)流行性角結膜炎

表 II-2-14 に流行性角結膜炎の定点あたり報告数と警報発生状況を示す。1999-2003 年度 5 年間における警報あり延べ週数の割合は 1999 年度:1.7 %、2000 年度:4.2%、2001 年度:3.3 %、2002 年度:2.5%、2003 年度:1.6%と 1999,2003 年度以外は 1993-1997 年の範囲内(2.3-5.0 %)であった。

図 II －２－１に各疾患における 1999-2003 年度の年間定点あたり報告数を 1993-1997 年の定点あたり報告数の範囲(最小値、最大値)と比較したものを示す。5 年間範囲を外れた疾患として、A群溶血性レンサ球菌咽頭炎、水痘、ヘルパンギーナがあった。４年間範囲を外れた疾患として咽頭結膜熱があった。図 II －２－２に各疾患における 1999-2003 年度の全週に占める警報あり週の割合を、1993-1997 年の警報あり週の割合の範囲(最小値、最大値)と比較したものを示す。5 年間範囲を外れた疾患として百日咳が、4 年間範囲を外れた疾患としてA群溶血性レンサ球菌咽頭炎、水痘、ヘルパンギーナ、麻疹があった。