# THE TOPICS OF THE MONTH OF IASR (January 2005–December 2005)

#### Vol. 26 No. 1 January 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division. Ministry of Health, Labour and Welfare

Laboratory system for etiological test of gastroenteritis and trend of rotavirus detection, October 2001-September 2004–Ehime	3
Trend of group A rotavirus detection and G serotypes, September	
2000-July 2004–Okayama	4
Epidemiological analysis of group A rotavirus by G serotyping and P	
genotyping, 1999-2004-Nara	6
Trend of group A rotavirus G serotypes: collaborating study of	
medical institutions in five areas in Japan, 1984-2003	7
Trend of group A rotavirus G serotypes: detection from pediatric	
patients, 1971-1990-Aichi	8
Outbreaks of group A rotavirus gastroenteritis at a primary school and kindergartens, March 2004–Shiga	10
Comparative studies on rotavirus infection and norovirus infection	
at a sentinel hospital in Nara, July 1998-June 2003	11

Group A rotavirus genome detection from cerebrospinal fluid of
gastroenteritis cases, November 2003-January 2004-Gifu13
Current status and a perspective of rotavirus vaccine14
Isolation of influenza virus type AH1N1, December 2004–Saitama16
Isolation of coxsackievirus A24 variant from a keratoconjunctivitis
case returning from the Philippines, September 2004–Osaka City.16
Outbreaks of norovirus gastroenteritis, May-June 2004–Kyoto City17
A local epidemic of keratoconjunctivitis due to adenovirus types 37
and 8 at a clinic, August-September 2004–Fukui18
An outbreak of EHEC O157:H7 infection at a nursery school,
August 2004–Kanagawa18
A fatal case of Salmonella Haifa food poisoning, September 2004
-Nagasaki City19
A familial outbreak of food poisoning due to Staphylococcus aureus
not producing enterotoxins A-E, June 2004–Sendai City20

#### <THE TOPIC OF THIS MONTH> Rotavirus as of 2004, Japan

Rotaviruses are RNA viruses that belong to the family Reoviridae and are classified into groups A-G. Viruses from groups A-C are detected from humans. Main symptoms of rotavirus gastroenteritis are vomiting and diarrhea, with prognosis usually being good. However, gastroenteritis due to rotavirus is typically severer than that caused by norovirus (see p. 11 of this issue); in rare cases, it is accompanied by hepatic damage, seizures, or acute encephalitis (see IASR, Vol. 18, No. 1). Rotavirus is a major cause of childhood deaths in developing countries. In 1998, a tetravalent oral vaccine consisting of G1-4 serotypes of rotavirus was approved in the U.S. However it was withdrawn due to a suspicion of increasing risk of intussusceptions. Subsequently, a G1 monovalent vaccine developed by a different vaccine manufacturer has been approved in Mexico in July 2004 (see p. 14 of this issue). As many as 1010 rotaviruses are shed in one gram of stool of infected persons, often resulting in high frequency of fecal-oral transmission. Therefore, proper disposal of diapers, hand washing, and disinfection of contaminated clothing with hypochloride form the bases for prevention of infection spread.

Through the National Epidemiological Surveillance of Infectious Diseases (NESID) based on the Infectious Diseases Control Law (enacted in April 1999 and amended in November 2003), cases of infectious gastroenteritis, a Category V disease, have been reported by approximately 3,000 pediatric sentinel clinics nationwide. Infectious gastroenteritis denotes a syndrome caused by multiple infectious agents, and at prefectural and municipal public health institutes (PHIs), pathogen testing is conducted on fecal specimens of gastroenteritis cases collected by a portion of pediatric sentinel clinics, as part of the Infectious Agents Surveillance. Furthermore, infectious agent testing is also performed at PHIs during outbreaks.

Trends in infectious gastroenteritis under the NESID: Reported cases tend to increase abruptly from November through December every year, decrease between the end of the year and the beginning of the following year, then after another increase, decrease again after March-April (see http://idsc.nih.go.jp/idwr/kanja/weeklygraph/04gastro.html). In recent years, noroviruses have been detected mainly during the first half and rotaviruses during the latter half of epidemics (see IASR, Vol. 19, No. 11 and http://idsc.nih.go.jp/iasr/prompt/graph/sr5.gif). In looking at the infectious agents detected from sporadic cases of infectious gastroenteritis during 2000-2004 by age, a large proportion of rotavirus detections occurred among the younger ages (Fig. 1).

Reports of rotavirus detection: Reports of rotavirus detection peaked during the 1985/86 season, then subsequently decreasing to between 500-800 annual reports in recent years (Table 1). Group C virus has been reported in small numbers with the majority of cases caused by group A virus. During 2000-2004, group A and group C viruses were reported from 53 and 15 PHIs, respectively. Group B virus has yet to be reported in Japan.

Monthly detection of rotavirus (Fig. 2 on p. 3): In any of the seasons during 1979/80-1983/84, virus detection peaked in January, while during 1984/85-1988/89, detections peaked in February. Thereafter, detection peaks have tended to occur later; during 1996/97-1997/98, the peak occurred in April. During 1999/2000-2003/04, the peak has occurred in March every year.

Ages of rotavirus-detected cases (Fig. 3): Of the 2,897 cases from which group A rotavirus was detected during 2000-2004,

36% were one year of age, 24% were 0 years, 15% were 2 years, and a few were over 2 years. Of infants 0 years of age, a large proportion were 6 months and older. In contrast, among the 70 cases from which group C virus was detected, 36% were 5-9 years of age and 33% were 10-14 years.

Methods of rotavirus detection (Fig. 4): In 1997, changes were made to the categories of detection methods on the IASR report form. During 1988-1996, the primary methods utilized were enzyme immunoassay (EIA), electron microscopy (EM), and reverse passive hemagglutination (RPHA); latex agglutination (LA) was also used. Since 1997, EIA has become the primary method of diagnosis, although polymerase chain reaction (PCR) and immunochromatography (IC) have been used increasingly

Figure 1. Reports of pathogen detections from sporadic infectious

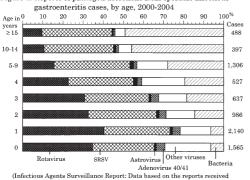


Table 1. Detection of rotavirus, in seasons 1981/82-2003/04, Japan

Season*	Total	Group A**	Group C**	Group unknown	Season*	Total	Group A**	Group C**	Group unknown
1981/82	660		•	660	1993/94	941	•	-	941
1982/83	842			842	1994/95	795		-	795
1983/84	1,129			1,129	1995/96	791		18	773
1984/85	1,393		•	1,393	1996/97	501	356	-	145
1985/86	1,768		•	1,768	1997/98	695	584	5	106
1986/87	1,258		•	1,258	1998/99	792	698	29	65
1987/88	1,526		27	1,499	1999/2000	750	680	30	40
1988/89	1,054		6	1,048	2000/01	537	504	14	19
1989/90	654		-	654	2001/02	602	570	-	32
1990/91	607		8	599	2002/03	742	690	29	23
1991/92	533		1	532	2003/04	548	542	-	6
1992/93	815		18	797	*From Sept	tember t	hrough A	ugust ne	xt vear

\*\*Group C was divided from group unknown since 1988, and group A since 1997. (Infectious Agents Surveillance Report: Data based on the reports received before December 10, 2004)

since 2000. Because commercial kits commonly used at PHIs can only detect group A virus, reports of group C virus have been scarce. Group A virus has been detected in cerebrospinal fluid of five cases, including a fatal case of encephalitis, by PCR (see p. 13 of this issue).

Outbreak incidents: Although rotavirus gastroenteritis occurs mainly in infants 0-1 year of age, outbreaks have been observed among children in nursery schools, kindergartens and primary schools (see p. 10 of this issue), as well as among adults in hospitals, nursing homes, and other welfare facilities. During 2000-2004, 27 outbreaks caused by group A virus and eight due to group C virus were reported (Table 2). Of the outbreaks involving 50 or more cases, six were due to group A virus and five due to group C virus (Table 3). Person-to-person infection was thought to be the mode of transmission in many of these outbreaks.

G serotyping of group A rotavirus: Group A rotaviruses are comprised of G serotypes 1-14, based on the outer capsid structural viral protein 7 (VP7). P genotyping of the VP4 gene is also conducted. Since January 2004, reports based on G serotyping of group A virus have become possible in IASR. Five PHIs have reported 256 cases retrospectively to 2000, among which G3 was most predominant, followed by G1. EIA and PCR have been utilized equally for most G serotypes, although only PCR has been utilized for G9 and G12 (Table 4).

During 1984-2003, according to laboratory results of pediatric outpatients in five districts (see p. 7 of this issue), the rotavirus-positive rate was approximately 30%; G1-positive rates increased from the latter half of the 1980s to 80-90% of all rotavirus cases in the 1990s, subsequently followed by a sudden decrease. G2-positive rates were 30-40% of rotavirus cases during 2000-2002. Both G3- and G4-positive rates increased during 2002-2003. G9-positive rates were approximately 20% during 1999-2003. G1 was predominant in Aichi Prefecture during 1971-1990, although prevalent serotypes varied from year to year (see p. 8 of this issue). G3 has been most common in Okayama and Ehime Prefectures in recent years (see p. 3&4 of this issue). predominant in Nara Prefecture during 2003-2004, followed by G3 (see p. 6 of this issue). G12 has been detected in Okayama (see p. 4 of this issue)

Although G8 and G5 have never been detected in Japan, both have been increasingly detected in tropical areas of Asia, Africa and South America (see p. 14 of this issue). Because these serotypes may be introduced into Japan one day, surveillance for serotype trends will be needed.

Future problems: Since 1986, reports of rotavirus detection have been decreasing in Japan. As testing at medical institutions became possible, fewer specimens positive for

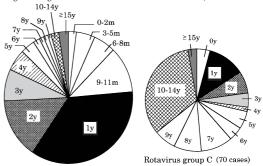
rotavirus have been submitted to PHIs. Understanding trends in rotavirus infections, as well as collection of more precise data for infection control measures will require, under the cooperation of collection medical institutions, appropriate samples from infectious gastroenteritis cases, detection rotaviruses including group C, and specific testing such as group A serotyping.

Table 2. Outbreaks of rotavirus gastroenteritis and food poisoning, January 2000-

November 2004, Japan						
Cases	Group A	Group C	Total			
2-19	13	2	15			
20-49	6	1	7			
50-	6	5	11			
No data	2	-	2			
Total	27	8	35			

(Infectious Agents Surveillance Report Data based on the reports received before December 10, 2004)

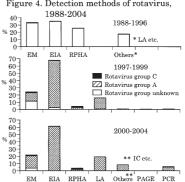
Figure 3. Age distribution of rotavirus-detected cases, 2000-2004



Rotavirus group A (2,897 cases)

(Infectious Agents Surveillance Report: Data based on the reports eceived before December 10, 2004

Figure 4. Detection methods of rotavirus



## EM EIA RYTHA LA Others PAGE PCF
Group A before 1997 was included unknown group
EM: electron microscopy, EIA: enzyme immunoassay,
RPHA: reverse passive hemagglutination test,
LA: latex agglutination test, PAGE: polyacrylamide gel
electrophoresis, IC: immunochromatography,

PCR: polymerase chain reaction Including cases from which rotavirus was detected by

multiple methods.
(Infectious Agents Surveillance Report: Data based on the reports received before December 10, 2004)

Table 4. G serotypes of group A rota-

viruses, 2000-2004, Japan							
G serotype	EIA	PCR	Cases				
G1	67	9	76				
G2	1	16	17				
G3	44	78	122				
G4	16	4	20				
G9	-	20	20				
G12*	-	1	1				
Total	128	128	256				

\*Sequence of PCR product

(Infectious Agents Surveillance Report: Data based on the reports received before December 10, 2004)

Table 3 Outbreaks of rotavirus infection, January 2000-November 2004

No.	Prefecture	Year	Period	Suspected route of infection	Setting of outbreak	Suspected cause	Cases*	Age of cases in year	Group (Pos./Exam.**)	Reference in IASR
1	Chiba P.	2000	Mar. 13-	Foodborne	Primary school	Unknown	100	No data	A (10 / 10)	21(7):145
2	Saga P.	2000	Apr. 18-26	Person to person	Dormitories	Unknown	309	12-18	C (17 / 56)	22(2):32-33
3	Okayama P.	2000	May 23-30	Unknown	Camp	Unknown	96	11-56	C (18 / 25)	21(8):169-170
4	Tokyo M.	2001	Mar. 16-19	Unknown	Primary school	Unknown	51	7-12	A (35 / 79)	
5	Tokyo M.	2001	Mar. 27	Unknown	Primary school	Contamination	53	No data	C (30 / 56)	
									A (5 / 56)	
6	Shizuoka P.	2001	May 18-	Unknown	Primary school	Unknown	111	6-12	A (17 / 18)	
7	Tokyo M.	2002	Jan. 30·31	Unknown	Hospital	Unknown	97	No data	A (72 / 142)	
8	Oita P.	2003	Feb. 18-21	Unknown	Primary school	Unknown	124	No data	C (3 / 10)	
9	Toyama P.	2003	Apr. 28-May 2	Person to person	Primary school	Unknown	101	No data	C (2 / 8)	
10	Shiga P.	2004	Mar. 3-12	Person to person	Primary school	Unknown	205	6-12	A (5 / 7)	p. 10 of this issue

P.: Prefecture, M.: Metropolitan, \*Outbreaks including more than 50 cases, \*\*( ): Positive cases/Examined

(Infectious Agents Surveillance Report: Data based on the outbreak reports from public health institutes received before December 10, 2004)

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases

#### Vol. 26 No. 2 February 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Epidemiology of meningococcal meningitis and meningococcal vaccines worldwide
Molecular epidemiological analysis of Neisseria meningitidis isolates
from 1974-2003 in Japan by multilocus sequence typing-NIID 36
Trends in meningococcal meningitis and analysis of Neisseria
meningitidis isolates, January 2003-June 2004-Kanagawa 37
Carrier rates of Neisseria meningitidis among healthy individuals
in Japan, September 2000-March 2003: collaborative study
between 10 PHIs and NIID
A mixed epidemic of influenza AH1 and AH3 viruses, December
2004–Sendai City
Local outbreaks of influenza AH1 virus, November-December 2004
-Miyagi

Two cases of congenital rubella syndrome, October-November 2004	
-Oita	.41
Isolation of mumps virus from local outbreak of mumps, November-	
December 2004-Kobe City	.42
Incidence of scrub typhus and detection of Orientia tsutsugamushi	
DNA by PCR, 2000-2004-Aomori	.43
Two outbreaks of food poisoning due to nalidixic acid-resistant	
Campylobacter jejuni, August&October 2004-Shizuoka City	.44
An outbreak of EHEC infection in a nursery school, September	
2004-Miyagi	.45
An outbreak of food poisoning due to Staphylococcus aureus caused	
by ingredients in rice balls, November 2004-Niigata City	.46
AIDS and HIV infections in Japan. October-December 2004	.49

### <THE TOPIC OF THIS MONTH> Meningococcal meningitis, 1999-2004, Japan

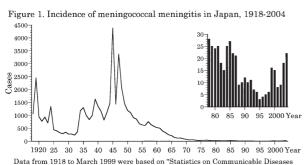
Neisseria meningitidis, or meningococcus, is a gram-negative diplococcus that colonizes the nasopharynx of humans and causes infection via person-to-person transmission of respiratory droplets or oral secretions. Neisseria meningitidis, along with Haemophilus influenzae and Streptococcus pneumoniae, is known as a causative agent of suppurative meningitis. However, only meningococcus gives rise to epidemics of meningitis. Hence, meningococcal meningitis is also referred to as "epidemic meningitis." Meningococcal meningitis is a vaccine-preventable disease, with vaccine efficacy being serogroup-specific.

Meningococcal meningitis, a Category V notifiable disease under the National Epidemiological Surveillance of Infectious Diseases (NESID) (based on the Infectious Diseases Control Law that was amended in November 2003), is a nationally notifiable disease in Japan. While *H. influenzae* is by far the most common etiologic agent of bacterial meningitis in children, followed by *S. pneumoniae*, group B streptococcus, and *Escherichia coli* (see IASR 23: 31-32, 2002), *N. meningitidis* is recognized as a rare cause in Japan. However, cases of meningococcal meningitis are frequently seen abroad, either developing countries such as Africa or industrialized countries such as the Northern European nations and the United States. According to the World Health Organization (WHO), approximately 500,000 cases and 50,000 deaths attributed to meningococcal meningitis are reported worldwide each year. In today's borderless world, a result of advances in air travel, epidemics of meningococcal meningitis abroad should be regarded as equally threatening events in Japan. Therefore, monitoring trends in the incidence of meningococcal meningitis in Japan is necessary toward developing and implementing future prevention and control measures.

Annual trend of meningococcal meningitis: Prior to the enactment of the Infectious Diseases Control Law, cases had been notified as "epidemic cerebrospinal meningitis" under the Communicable Diseases Prevention Law. According to the "Statistics on Communicable Diseases in Japan," over 4,000 cases were reported around the end of World War II. Despite the fact that active control measures, such as vaccination, were not implemented at that time, the incidence of meningococcal meningitis fell sharply after the war to less than 100 cases per year after 1969. Subsequently, incidence decreased to less than 30 cases per year after 1978 and to single digits in the 1990s. Since the implementation of the Infectious Diseases Control Law in 1999, 8-22 cases have been reported annually (Fig 1).

Notified cases through NESID: From April 1999 to December 2004, 82 cases of meningococcal meningitis were reported through NESID. Of these, eight were fatal at the time of notification (Fig 2). All cases, except one with a history of travel to Australia (and five cases with no data available), were acquired domestically.

Serotyping of N. meningitidis: N. meningitidis species are classified into 13 serogroups based on differences in their



Data from 1918 to March 1999 were based on "Statistics on Communicable Diseases in Japan." Data after April 1999 were based on the reports received before January 6, 2005 under the National Epidemiological Surveillance of Infectious Diseases.

Figure 2. Monthly cases of meningococcal meningitis, April 1999-December 2004, Japan 5 Deaths by the time of reporting 3 10 10 10 10 10 1999 2000 2001 2002 2003 (National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received

fonth

Unknown 40 cases

(48.8%)

Untypable 1 case (1.2%)
(National Epidemiological Surveillance of Infectious Diseases
Data based on the reports received before January 6, 2005)

82 cases

capsular polysaccharides. Serogrouping provides important epidemiological information for vaccine planning. However, serogroup data was available for isolates from only nine cases at the time of reporting (group A 2 cases, group B 7 cases). Even after additional information was obtained from local municipalities, serogroup data remained unknown for

Figure 3. Serogroup of Neisseria meningitidis isolates from meningitis cases, April 1999-December 2004, Japan — A 3 cases (3.7%)

> B ///// 22 cases

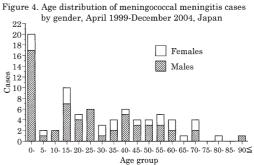
15 cases

(18.3%)

(1.2%)

approximately half of the cases. Of those with available serogroup information, serogroup B was the most prevalent with 22 cases, followed by serogroup Y with 15 cases (Fig 3).

Results of a retrospective survey conducted by a research group found that 70% or more of domestic isolates over the past 30 years were either from serogroups B or Y (see p. 36 of this issue). This serogroup distribution in Japan is unique, since serogroups A, B and C are the major ones circulating abroad (see p. 36 of this issue). On the other hand, although no serogroup A isolates were identified from 182 isolates of N. meningitidis over the past 30 years (see p. 36 of this issue), serogroup A was isolated from three cases after 1999. Of these three cases, one traveled to China prior to the illness and the other had relatives that traveled there. Molecular epidemiological classification using multilocus sequence typing (MLST) found that both isolates were genotypically indistinguishable from a recent epidemic strain in China (see p. 37 of this issue and IASR 24: 264, 2003). Only one case of group C was reported (Tokyo, 2003); serogroup C is rarely isolated from domestically infected cases (see IASR 25:207, 2004).



(National Epidemiological Surveillance of Infectious Diseases Data based on the reports received before January 6, 2005)

Seasonal variations: In the high-risk area of meningococcal meningitis, referred to as the African "meningitis belt" just the north of the equator, disease incidence is very high during the dry season (http://www.who.int/emc-documents/meningitis/whoemcbac983c.html). In Japan, such large seasonal variations are not observed, although slight increases in case counts have occurred during the late winter (February-March) and rainy (June-July) seasons (Fig. 2). Data from the "Statistics on Communicable Diseases in Japan" show similar seasonal trends in the past. Therefore, these same trends may persist at present, even after drastic decreases in reported cases have occurred.

Age and gender of cases: Reported meningococcal meningitis cases in Japan have occurred most frequently in infants and children 0-4 years of age, followed those 15-19 years (Fig. 4). In other developed countries (e.g. UK, USA) with large numbers of cases, children 0-2 years of age and college students living in dormitories also represent the most frequently affected groups. Although male cases (59) largely outnumbered female cases (23) in Japan, no such gender differences have been observed in other countries. As such, this trend may be characteristic of Japan.

**Incidence by prefecture:** Meningococcal meningitis cases were reported from 23 out of 47 prefectures. Tokyo and Kanagawa reported the most cases with 20 and 15 cases, respectively, followed by Chiba (6), Aichi (5), and Fukuoka (5). The fact that more cases are reported from metropolitan and other populated areas, where active mixing of populations takes place, may be explained by the fact that *N. meningitidis* is only spread from person to person. Further accumulation and analysis of large numbers of cases will be necessary to help explain this regional difference.

The number of meningococcal meningitis cases worldwide is large, increasing the risk of contracting disease among Japanese who travel to endemic areas or have contact with imported cases. From the perspective of early detection of imported cases and prevention of further spread, it is important to obtain serogroup data on N. meningitidis isolates in Japan. Because not all isolates are currently serogrouped, it will be necessary to strengthen future pathogen surveillance. All medical institution and laboratories are asked to actively conduct serogrouping of N. meningitidis isolates. The National Institute of Infectious Diseases also performs detailed analyses of N. meningitidis using MLST (see p. 36 of this issue), and willingly accepts isolates, including those difficult to serogroup, for further identification.

Current reporting criteria for meningococcal meningitis are based on the judgment of the examining physician. If the disease is suspected, based on symptoms and physical findings, pathogen identification is performed by isolation of N. meningitidis from cerebrospinal fluid. The reporting criteria do not specify situations in which meningococcus is isolated from blood of patients with meningococcemia. However, a N. meningitidis strain causing septicaemia may subsequently cause meningitis. Revisions to the reporting criteria are under review in order to strengthen laboratory diagnostic systems to cover all meningococcal infections.

According to WHO's practical guidelines for "Control of Epidemic Meningococcal Disease," post-exposure chemoprophylaxis is appropriate for the prevention of secondary cases in small groups, such as household members and boarding school pupils (http://www.who.int/emc-documents/meningitis/whoemcbac983c.html). CDC also recommends chemoprophylaxis with rifampin or other antimicrobial agents for household contacts and residents of treatment facilities, as the attack rate in these groups is 500-800 times higher than that of the general population (http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00046263.htm). In Japan, however, chemoprophylaxis is not implemented except under special direction from health centers or other authorities. This stems from the fact that administration of antimicrobial agents to healthy people is not recommended nor covered by health insurance. Future consideration toward developing national guidelines for post-exposure chemoprophylaxis will be necessary.

At present, due to the small number of cases in Japan, the probability of an urgent introduction of vaccination is felt to be low. Meningococcal vaccine is presently not commercially available in Japan, and is therefore administered in only a few institutions. Individuals traveling to areas with epidemic or endemic meningococcal meningitis activity may choose to be vaccinated either 1) with a vaccine personally imported by a physician prior to travel or 2) in the country of destination. With recent epidemics occurring in neighboring countries such as China and the Philippines, we must recognize that meningococcal meningitis is certainly not a rare disease any longer.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases
Toyama 1-23-1, Shinjuku-ku, Tokyo 162-8640, JAPAN Fax (+81-3)5285-1177, Tel (+81-3)5285-1111, E-mail iasr-c@nih.go.jp

### Vol. 26 No. 3 March 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Genetic diversity and antigenic variants of Bordetella pertussis strains circulating in Japan	63
Nosocomial infections and a familial outbreak of pertussis recently	
occurring in Japan	64
Clinical characteristics of Bordetella pertussis infections among	
adults differing from those among infants and young children	66
Monitoring of DPT vaccination and history of pertussis infection	
at 3-years' health check, April-December 2004-Akita	67
Susceptibilities to various antimicrobials of Bordetella pertussis	
isolated during 2001-2002 in Japan	68
Current trend of pertussis in US	69

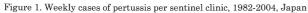
New Escherichia coli serogroups O174-O181 and attempts to serotype untypable EHEC strains in Japan	.70
Norovirus gastroenteritis: 4 foodborne outbreaks and 5 outbreaks	
caused by person-to-person transmission, December 2004	
-Kanagawa	.71
The first isolation of B/Victoria-lineage influenza virus in 2004/05	
season-Sapporo City	.72
An outbreak of EHEC O26 infection among nursery-school children	
and their family members, June-August 2004-Hyogo	.73
Isolation/detection and serotype identification of parechovirus,	
June- November 2004–Aichi	.74

#### <THE TOPIC OF THIS MONTH> Pertussis, Japan, 1997-2004

Bordetella pertussis is a gram-negative aerobic short rod, producing such virulence factors as pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN) and adenylate cyclase toxin (ACT). It is transmitted through droplets of upper respiratory secretions and highly infectious. In Japan, diphtheria-tetanus-acellular pertussis (DTaP) combined vaccine containing purified antigen (the main principles are detoxified PT and FHA) has been introduced since 1981. Mass immunization used to be practiced to children ≥2 years of age in principle, whereas it has been changed since April 1995 to individual immunization to infants over 3 months after birth by the 1994 amendment of the Preventive Vaccination Law. Vaccines produced by some manufacturers contained a small amount of gelatin, which was found to induce anti-gelatin IgE antibody (Sakaguchi M. & Inouye S., Jpn. J. Infect. Dis. 53:189-195, 2000), and DTaP vaccines of all Japanese manufacturers were improved to "gelatin-free" before 2000.

Incidence of pertussis cases: Pertussis, a Category V infectious disease under the National Epidemiological Surveillance of Infectious Diseases (NESID) based on the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infectious (the Infectious Diseases Control Law), is reported every week by about 3,000 pediatric sentinel clinics nationwide. During 1950-70, pertussis epidemics occurred every 4 years, then gradually became smaller in scale afterward until only small increases in number of cases were recognized in 1982-83, 1986, and 1990-91 (see IASR 18:101-102, 1997). Since 1997, distinct peaks indicating epidemics have disappeared (Fig. 1).

Looking at incidence by prefecture during 2000-2004, 11 prefectures reported two or more cases per sentinel in 2000, while in 2001 and later, only Yamagata, Tokushima, and Tochigi Prefectures did so (Fig. 2). From these facts, pertussis epidemics spreading over prefectures may already have disappeared. In Fig. 3, reports of yearly pertussis cases by age group (per sentinel) during 1982-2004 are shown. After introduction of DTaP vaccine, cases aged 1-4 years, which used to account for about 40% of all cases, decreased markedly. Cases aged 0 year also decreased, although a 4- year-epidemic cycle still exists. In 2004, the number of cases per sentinel increased slightly in all age groups. Since 2000, 0-year cases have outnumbered 1-4 year ones. The increases in rates of younger cases have also been observed in other diseases (see IASR 25:318-320, 2004). One of the reasons is that sentinels have been changed to principally pediatric clinics and hospitals after enactment of the Infectious Diseases Control Law in 1999.



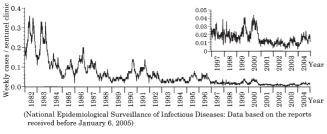


Figure 3. Yearly incidence of pertussis by age group, 1982-2004, Japan (National Epidemiological Surveillance of Infectious Diseases)

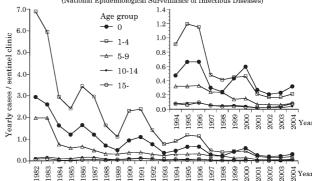
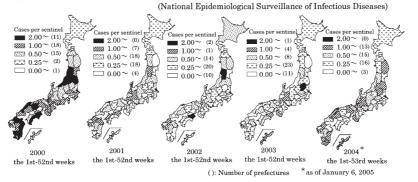


Figure 2. Incidence of pertussis by prefecture, 2000-2004, Japan



Figure~4.~Pertuss is~antibody~prevalence~by~age~group,~2003,~Japan~(National~Epidemiological~Surveillance~of~Vaccine-Preventable~Diseases)

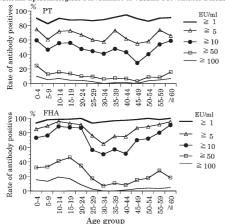
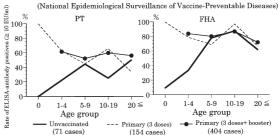
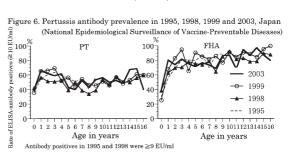


Figure 5. Pertussis antibody prevalence by history of vaccination, 2003, Japan





Pertussis antibody prevalence: By the National Epidemiological Surveillance of Vaccine-Preventable Diseases in 2003, healthy population was surveyed for pertussis ELISA antibody prevalence (in 2003, the survey covered for the first time all age groups including not only infants but also adults). FHA and PT, the major components of the vaccine, possess independent antigenicities, and antibodies against FHA and PT are considered protective against symptomatic and asymptomatic infection. From the lowest titers of convalescent sera of pediatric pertussis cases, an antibody titer of 10 EU/ml was determined to be the protective against infection. Therefore, the prevalence rate of antibodies higher than 10 EU/ml against FHA and PT will be considered here. In the survey for antibody prevalence by age group, the anti-PT antibody prevalence of age groups of 45-49 years was the lowest at 28%. Although, the prevalence in other age groups ranged between 41-60%, no significant difference by specific age groups was seen (Fig. 4). On the other hand, prevalence of anti-FHA antibody was somewhat low in the age group of 25-44 years (51-57%), whereas in other age groups antibody prevalence was high, being 71-91%. The age group of 25-29 years reflects the temporary interruption of vaccination in 1975 and the low vaccine coverage period until introduction of DTaP vaccine in 1981. The 30 to mid-40 age groups reflect the vaccination period of whole-cell vaccine.

The antibody prevalence by vaccination history indicates that the prevalence of both anti-PT and anti-FHA antibodies at 10 EU/ml or higher was not affected by booster immunization (Fig. 5). In non-vaccinees, both anti-PT and anti-FHA antibody prevalence increased with age, indicating that *B. pertussis* is circulating in the community and infection of unvaccinated children occurs even at present when cases have markedly decreased. Since both anti-PT and anti-FHA antibody prevalence among 1-16 year children is nearly constant and no difference has been seen since 1995 (Fig. 6), no change in the quality of the current vaccine is likely to have occurred.

Current problems: Although pertussis epidemics have already disappeared in Japan, small outbreaks (nosocomial infection) in maternity and children's wards (see p. 64 of this issue) and some familial infections (see p. 64 & 66 of this issue) still occur. It is considered that adolescents and adults who lack typical symptoms are not diagnosed as pertussis and are likely to make infection sources. Because the rate of *B. pertussis* isolation (necessary for confirmatory diagnosis) is low, and a large amount of time is required for antibody detection, diagnosis is solation (necessary for confirmatory diagnosis) is low, and a large amount of time is required for antibody detection, diagnosis is symptoms in the clinical setting. Molecular diagnosis by PCR assay is also carried out at the research laboratory level, although neither specificity nor sensitivity is sufficient. In reality, there may be many hidden sporadic cases and outbreaks that are neither diagnosed nor reported. From now on, development of rapid and easy molecular diagnosis methods seems necessary.

Since the lowering of the age of vaccine administration due to the amendment of the Preventive Vaccination Law in 1995, cases aged 1-4 years have decreased. However, cases of 0 year of age have recently not decreased, therefore giving vaccination soon after turning 3 months of age are desirable. This is supported by the relationship between vaccination history and incidence (see p. 67 of this issue). In the US, where high vaccination coverage is maintained, increases in case counts have been observed, thereby characterizing pertussis as a re-emerging disease (see p. 69 of this issue). The cause of the re-emergence of pertussis in foreign countries is not clear, although genetic diversity of circulating strains (see p. 63 of his issue) and increase in cases among adolescents has been recognized (see p. 66 of this issue). In the US, the emergence of macrolide-resistant B. pertussis strains has been confirmed (see p. 68 of this issue).

Presently, at a time when pertussis cases have markedly decreased, sentinel surveillance is difficult to detect local outbreaks in each area where there is no sentinel. In order to accurately grasp trends in case incidence, it will be necessary to develop a surveillance system incorporating pertussis as a nationally notifiable desease. Possible increases in pertussis cases, due to such factors as the emergence of drug-resistant strains or infection of adults with decreased antibody levels against *B. pertussis*, can not be ruled out in Japan. It will be necessary to strengthen infectious agents' surveillance for active pathogen isolation and analysis of *B. pertussis*.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases

 $Toyama \ 1-23-1, Shinjuku-ku, Tokyo \ 162-8640, JAPAN \\ Fax \ (+81-3)5285-1177, Tel \ (+81-3)5285-1111, E-mail \ iasr-c@nih.go.jp \ (-81-3)5285-1177, Tel \ (+81-3)5285-1111, E-mail \ iasr-c@nih.go.jp \ (-81-3)5285-1177, Tel \ (-81-3)5285-1111, E-mail \ iasr-c@nih.go.jp \ (-81-3)5285-1111, E-mail$ 

#### Vol. 26 No. 4 April 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Current trend in susceptibilities of Salmonella Typhi and Paratyphi A to antimicrobials in Japan
An outbreak of typhoid fever among participants of a Bangladesh
study tour during spring vacation in 2004
Treatment of typhoid and paratyphoid fever – from surveys during 2001-2003 by the Research Group for Infectious Enteric Diseases,
Japan
Nomenclature of the genus Salmonella: Opinion of the Judicial
Commission of the International Committee on Systematics of
Prokaryotes, January 2005 99
Change in serotype, biochemical nature and phage type of Salmonella
isolates during April 2002-December 2004-Yamaguchi

Problems in identification of Shigella: a result of questionnaire survey to prefectural and municipal public health institutes......94 Influenza epidemic and viral analyses in 2004/05 season-Tokyo.......96 An outbreak of norovirus gastroenteritis caused by delivered boxed lunch, December 2004-Osaka..... Three outbreaks of norovirus genogroup II infection at elderly-care facilities, December 2004-January 2005-Osaka ..... An outbreak of sapovirus gastroenteritis caused by person-to-person transmission in a care facility for the mentally handicapped, February 2005-Chiba ..... An outbreak of group C rotavirus gastroenteritis among adults admitted to a welfare care facility, December 2004–Okayama ..... 100  $\,$ 

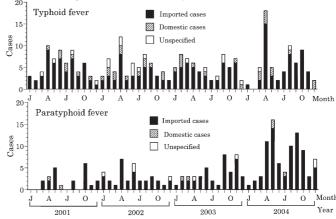
#### <THE TOPIC OF THIS MONTH> Typhoid fever and paratyphoid fever in Japan, 2001-2004

Typhoid fever and paratyphoid fever are infectious diseases caused by Salmonella enterica subsp. enterica serovar Typhi (S. Typhi) and Salmonella enterica subsp. enterica serovar Paratyphi A (S. Paratyphi A), respectively. Both diseases are characterized by bacteremia due to multiplication of bacteria in the reticuloendothelial system and localized intestinal lesions, and are distinguishable from ordinary Salmonella infections. Salmonella organisms other than S. Typhi and S. Paratyphi A also cause human typhoid-like illnesses (e.g., S. Sendai, S. Paratyphi B, S. Paratyphi C); however these infections are treated as ordinary Salmonella infections in Japan.

In the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law), enacted in April 1999, both typhoid fever and paratyphoid fever are classified as Category II notifiable infectious diseases. All physicians who have diagnosed confirmed cases, suspected cases and asymptomatic carriers are requested to promptly notify the prefectural governor through the nearest health center. In compliance with the revision of the Enforcement Regulation of the Food Sanitation Law in December 1999, S. Typhi and S. Paratyphi A have been included as etiological agents of food poisoning. When food items are suspected to be involved in cases of typhoid and paratyphoid fever, investigations of food poisoning are required under the Food Sanitation Law. Furthermore, bacterial isolates from cases of typhoid and paratyphoid fever are to be submitted to the National Institute of Infectious Diseases (NIID) for detailed analysis. The Department of Bacteriology I performs phage typing and drug-susceptibility testing and provides results back to the prefectures. For disease trends up until 2000, refer to the preceding Topic of This Month (IASR 22:55-56, 2001).

The National Epidemiological Surveillance of Infectious Diseases (NESID): From 2001-2004, between 60-66 cases of typhoid fever occurred annually, without showing large increases or decreases (Table 1). Cases of paratyphoid fever decreased to as few as 20 in 2000, increased slightly to 22 in 2001, 35 in 2002, 41 in 2003, then sharply increased to 85 in 2004 (reported as of February 22, 2005). In 2004, the proportion of imported cases of typhoid and paratyphoid fever increased to 82% and 94%, respectively. Cases frequently occurred from April-May and from August-October (Fig. 1). Taking into consideration the incubation period and number of days from disease onset to diagnosis, it is estimated that acquisition of infection occurs during spring (February-April) and summer (July-September) vacations when people travel to endemic areas such as Southeast Asia and the Indian Subcontinent. The age distribution of cases of typhoid fever and paratyphoid fever indicates that the largest number of cases in the group of 20-39 years (Fig. 2), suggesting that students and office workers traveled overseas during long vacations such as spring and summer breaks (see p. 90 of this issue)

Figure 1. Monthly incidence of typhoid and paratyphoid fever, January 2001-December 2004, Japan



(National Epidemiological Surveillance of Infectious Diseases; Data based on the reports received before February 22, 2005)

Table 1. Incidence of typhoid and paratyphoid fever in Japan, 2001-2004

-	Year	Ту	phoid fe	ever	Para	typhoid	fever
	rear	Cases	%	Isolates	Cases	%	Isolates
	2001	65 (53)	82%	52 (35)	22 (20)	91%	18 (15)
	2002	63 (40)	63%	57 (36)	35 (31)	89%	28 (22)
	2003	62 (48)	77%	50 (34)	44 (40)	91%	38 (34)
	2004	66 (54)	82%	56 (45)	85 (80)	94%	65 (60)

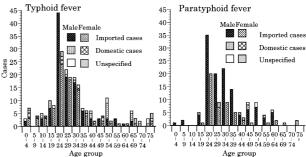
Cases: Confirmed and suspected patients and carriers (National Epidemiological Surveillance of Infectious Diseases)

( ): Imported cases included in the total

%: Ratio of imported cases to the total

Isolates: Strains forwarded to the Department of Bacteriology I. the National Institute of Infectious Diseases.

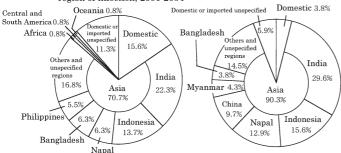
Figure 2. Age distribution of typhoid and paratyphoid fever cases, 2001-2004



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports

received before February 22, 2005

Figure 3. Typhoid and paratyphoid fever cases in Japan, by suspected region of infection, 2001-2004



Typhoid fever 256 cases

Paratyphoid fever 186 cases

(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before February 22, 2005)

Table 3. Phage types of S. Paratyphi A isolates in Japan, 2001-2004 Phage type 2001 2002 2003 2004 12 7 ( 1 ( 1 1 7) 4 6 5) 9 8) 9 12) 2 2 1 1) 5 11 ( 10) UT 10) Total 18 ( 15 ) 28 ( 22 ) 38 ( 34 ) 65 ( 60 )

UT: untypable, ( ): Imported cases included in the total Data from the Department of Bacteriology I, the National Institute of Infectious Diseases

Table 2. Phage types of S. Typhi isolates in Japan, 2001-2004

ible 2.1 mage types of B. Typin isolates in Sapan, 2001 2004								
Phage type	2001	2002	2003	2004				
Α	4 ( 2)	4 (3)	8 (3)	2 (1)				
B1	2 (1)	1	8 ( 6)	8 ( 6)				
B2	3 (2)	-	1 ( 1)	1 ( 1)				
C5	-	1 ( 1)	1 ( 1)	-				
D1	1	1	-	1 ( 1)				
D2	6 ( 6)	8 ( 5)	3 (2)	5 (3)				
E1	15 ( 11 )	16 ( 14 )	13 (7)	9 (8)				
E2	3 (2)	4 (2)	3 (3)	1 (1)				
E6	-	-	-	1				
E9	1	-	1 ( 1)	13 ( 13 )				
E10	-	2 ( 2)	-	-				
E14	1 ( 1)	-	-	-				
F6	-	1 ( 1)	3 (3)	1 (1)				
F9	-	-	1 ( 1)	-				
H	-	2	-	-				
J1	1 ( 1)	-	1	-				
M1	1	5 (2)	-	1				
M4	1 ( 1)	-	-	-				
36	-	-	-	1 (1)				
40	1	-	1 (1)	-				
43	1 (1)	-	2 (1)	1				
46	-	2	1 ( 1)	-				
56	-	1	-	-				
DVS	2 (1)	-	-	-				
UVS1	6 (4)	6 (5)	2 ( 2)	7 (6)				
UVS3	2 ( 2)	1 ( 1)	-	-				
UVS4	-	-	-	3 (2)				
Vi-	-	2	-	-				
UT	1	-	1 ( 1)	1 ( 1)				
Total	52 ( 35 )	57 ( 36 )	50 ( 34 )	56 (45)				

DVS: Degraded Vi-positive strain

UVS1: Untypable Vi-positive strain group 1 UVS3: Untypable Vi-positive strain group 3

UVS4: Untypable Vi-positive strain group 4

UT: Untypable, ( ): Imported cases included in the total Data from the Department of Bacteriology I, the National

Institute of Infectious Diseases

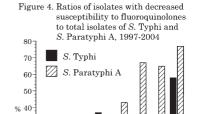
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20

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Countries where cases of typhoid and paratyphoid fever were presumed to have acquired infection from 2001-2004 are shown in Fig. 3. Typhoid fever acquired in Asia accounted for 71% of the cases; 57 cases in India, 35 in Indonesia, 16 each in Nepal and Bangladesh, 14 in Philippines, four each in Thailand and Cambodia, three each in China, Myanmar, Pakistan, and one each in Hong Kong, Taiwan, Laos, Afghanistan, Singapore, Sri Lanka, Turkey, Viet Nam. In addition, infection was acquired in Papua New Guinea, Marshal Islands, Mexico, Peru, Nigeria, and West Africa (1 case each). Paratyphoid fever infection acquired in Asia accounted for 90%; 55 cases in India, 29 in Indonesia, 24 in Nepal, 18 in China, eight in Myanmar, seven in Bangladesh, two each in Cambodia and Thailand, and one each in Sri Lanka and Viet Nam.

Phage type: Among the phage types of S. Typhi, E1 and D2 were predominant in both 2001 and 2002, while E1, A, and B1 were most common in 2003 and E9, E1, and B1 in 2004, demonstrating a slight change in phage type trends (Table 2). Strains imported from India in the past were mostly E1, but in 2004 E9 has appeared. The phage types of S. Paratyphi A were mostly 1 and 4 in 2001 and 2002, but in 2003 and 2004, a slight change was seen in phage type trends, as type 6 became predominant in addition to types 1 and 4 (Table 3).



1997 1998 1999 2000 2001 2002 2003 2004 Year (Data from the Department of Bacteriology I, the National Institute of Infectious Diseases)

Drug-susceptibility and treatment: Typhoid and paratyphoid fever are treated with fluroquinolones administered orally. In recent years, however, nalidixic acid (NA)-resistant strains to which fluoroquinolones are hardly effective have increasingly been detected in Japan (Fig. 4 and see p. 89 of this issue). Travel destinations of cases infected with NA-resistant strains have mainly been India, Bangladesh, and their neighboring countries. In typhoid and paratyphoid fever caused by infection with NA-resistant organisms, the febrile period is prolonged by the ineffectiveness of fluoroquinolones, resulting in prolongation of the therapeutic period (see p. 91 of this issue). For these types of cases, combination therapy with third generation cephalosporins may be indicated (see p. 90 of this issue).

Conclusion: Infection in endemic areas primarily occurs via consumption of water or uncooked food. In particular, consumption of unboiled water, ice, raw fish or shellfish, fruits, raw vegetables, half-cooked food, and unrefrigerated food items should be avoided. Thoroughly cooked food, hermetically sealed beverages, and peeled fruits and vegetables are generally considered safe to consume. Unless the safety of water is certain, boiled or commercial mineral water should be used for drink and tooth brushing. In recent years, cases have increased among long-term foreign residents of Japan who temporarily return to their home countries in Southeast Asia, the Indian Subcontinent or China, become infected there, and develop disease after returning to Japan.

Since necessity for surveillance of resistant organisms influencing therapy is increasing, we ask again that strains isolated from cases of typhoid and paratyphoid fever be sent to the National Institute of Infectious Diseases.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases

### Vol. 26 No. 5 May 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Increase in number of clients as a result of Sunday HIV-testing/ counseling—Kawasaki City115	An influenza outbreak in a primary school due to influenza virus B/Victoria-lineage strain, January 2005–Gifu121
Re-evaluation of HIV-1 virology by establishing infectious DNA	Isolation of influenza virus types AH3 and B from child cases with
clones from field primary isolates116	probable influenza encephalopathy, March 2005-Akita 121
Current status and perspective on the problems of HIV vaccine	Sporadic cases of infectious gastroenteritis from which norovirus
development	and rotavirus or another virus were detected from the same
Detection and isolation of influenza virus type AH5N1 from blow	specimen, November 2004-January 2005-Chiba City 122
flies collected in an area where highly pathogenic avian	Rate of symptomatic norovirus infection by age of residents in
influenza had occurred in Japan, March 2004119	elderly care facilities, January 2004-January 2005–Ibaraki 123
	AIDS and HIV infections in January March 2005 125

#### <THE TOPIC OF THIS MONTH> HIV/AIDS in Japan, 2004

HIV/AIDS surveillance was initiated in 1984 and conducted in compliance with the AIDS Prevention Law during 1989-From April 1999, it has been implemented as part of the National Epidemiological Surveillance of Infectious Diseases (NESID), in accordance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law). Since the amendment of the Law in November 2003, HIV/AIDS have been classified as category V notifiable infectious diseases (for reporting guidelines, refer to http://www.mhlw.go.jp/topics/bukyoku/ kenkou/kansennsyo/kijun5a.html#7). The numbers of HIV-infected cases (persons who have not developed AIDS) and AIDS patients reported in this article are based on figures from the 2004 annual report of the National AIDS Surveillance Committee (ascertained on April 25, 2005) which has been released by the Specific Disease Control Division (SDCD), the Ministry of Health, Labour and Welfare (MHLW) (http://www.acc.go.jp/mlhw/mlhw\_frame.htm).

1. Trends in HIV/AIDS cases during 1985-2004: In 2004, 780 new HIV cases (698 males, 82 females) and 385 new AIDS patients (344 males, 41 females) were reported, both the largest ever and significantly exceeding figures in 2003 (Fig. 1). Japanese males accounted for 82% of all HIV cases (78% in 2002, 82% in 2003) and for 75% of all AIDS patients (75% in both 2002) and 2003).

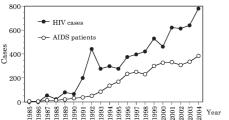
During 1985-December 31, 2004, 6,560 HIV cases and 3,277 AIDS patients were reported (excluding those infected through coagulation factor products), corresponding to 5.140 HIV cases and 2.568 AIDS patients per 100,000 population, respectively. In addition, 1,434 HIV cases infected through coagulation factor products (including 167 living and 564 deceased AIDS patients) were reported by an independent national survey (as of May 31, 2003).

Nationality and gender: Among HIV cases, the number of Japanese males continues to increase (Fig. 2-a), with a significant rise to 636 cases in 2004 (525 in 2003). In contrast, the numbers of Japanese females and non-Japanese males and females have remained level over the past few years (Fig. 2-a). Among AIDS patients, the number of Japanese males continues to increase (Fig. 2-b), with 290 reported in 2004 (252 in 2003).

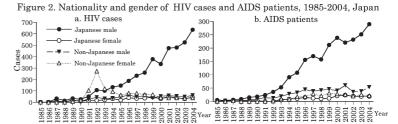
Modes of infection and age distribution: In 2004, record-highs of 449 HIV cases and 126 AIDS patients due to homosexual contact (including bisexual contact) were reported (Fig. 3). The numbers of Japanese HIV male cases infected through homosexual contact have been increasing in every age group category (15-24 years [Fig. 4-a], 25-34 years [Fig. 4-b], and 35-49 years [Fig. 4-c]), with a significant increase observed in the 25-34 year group. Although small increases have occurred in male HIV cases ≥50 years of age over the past few years, the proportion of cases infected via heterosexual contact in this age group has been higher than in other age groups (Fig. 4-d). Most HIV cases among Japanese females are between 25-34 years of age, and have occurred through heterosexual contact.

Infections due to intravenous drug abuse or mother-to-child infection accounted for less than 1% of all HIV cases and AIDS patients, figures that are lower than in other countries. In 2004, 5 cases of infection due to intravenous drug abuse (3 HIV cases, 2 AIDS patients) and 2 cases due to mother-to-child infection (1 HIV case, 1 AIDS patient) were reported.

Figure 1. HIV cases and AIDS patients, 1985-2004, Japan

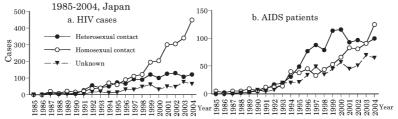


(The 2004 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee, Ministry of Health, Labour and Welfare)



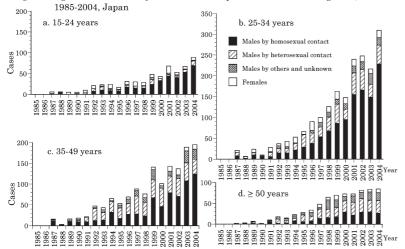
(The 2004 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee, Ministry of Health, Labour and Welfare)

Figure 3. Mode of infection of Japanese male HIV cases and AIDS patients,



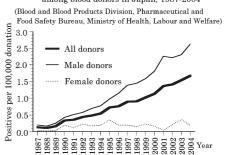
(The 2004 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee, Ministry of Health, Labour and Welfare)





(The 2004 Annual Report on HIV/AIDS Surveillance in Japan, the National AIDS Surveillance Committee Ministry of Health, Labour and Welfare)

Figure 5. HIV-antibody positives (by the confirmatory test) among blood donors in Japan, 1987-2004



In 2000, 2001, 2002, 2003 and 2004, three of 67, one of 79, two of 82, two of 87 and two of 92 donors, respectively, were positive only by the nucleic acid amplification test.

Regions of acquiring infection/of reporting: In 2004, most of the HIV cases and AIDS patients were presumed to have acquired infection in Japan (82% of HIV cases, 70% of AIDS patients). HIV cases have been on the increase in all district, with more than 10 cases reported in each of the following 13 prefectures (listed in descending order of case counts): Tokyo, Osaka, Kanagawa, Aichi, Chiba, Kyoto, Shizuoka, Hyogo, Saitama, Nagano, Hiroshima, Okinawa, Ibaraki. Hiroshima and Okinawa Prefectures, which reported noticeable increases in HIV cases in 2003 despite low numbers of cases overall, experienced further increases in numbers of HIV cases in 2004.

2. Deaths due to AIDS: Up until March 31, 1999, there were 596 deaths due to AIDS, of which 485 were Japanese (445 males, 40 females) and 111 non-Japanese (77 males, 34 females). During April 1999-December 31, 2004, the number of fatal cases reported to SDCD, MHLW by case-follow-up data (alive→death) totaled 195, consisting of 162 Japanese (151 males, 11 females) and 33 non-Japanese (21 males, 12 females). In 2004, there were 25 AIDS deaths, of which 23 were Japanese (21 males, 2 females) and two non-Japanese (1 male, 1 female). Because case-follow-up reporting is voluntary, the number of death reports may not necessarily be high. Therefore, these figures may represent considerable underestimates of actual numbers of fatalities.

3. HIV-antibody-positive rates among blood donors: HIV-antibody-positive rates of blood donors have been steadily increasing every year. In 2004, among 5,473,119 blood donations, 92 positive individuals were identified (88 males, 4 females), corresponding to 1.681 positives per 100,000 donations (2.629 for males, 0.188 for females) (Fig. 5). In view of these results, an increase in latent HIV cases in this country has been suggested. There is also the possibility that many people are donating blood as a means of getting tested for HIV. To prevent such blood donations, it will be necessary to strengthen measures described in section 4 that will allow easier access to testing.

4. HIV antibody testing and consultation/counseling at health centers: In 2003, 75,539 HIV tests were conducted at health centers operated by municipalities; this figure increased to 89,004 in 2004. The number of consultation/counseling sessions also increased from 130,153 in 2003 to 146,585 in 2004. In Kawasaki City, the number of test subjects and positive detection rate both increased after free, drop-in anonymous testing services on Sundays were established (see p. 115 of this issue). According to an investigation conducted on October 20, 2004 by SDCD, MHLW, targeting health centers that introduced rapid HIV testing and late night/holiday testing after 2002, the monthly average number of examinees increased a maximum of about 9–fold in health centers introducing rapid, same-day results testing and approximately 5-fold in those introducing testing at night. On October 29, 2004, a notice by the Head of SDCD, MHLW, titled "Promoting the introduction of rapid methods of HIV antibody testing" was issued. With HIV cases on the increase in every district, it is necessary to further encourage and promote HIV testing and counseling programs, centering on health centers, and to work toward early diagnosis, treatment, and control of spread of HIV infection.

Conclusion: Numbers of HIV and AIDS cases in 2004 were the largest ever recorded, surpassing 1,000 combined and representing a persistent, increasing trend. Moreover, the cumulative number of reported cases as of the first quarter of 2005 has now exceeded 10,000 (see p. 125 of this issue). HIV cases and HIV antibody positive rates among blood donors have doubled over the past 7 years. Although various prevention measures have been developed, these increasing trends show no sign of touching bottom. HIV/AIDS guidelines released in October 1999 are reviewed and revised once every five years, and at present, are being prepared for submission to the Section of Infectious Diseases, Health Sciences Council.

The increase in infections among males via homosexual contact between 2003 and 2004 was conspicuous. Upward trends in both young male and female Japanese HIV cases continue, calling for further attention toward this age group. Social education to help disseminate knowledge of HIV/AIDS and promote prevention behaviors will become more critical, and increased efforts by public health and education officials will be expected.

**Reports of AIDS patients:** These are reports of HIV cases with AIDS-defining disease already developed at diagnosis. They might not notice their HIV infection before development of AIDS.

Reports of HIV-infected: These are reports of those whose infection became clear by a chance (blood test, consultation of a hospital, or blood donation) after infection with HIV and before developing AIDS-defining disease, being 10 years on the average (see IASR Vol. 23, No. 5). Once reported as HIV-infected, they may not be reported as AIDS patients even developing AIDS-defining disease later (in this case, reported voluntarily as separate case-follow-up data for HIV-AIDS). The number of HIV/AIDS reports, therefore, reflect the infection status during the past 10 years and the opportunity to receive HIV testing or medical consultation, not indicating the real-time infection status.

Case-follow-up data for alive → death: If reported as AIDS patient and die later, the physician will report voluntarily the case-follow-up data.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

### Vol. 26 No. 6 June 2005 Infectious Agents Surveillance Report

http://idsc.nih.go.jp/iasr/

National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Serotypes and VT types of EHEC isolates during 2003-2004	9
cases in wide areas in Japan in 200414	0
EHEC O26 infection in 2004 including two outbreaks-Ehime14	0
An outbreak of EHEC O111 and other serotypes infection among	
high school students during a school excursion to Korea, July	
2004-Kanazawa City14	1
An outbreak of EHEC O157:H7 infection at a nursery school, July	
2004-Mie	2
An outbreak of EHEC O157 infection including a fatal case at a	
nursing care home for the aged, July-August 2004-Tokyo14	4
An outbreak of EHEC O26 infection at a nursery school,	
September 2004-Koriyama City14	5
Community outbreak of EHEC O157:H7 infection caused by same	
PFGE type, October-November 2004–Ehime	6
An outbreak of EHEC O111 infection among children of a	
kindergarten and a primary school, October-December 2004	
-Koriyama City14	7

An outbreak of mixed infection of EHEC O26:H11 and norovirus genogroup II at a nursery school, January 2005—Shimane A winter outbreak of EHEC O26:H11 infection at a nursery school,	
February-March 2005-Miyagi	148
An outbreak of EHEC 0157:H7 infection at a barbecue restaurant, March 2005–Kumamoto City	149
A winter epidemic of hand, foot and mouth disease due to	
coxsackievirus A16, February-March 2005–Kawasaki City A local epidemic of norovirus gastroenteritis caused by water	150
supply, March 2005–Akita	150
Analysis of influenza virus strains isolated in 2004/05 season  -Sendai City	151
Double infection of influenza virus types AH3N2 and B, March 2005–Saitama	
A case of acute encephalopathy with febrile convulsion	102
accompanying human metapneumovirus infection, March 2005  Osaka City	153

### <THE TOPIC OF THIS MONTH> Enterohemorrhagic Escherichia coli infection as of May 2005

Enterohemorrahagic Escherichia coli (EHEC) infection is classified as a category III notifiable infectious disease under the National Epidemiological Surveillance of Infectious Diseases (NESID) in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infectious Diseases Control Law), and reporting by physicians is mandatory. When food is suspected as the source of EHEC infection, and notification of food poisoning is made by a physician or food poisoning is recognized by the director of a health center, investigation and reporting to the national government are conducted by each local municipality under the Food Sanitation Law.

Notified cases under the NESID: In 2004, 3,711 new symptomatic and asymptomatic cases of EHEC infection (hereafter referred to as cases of EHEC infection) were reported (Table 1). This figure is the second largest following that in 2001 after enactment of the Infectious Diseases Control Law. Weekly reports in 2004 increased in the summer as usual, with a peak occurring in the 29th week (July 12-18) due to an outbreak among high school students in Ishikawa Prefecture returning from a school excursion to Korea (see Table 2 and p. 141 of this issue) (Fig. 1). Incidence by prefecture in 2004 ranged from 0.90 to 14.8 per 100,000 population, showing considerable local differences (Fig. 2). The highest incidence was seen in Ishikawa Prefecture (14.8), followed by Okayama (9.83) and Tottori Prefectures (8.66). Districts experiencing high incidence during 1999-2003 also tended to demonstrate high incidence in 2004. The number of cases that acquired infection in foreign countries, which until 2002 did not exceed 20 to 30, increased to 66 in 2003 and 151 in 2004. In 2004, the largest number of cases occurred in those aged 0-

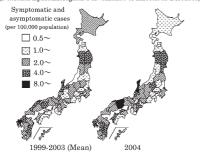
Table 1. Notified cases of EHEC infection

Year	Period	Cases
1996	Aug. 6-Dec. 31	1,287 *
1997	Jan. 1-Dec. 31	1,941 *
1998	Jan. 1-Dec. 31	2,077 *
1999	Jan. 1-Mar. 31	108 *
1999	Apr. 1-Dec. 31	3,114 **
2000	Jan. 1-Dec. 31	3,647 **
2001	Jan. 1-Dec. 31	4,336 **
2002	Jan. 1-Dec. 31	3,185 **
2003	Jan. 1-Dec. 31	2,998 **
2004	Jan. 1-Dec. 31	3,711 **
2005	Jan. 1-May 29	390 **

Including symptomatic and asymptomatic cases \*Statistics on Communicable Diseases in Japan (Ministry of Health and Welfare)

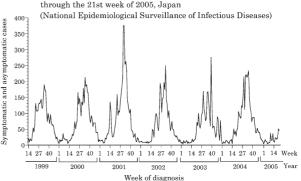
(Data based on the reports as of June 3, 2005)

Figure 2. Incidence of EHEC infection by prefecture, 1999-2004, Japan (National Epidemiological Surveillance of Infectious Diseases

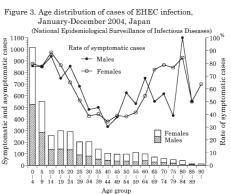


(Data based on the reports received before April 20, 2005)

Figure 1. Weekly incidence of EHEC infection from the 14th week of 1999 through the 21st week of 2005, Japan



Week of diagnosis (Data based on the reports received before June 3, 2005)



Age group
(Data based on the reports received before April 20, 2005)

<sup>\*\*</sup>National Epidemiological Surveillance of Infectious Diseases

Table 2. Outbreaks of EHEC infection, 2004

No.	Prefecture /City	Period	Suspected route of infection	Setting of outbreak	Serotype	VT type	Symptomatic cases	Consumers	Positives /examined	Familial infection	Reference in IASR
1	Ehime P.	May 27-Jun. 29	Person to person	Kindergarten	O26:H11	VT1	N.D.	• • •	38 / 460	Yes	p. 140 of this issue
2	Chiba C.	Jun. 12-16	Unknown	Primary school a)	O121:H19	VT2	63	110	[ 17 / 121	No	Vol.25, No.11
					O157:H7	VT1&2			2 / 121		
3	Hyogo P.	Jun. 27-Aug.	Unknown	Nursery school	O26:H11	VT1	2	N.D.	11 / >149	Yes	Vol.26, No.3
4	Miyagi P.	Jul.	Person to person	Nursery school	O26:H11	VT1	N.D.	• • •	12 / 119		
5	Ishikawa P.	Jul. 4-16	Foodborne	High school b)	O111:H-	VT1&2	110	377	103 / 715	Yes	p. 141 of this issue
6	Tokyo M.*	Jul. 29-Aug. 6	Unknown	Home for the aged	O157:H7	VT1&2	19	N.D.	10 / 147	No	p. 144 of this issue
7	Sendai C.	Jul. 30-Aug. 26	Person to person	Nursery school	O26:H11	VT1	9	• • •	23 / 188	Yes	Vol.25, No.12
8	Kanagawa P.	Aug. 4-	Unknown	Nursery school	O157:H7	VT2	2	N.D.	17 / 276	Yes	Vol.26, No.1
9	Ehime P.	Aug. 4-Sep. 3	Person to person	Nursery school	O26:H11	VT1	Several	• • •	15 / 416	Yes	p. 140 of this issue
10	Mie P.	Aug. 7-17	Person to person	Nursery school	O157:H7	VT2	18	• • •	23 / 278	Yes	p. 142 of this issue
11	Miyagi P.	Sep. 7-	Person to person	Nursery school	OUT:H-	VT1	2	•••	10 / 236	Yes	Vol.26, No.2
12	Fukushima P.	Sep. 1-18	Unknown	Nursery school	O26:H11	VT1	7	N.D.	15 / 147	Yes	p. 145 of this issue
13	Fukushima P.	Oct. 30-Nov. 27	Unknown	Kindergarten &	O111:HNT	VT1&2	12	N.D.	26 / 1,108	Yes	p. 147 of this issue
				Primary school							
14	Shimane P.	Nov. 15-Dec.	Unknown	Nursery school	O26:H-	VT1	6	N.D.	14 / 82	Yes	

M.: Metropolitan, P.: Prefecture, C.: City, NT: Not typed, N.D.: No data, ··· No information was entered because person to person infection was suspected. Including 10 or more EHEC positives, \*Including a fatal case, a) Patients occurred after a visit to a dairy farm. b) Patients occurred after a school excursion to Korea. (Data based on the outbreak reports from public health institutes received before May 26, 2005 and references in IASR)

4 years, followed by those aged 5-9 years. Males predominated among cases 0-14 years of age, with females predominating among those aged 15 years or over. The proportion of symptomatic patients was high in the younger and elderly age groups, as is typically seen yearly ( $\leq$ 19 years -79%,  $\geq$ 65 years -66%), and less than 45% in those aged 30-50s (Fig. 3).

EHEC isolation: In 2002, 1,800 EHEC isolations were reported from prefectural and municipal public health institutes (PHIs) to the Infectious Diseases Surveillance Center (IDSC) of the National Institute of Infectious Diseases (NIID); this number decreased to 1,400 in 2003, followed by an increase to 1,800 in 2004. These figures differ from those of reported cases in Table 1. These discrepancies can be explained by the fact, under the present system, a portion of the information of strains detected in laboratories other than PHIs are not reported to PHIs. During 1991-1995, more than 80% of isolates were 0157:H7, while serotypes other than 0157, such as 026 and 0111, increased. In 2004, 0157:H7 isolations decreased by about 50%, while 026 and 0111 increased by 24% and 8.2%, respectively (see p. 139 of this issue). In addition, various other serotypes were detected, including some Verocytotoxin (VT)-producing isolates that are untypable using commercially available antisera (see IASR 25:141-143, 2004). For identification of EHEC, confirmation of VT is important. Looking at VT types (or VT gene types) of EHEC isolates (see p. 139 of this issue), VT1 & VT2 comprised 63% of 0157 isolates in 2004, similar to previous years (53-68% during 1997-2003). Of the 026 isolates, VT1 alone has accounted for more than 90% every year, reaching 97% in 2004. Among 0111 isolates, VT1 alone comprised more than 60% of the isolates, but in 2004, VT1 & 2 accounted for 86%, reflecting the occurrence of a large-scale outbreak (Table 2).

In 2004, 14 cases of hemolytic uremic syndrome (HUS) were reported among the 1,809 EHEC-positive cases, of which O157 was found in 13 cases (VT1 & 2-8 cases, VT2 alone -5 cases) and O165 (VT2) in one case. Reported symptoms of 1,114 cases from which O157 was detected were bloody diarrhea (31%), diarrhea (47%), abdominal pain (41%), and fever (17%). Of the 124 cases of HUS reported during 2000-2004, 12 were aged one year or under (1.5% of 796 cases), 61 were aged 2-5 years (3.2% of 1,902 cases), 32 were aged 6-15 years (1.9% of 1,672 cases), 7 were aged 16-39 years (0.3% of 2,379 cases), and 12 were aged 40 years or over (0.6% of 1,949 cases). The number of cases and incidence rate of HUS were high in the younger ages.

Outbreaks: Among outbreaks involving 10 or more EHEC-positive cases reported to IDSC in 2004, one was thought to be due to food-borne transmission and six due to person-to-person transmission (Table 2). In 2004, there were 18 incidents of EHEC food poisoning (excluding foreign-acquired incidents) involving 70 cases, reported from prefectural governments in compliance with the Food Sanitation Law (note: the number of cases was much lower than that reported under the Infectious Diseases Control Law, due to the fact that incidents in which food was incriminated as the source of infection were few, and also that incidents involving only a single case are not always reported as food poisoning).

In 2004, outbreaks in nursery schools and kindergartens remained high, with 11 events reported. The etiologic serotype was identified as O26 in more events than O157. To prevent outbreaks due to person-to-person transmission in nursery schools, it is necessary to take proper precautions, including hand washing by children and staff members and sanitary control of paddling pools for children (see p. 142 of this issue). Furthermore, a characteristic feature of EHEC infections is the frequent occurrence of secondary infections among family members (Table 2). Thorough instruction of family members is required to prevent secondary infections.

There are many incidents in which the route of infection is unknown (neither person-to-person infection nor food-borne), and a fatal case has been reported in a home for the aged (see p. 144 of this issue).

After a report from Fukuoka Prefecture in 2003 (see IASR 25:147-148, 2004) of an outbreak during a school excursion to Australia, another outbreak among participants of a school excursion to Korea was reported from Ishikawa Prefecture in 2004 (Table 2). One hundred and ten cases were examined and treated at more than 25 different medical clinics, with health centers deluged with outbreak response activities such as the provision of information. It has been pointed out that health risk management is necessary when planning overseas school excursions (see p. 141 of this issue).

**Pulse-Net Japan:** In 2004, seven clusters of O157 strains and one cluster of O26 strains were found; each cluster consists of strains showing the indistinguishable PFGE pattern and was isolated in more than five prefectures (see p. 140 of this issue). Construction of a system that can respond to outbreaks and events on an international scale is in progress, led by the US CDC. In 2004, PFGE patterns of strains originating from an O157 incident on a US Air Force Base in Okinawa were shared by the US and Japan, resulting in the recall of approximately 40,000 tons of US beef suspected of being the source of infection (MMWR 54:40-42, 2005).

**Update 2005:** A total of 390 cases of EHEC infection have been reported over the first 21 weeks of this year (Table 1). Small peaks were seen in the 3rd, 10th and 13th weeks (see Fig. 1 and p. 147-150 of this issue). This coming summer, further increases in cases of EHEC infection are anticipated, thereby necessitating further attention to infection control and prevention.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases

### Vol. 26 No. 7 July 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

A cryptosporidiosis outbreak among users of a hotel with gymnasiums and swimming pools as a training camp, August 2004–Nagano167
Detection of <i>Cryptosporidium parvum</i> from cases of diarrhea from an outbreak occurring after a swimming training camp in Nagano,
August 2004–Chiba City168
An outbreak of secondary infection of Cryptosporidium through
swimming pools, August-September 2004–Chiba169
Clinical symptoms of cryptosporidiosis cases and follow-up of
evacuation numbers of oocysts in stools-Saitama170
An outbreak of cryptosporidiosis among guests and employees of
a hotel, April 2002–Hokkaido173
An outbreak of cryptosporidiosis among high school students having
contact with calves on a farm in Hokkaido, June 2002–Chiba 172
Genotype analysis of <i>Cryptosporidium</i> from sporadic and outbreak
cases

Current trend of cryptosporidiosis among HIV-infected cases and its treatment
Composition of the 2005/06 influenza HA vaccine in Japan 176
Two cases of scrub typhus (Tsutsugamushi disease), May 2005
-Yamagata
Isolation of coxsackievirus A16 from cases of hand, foot and mouth
disease, April-May 2005–Mie
April-May 2005–Aichi
An outbreak of mixed infection of norovirus genogroups I and II at
a nursery school, May 2005–Sakai City
Outbreaks of norovirus infection among children of primary schools
and other settings, May-June 2005–Osaka 179
A post-epidemic outbreak of influenza AH3, May 2005–Osaka 180

#### <THE TOPIC OF THIS MONTH> Cryptosporidiosis, as of June 2005

Cryptosporidiosis is a disease caused by infection with Cryptosporidium, an enteric protozoon of coccidian parasites. Infection occurs when oocysts (about 5  $\mu$ m in diameter) excreted in feces are orally ingested, and is spread through contaminated water or food, or through contact with an infected patient or animal. Since the occurrence of a large-scale waterborne infection, the Ministry of Health and Welfare (MHW at that time) established provisional guidelines for control of Cryptosporidium in tap water (Notice from Water Supply Division, Health Service Bureau, MHW) in October 1996. These guidelines indicated that public water service departments and prefectures needed to begin immediate preparations for preventive and emergency measures. Furthermore, intensification of water treatment with turbidity control and thorough maintenance of environmental conditions are required to prevent contamination (partly amended in June 1998 and finally amended in November 2001).

The incubation period of cryptosporidiosis is usually 4-8 days and symptoms such as nonhemorrhagic watery diarrhea last for about 10 days (range 2-26 days). Excretion of oocysts may continue even after the disappearance of symptoms for as long as approximately 2 months (see p. 170 of this issue). When immunosuppressed patients are affected, the disease tends to be prolonged and severe. Treatment of HIV/AIDS patients with paromomycin or nitazoxanide are currently being attempted (see http://www.ims.u-tokyo.ac.jp/didai/orphan/index.html, the Research Group on Chemotherapy of Tropical Diseases, Japan Health Science Foundation). Improving the immune function of these immnosuppressed cases has resulted in an increase in positive therapeutic outcomes (see p. 174 of this issue). In August 1997, the MHW called attention to the prevention of *Cryptosporidium* infection among immunosuppressed persons such as AIDS patients.

Etiological diagnosis: About 13 species of protozoa in the genus Cryptosporidium have been reported from various living species, such as mammals, reptiles and fishes. Human infection occurs mostly with C. parvum. In laboratory diagnosis, oocysts are detected by microscopic observation (see http://www.nih.go.jp/niid/para/atlas/japanese/manual/cryptosporidium.pdf). The fluorescent-antibody staining method (insurance inapplicable as a laboratory reagent) highly sensitive in detecting oocytes, and is widely used in examinations of tap water. Molecular epidemiological methods are progressively being used to investigate sources and routes of infection (see p. 174 of this issue).

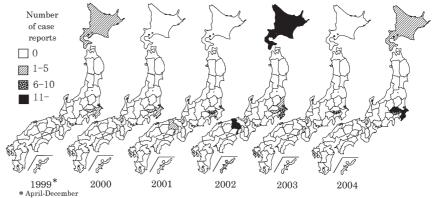
National Epidemiological Surveillance of Infectious Diseases (NESID): Cryptosporidiosis, in addition to other enteric protozoal infections such as giardiasis and amebic dysentery, are considered category V notifiable infectious diseases in the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law), requiring all physicians to report any identified cases. During April 1999 to June 24, 2005, the period of enactment of the Infectious Diseases Control Law, 233 cases were reported (Table 1), a large increase from the last Topic of This Month (IASR 22:159-160, 2001). However, cases were reported from 10 prefectures in the Hokkaido, Kanto, and Kansai districts (Fig. 1). Most cases were part of outbreaks occurring in 2002 (100 cases) and 2004 (80 cases), while in those other than these cases, reported were 53, being 3-13 cases annually (Fig. 2). Reported cases of cryptosporidiosis, including cases from outbreaks, have been considerably fewer than those of giardiasis (614 cases) and amebic dysentery (2,998 cases).

Table 1. Notified cases of cryptosporidiosis, April 1999-June 2005

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Year of diagnosis	Reported cases
1999	4
2000	3
2001	11
2002	109
2003	8
2004	93
2005	5

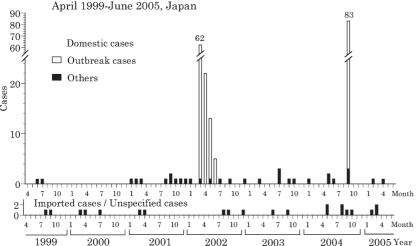
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before June 24, 2005)

Figure 1. Reported cases of cryptosporidiosis, by prefecture, 1999-2004, Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before June 24, 2005)

Figure 2. Monthly cases of cryptosporidiosis, by suspected region of infection,



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before June  $24,\,2005$ )

The age range of 53 non-outbreak related cases was 17-88 years, with a peak occurrence among those 20-24 years; a 5:1 male to female ratio was observed (Fig. 3). These observations may be explained by the fact that cryptosporidiosis is often seen as an opportunistic infection in HIV/AIDS patients. In contrast, the sex ratio during an outbreak in Ogose Town, Saitama Prefecture, was approximately 1:1.

Of the 53 non-outbreak related cases, 32 were infected domestically while 21 acquired infection abroad. Among the domestic infections, contact with livestock and homosexual contact were mentioned in many reports (Table 2). Suspected small outbreaks of disease among male homosexuals in Tokyo and its vicinities have been reported (see p. 174 of this issue). Most of the 14 cases

suspected small outbreaks of disease among male homosexuals in Tokyo and its vicinities have been reported (see p. 174 of this issue). Most of the 14 cases were presumably infected while traveling in the Indian subcontinent, although three were infected in Africa, two in China, and one each in Vietnam and South America.

Outbreaks: Cryptosporidium has often caused large-scale waterborne infections. In 1993, 400,000 people were infected by a water-supply accident in Milwaukee, Wisconsin, US. In Japan, large outbreaks also occurred in Hiratsuka City, Kanagawa Prefecture in 1994 (see IASR 15:248-249, 1994) and Ogose Town, Saitama Prefecture in 1996 (see IASR 17:217-218, 1996). Waterborne cryptosporidiosis is characterized by very high morbidity; in Milwaukee, as high as 52% and in Ogose Town 70% (8,700 people) of all city-water recipients were affected.

After the last Topics of This Month, four outbreaks have occurred in this country; three in 2002 and one in 2004. Two outbreaks occurred in February and April 2002 among groups traveling to the Iburi area, Hokkaido; one in students from a high school in Hyogo Prefecture (see IASR 23:145-145, 2002), two months later another one in students from a professional school in Sapporo City (see p. 171 of this issue). Neither the source of infection nor transmission routes was identified.

Outbreaks caused by contacts with animals: During an outbreak that occurred in June 2002, high school students from Chiba Prefecture developed disease after visiting a pasture in Tokachi area, Hokkaido, reporting a history of contact with calves (see p. 172 of this issue). In Scotland, an outbreak occurred in a petting zoo in late April of this year (see Eurosurveillance Weekly, Issue 17, 2005). Because there are many similar facilities in Japan, health surveillance and control of animals, in addition to adequate hygiene instructions to visitors, are needed at these facilities. In May 2003, the Ministry of Health, Labour and Welfare issued guidelines on the prevention of zoonotic disease at animal exhibition facilities to enhance awareness among the general public (refer to http://idsc.nih.go.jp/jinju\_hp/guideline03/index.html).

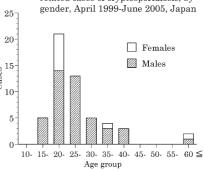
Outbreaks through swimming pools: In August 2004, groups of primary school, high school and college students were infected through swimming pools and other facilities at a camping facility in Nagano Prefecture. Morbidity was greater than 90% among the primary school group that used the swimming pool (see p. 167-169 of this issue). Infected children from this outbreak subsequently contaminated a swimming pool in Chiba Prefecture, resulting in another outbreak of cryptosporidiosis (see. p. 169 of this issue). In the US, 62 waterborne outbreaks were reported during 1991-2002, of which 50 were caused by contaminated water in swimming pools and other facilities [MMWR, 42 (SS05),1993; 45 (SS01), 1996; 47 (SS05), 1998; 49 (SS04), 2000; 53 (SS08), 2004].

With the arrival of summer, it will be necessary to maintain hygienic management of recreational water facilities, and to conduct surveillance and appropriate measures in response to outbreaks, including restricting the use of swimming pools by cases of cryptosporidiosis and other diarrheal diseases. For early detection of *Cryptosporidium* infection, protozoan laboratory testing of stool specimens from diarrheal patients should widely be performed (see p. 168 of this issue).

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

### Infectious Disease Surveillance Center, National Institute of Infectious Diseases

Figure 3. Age distribution of 53 non-outbreak related cases of cryptosporidiosis, by



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before June 24, 2005)

Table 2. Transmission route and background factor of domestic *Cryptosporidium* infection

Transmission route/ background factor	Reported cases
Contact to calves	7
Visit to stock farm	1
Homosexual contact	7
HIV infection	1
Unknown	16
Total	32

Descriptions of 32 domestic cases excluding outbreak cases (National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before June 24, 2005)

### Vol. 26 No. 8 August 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

The necessity of strengthening the system for prevention of zoonoses	Control measures for anthropozoonoses and zooanthroponoses in animal-exhibiting facilities
Three principles of control measures for zoonoses	Strategy to prevent importation of Marburg disease into Japan,
Infections from non-human primates	2005
Zoonoses caused by imported exotic pets	Laboratory diagnostic system of filovirus infections in Japan
Zoonoses exempt from notification under the Infectious Diseases	Legionella pneumophila serogroup 1 infection from homemade
Control Law	leaf mold, November 2004–Saitama
Incidence of rabies worldwide and the risk of introduction into	Isolation of influenza virus type AH3 from a traveler returning
Japan204	from Vietnam, July 2005–Osaka
Incidence and laboratory diagnosis of tularemia206	An epidemic of hand, foot and mouth disease and herpangina due
Monitoring dead crows in parks in Japan for early detection of	to coxsackievirus A6, April-June 2005–Nara
West Nile fever207	An outbreak of norovirus genogroup I infection in a primary
Leptospirosis cases infected from imported American flying	school, June 2005–Shimane
squirrels, April-June 2005-Shizuoka City209	An outbreak of norovirus genogroup I infection probably caused
Four cases of psittacosis pneumonia in a family March-April	by secondary contamination of dishes at a restaurant, March
2005-Nagasaki City211	2005-Yamaguchi
Tuberculosis among Japanese monkeys in a zoo, July 2004-March	Isolation and genotyping of adenovirus type 17, February 2005
2005–Osaka City	-Osaka City

### <THE TOPIC OF THIS MONTH> Zoonoses in Japan

R. Virchow, known as the father of pathology, labeled the term "zoonosis" as an animal disease transmissible to man. The Joint WHO/FAO Expert Committee Meeting (1958) defined zoonoses as "those diseases and infections which are naturally transmitted between vertebrate animals and man".

Zoonoses in Japan: Approximately 60% of microorganisms that are infectious to humans, representing over 800 species, originate from animals. In recent years, various species of animals have been identified as reservoir hosts or sources of infection for many emerging and re-emerging disease pathogens worldwide, highlighting the public health importance of zoonoses.

Japan has succeeded in controlling many zoonotic diseases, such as rabies and plague. This success has largely been due to inherent geographic and climatic advantages as an island country, with resulting limitations of direct invasion of terrestrial animals and decreases in activity of animals and vectors during the winter season. Efforts have thus focused on domestic countermeasures. Recently, however, many animals and livestock products have been imported from all over the world, and the introduction of animals from overseas under natural conditions, such as migratory birds, is a current reality. These factors suggest that the possibilities of introductions of new zoonoses into Japan are high, and are likely to occur through various routes of introduction.

National surveillance system: The National Epidemiological Surveillance of Infectious Diseases (NESID), in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law) enacted in April 1999, requires physicians to report 86 different infectious diseases, of which about 40% are zoonoses. By the amendment of the Infectious Diseases Control Law enacted in November 2003 (see IASR 25:1-4, 2004), leptospirosis, tularemia, lyssavirus infection, Nipah virus infection, monkeypox, avian influenza (AI) virus infection, and hepatitis E have been added as Category IV infectious diseases. Infectious diseases that require measures against animals and goods are classified as Category IV disease, particularly diseases that involve wildlife (including exotic pets and urban-type wild animals) as reservoir hosts or sources of infections. Infectious diseases related to livestock (livestock products) with high breeding densities are included among diseases that can cause large-scale outbreaks.

According to the Infectious Diseases Control Law, when there is suspicion that a person may have been infected by an animal, the prefectural governor or the national government has the authority to conduct active epidemiological investigations in order to determine the extent, trends, and cause of the infection.

Veterinarians who diagnose infected animals are required to report monkeys with Ebola hemorrhagic fever or Marburg disease, prairie dogs with plague, palm civet cats, Melogale and raccoon dogs with SARS, and since October 2004, monkeys with dysentery, birds with West Nile fever, and dogs with echinococcosis.

Restriction of animal import: Until now, measures have been taken to quarantine certain imported animals (monkeys, dogs, cats, foxes, raccoons, and skunks) and to prohibit other animals (some species of monkeys, prairie dogs, palm civet cats, Melogale, raccoon dogs, Mastomys, and bats).

However, no public health measures had been taken against the hundreds of thousands of other various vertebrate species imported every year, leaving importations of wild animals largely unchecked. Therefore, as countermeasures against the introduction of infectious diseases, importation of monkeys as pets has become prohibited since July 2005. Furthermore, from September 2005, animals allowed to be imported must be accompanied by a health certification issued by a government agency of the exporting country (see p. 196 of this issue). On the health certification, regardless of the purpose of importation, documentation is required verifying that rodents and their carcasses are free from infection with plague, rabies, monkey pox, hemorrhagic fever with renal syndrome, hantavirus pulmonary syndrome, tularemia, or leptospirosis, that lagomorphs are free of rabies or tularemia, that other terrestrial mammals are free from rabies, and that all species of birds are free of West Nile fever or AI virus infection.

**NESID:** Among cases of zoonoses shown in Table 1, newly assigned Category IV infectious diseases included leptospirosis (one case in 2003, 18 cases in 2004) and hepatitis E (30 cases in 2003, 36 cases in 2004), were reported. In particular, cases of hepatitis E infected after consuming raw liver of wild boars or raw meat of wild deer have been reported and continue to increase. Among pork liver sold commercially, hepatitis E virus genes have been detected, thereby requiring thorough cooking prior to consumption. No other new Category IV infectious diseases (tularemia, lyssavirus infection, Nipah virus infection, monkeypox, or AI virus infection) have been reported.

Table 1. Zoonosis cases reported under the NESID and major animal reservoirs or sources of infection

Section   Source   Category   Carrier   Category   Ca	Table 1. Zoollosis cases reported un	under the NESID and major animal reservoirs or sources of infection							
2000   2001   2002   2003   2004   Pet   Exotic pet   Livestock Ex		Year				Major reservoir/			
Category I									
Category		2000	2001	2002	2003	2004*	Pet	1	Livestock
Ebola hemorrhagic fever	Category I	1		l				1 Exotic pet	
Crimean-Congo hemorrhagic fever		0	0	0	0	U			<u> </u>
Severe Acute Respiratory Syndrome (SARS) (due to SARS coronavirus)				_					
CaARS  (due to SARS coronavirus)		<u>-</u>	- 0						
Plague		-	_		0	0		0	0
Marburg disease		0	0	0	0	0			
Lassa fever									
Category II   Shige  Doisis***			_						
Shigellosis***									L
Category III									
Enterohemorrhagic Escherichia coli infection***	Shigellosis***	843	844	699	473	577			
Category IV	Category III								
Category IV	Enterohemorrhagic Escherichia coli	0.040	4.405	0.100	0.000	0.040			
Category IV   Hepatitis E	infection***	3,642	4,435	3,183	2,999	3,643			O
Hepatitis E									
West Nile fever (including West Nile encephalitis)**		1	0	16	20	26			
encephalitis)**		4	0					<u> </u>	
Echinococcosis		-	_	0	0	0		0	
Yellow fever***		22	15	10	20	25			
Psittacosis									
Relapsing fever						_	_		
Q fever									
Rabies		_			_		_	_	
Avian influenza virus infection									0
Monkeypox									
Hemorrhagic fever with renal syndrome									
Anthrax									
Dengue fever***									
Nipah virus infection									
Japanese spotted fever   38   40   36   52   67   O     Japanese encephalitis   7   5   8   1   5   O     Hantavirus pulmonary syndrome   0   0   0   0   0   O     Herpes B virus infection   0   0   0   0   0   O     Herpes B virus infection   0   0   0   0   O   O     Herpes B virus infection   0   0   0   0   O   O     Herpes B virus infection   0   0   0   0   O   O     Herpes B virus infection   0   0   0   0   O   O     Herpes B virus infection   0   0   0   O   O     Epidemic typhus   0   0   0   0   O   O     Unuaremia   0   0   O   O     Lyme disease   12   15   15   5   4   O     Lyssavirus infection (excluding rabies)   0   0   O   O     Leptospirosis   1   18   O   O   O     Category V     Amebiasis***   378   429   465   505   587   O     Acute encephalitis (excluding Japanese   12   164   O     encephalitis and West Nile encephalitis)   149   134   108   99   -   O     Cryptosporidiosis***   3   11   109   8   91   O     Giardiasis***   98   137   113   103   85   O     Influenza (excluding avian influenza   769,964   305,441   747,010   1,162,290   769,202   O		10	30	32					
Japanese encephalitis		20	40	20					0
Hantavirus pulmonary syndrome									
Herpes B virus infection									0
Brucellosis									
Epidemic typhus         0         0         0         0         0         0         0         0         O         C           Tularemia         -         -         -         -         0         0         O         O         Lysavirus infection (excluding rabies)         -         -         -         0         0         O         O         O         Leptospirosis         -         -         -         0         0         O									
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$									0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		0	0						
Lyssavirus infection (excluding rabies)         —         —         —         0         0         O           Leptospirosis         —         —         —         —         1         18         O         O           Category V         —         —         —         —         —         505         587         O           Acute encephalitis (excluding Japanese encephalitis and West Nile encephalitis)         —         —         —         —         12         164         O           Cryptosporidiosis***         3         11         109         8         91         O           Giardiasis***         98         137         113         103         85         O           Influenza (excluding avian influenza virus infection)****         769,964         305,441         747,010         1,162,290         769,202         O		10	1.5						
Category V			15						
Category V  Amebiasis***  Acute encephalitis (excluding Japanese encephalitis and West Nile encephalitis)  149 134 108 99 - O  Cryptosporidiosis***  3 11 109 8 91 O  Giardiasis***  98 137 113 103 85 O  Influenza (excluding avian influenza virus infection)****  769,964 305,441 747,010 1,162,290 769,202		_							
Amebiasis***         378         429         465         505         587         O           Acute encephalitis (excluding Japanese encephalitis and West Nile encephalitis)         -         -         -         -         12         164         O           Cryptosporidiosis***         3         11         109         8         91         O           Giardiasis***         98         137         113         103         85         O           Influenza (excluding avian influenza virus infection)****         769,964         305,441         747,010         1,162,290         769,202         O		_			1	18	U		U
Amebiasis***         378         429         465         505         587         O           Acute encephalitis (excluding Japanese encephalitis and West Nile encephalitis)         -         -         -         -         12         164         O           Cryptosporidiosis***         3         11         109         8         91         O           Giardiasis***         98         137         113         103         85         O           Influenza (excluding avian influenza virus infection)****         769,964         305,441         747,010         1,162,290         769,202         O	Category V								
encephalitis and West Nile encephalitis)         149         134         108         99         —         O           Cryptosporidiosis***         3         11         109         8         91         O           Giardiasis***         98         137         113         103         85         O           Influenza (excluding avian influenza virus infection)****         769,964         305,441         747,010         1,162,290         769,202         O         O	Amebiasis***	378	429	465	505	587			
Cryptosporidiosis***         3         11         109         8         91         O           Giardiasis***         98         137         113         103         85         O           Influenza (excluding avian influenza virus infection)****         769,964         305,441         747,010         1,162,290         769,202         O         O	Acute encephalitis (excluding Japanese	_	_	_	12	164			
Giardiasis***         98         137         113         103         85         O           Influenza (excluding avian influenza virus infection)****         769,964         305,441         747,010         1,162,290         769,202         O         O		149	134	108	99			0	
Influenza (excluding avian influenza virus infection)****  769,964 305,441 747,010 1,162,290 769,202 O	Cryptosporidiosis***	3	11	109	8	91		0	
virus infection)****  769,964 305,441 747,010 1,162,290 769,202		98	137	113	103	85		0	
virus infection/"""	Influenza (excluding avian influenza	760.064	205 441	747.010	1 169 900	760 202			
	virus infection)****					709,202			0

Cases: based on the National Epidemiological Surveillance of Infectious Diseases

Of the infections which veterinarians are required to report after October 2004, 10 cases of shigellosis (in monkeys imported for research purposes) and 2 cases of echinococcosis (in dogs) have been reported. Every year, 470-840 shigellosis cases are reported (Table 1), with most of them thought to have been infected from non-animal sources. In contrast, echinococcosis (*Echinococcus multilocularis*) is prevalent in Hokkaido, with 10-25 new cases being reported annually since 2000. The infection rate in red foxes, the dead-end host of echinococcosis, is about 40% in Hokkaido. Beside countermeasures against this species of host animal, prevention of spread of echinococcosis to south of Honshu has become an important issue.

Conclusion: Zoonoses involve various animal reservoir hosts or sources of infection, such as wild animals, livestock, and pets (Table 1), as well as complex routes of transmission. In the future, surveillance systems that promote diagnostic pathogen surveillance of animals in Japan and abroad, together with prevention and outbreak control measures, need to be strengthened. Furthermore, based on outbreaks of threatening emerging zoonoses in Asian countries in recent years, efforts to control zoonoses from a global perspective will be necessary.

 $Toyama 1-23-1, Shinjuku-ku, Tokyo 162-8640, JAPAN \quad \acute{Fax} \ (+81-3)5285-1177, Tel \ (+81-3)5285-1111, E-mail \ iasr-c@nih.go.jp \ (+81-3)5285-1111, E-mail \$ 

<sup>\*</sup>Figures for 2004 are based on provisional reports as of January 28, 2005. SARS, hepatitis E, hepatitis A, avian influenza virus infection, monkeypox, Nipah virus infection, tularemia, lyssavirus infection and leptospirosis cases were notified beginning November 5, 2003. For acute encephalitis, all cases were notified beginning November 5, 2003 (shown in upper line), and a portion of the cases had been reported earlier from sentinel hospitals (shown in lower line).

<sup>\*\*</sup>West Nile encephalitis cases were notified beginning November 1, 2002.

<sup>\*\*\*</sup>Most cases of shigellosis, enterohemorrhagic *Escherichia coli* infection, yellow fever, dengue fever, amebiasis,

cryptosporidiosis, giardiasis and influenza were likely caused by non-zoonotic transmission.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

#### Vol. 26 No. 9 September 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Current problems in enterovirus-gene analysis	Local epidemic of influenza AH3 in summer, June-August 2005  -Okinawa	:43
Isolation of enteroviruses, January-July 2005–Ehime	2005–Nara	244
Local epidemic of hand, foot and mouth disease and isolation of coxsackievirus A16, May-July 2005–Miyagi239	Isolation of influenza virus AH1 in summer, June-July 2005  -Sendai City	
Local epidemics of hand, foot and mouth disease and isolation of coxsackievirus A16, April-July 2005—Okinawa	An epidemic of mumps and isolation of mumps virus, June-July 2005–Kanagawa	
A review on human infection of <i>Streptococcus suis</i> globally	Isolation of type A Clostridium botulinum from an infant botulism case, July 2005–Okazaki City 2	
Japan	A case of pneumonia due to Legionella longbeachae, August 2004  -Kobe City	247

#### <THE TOPIC OF THIS MONTH> Herpangina as of July 2005, Japan

Herpangina is a typical enterovirus infection that, similarly to hand, foot and mouth disease (HFMD), occurs annually among infants and young children mainly during the summer season. Surveillance for herpangina as one of the sentinel reportable diseases began in 1981 among approximately 2,500 pediatric and internal medicine sites under the National Epidemiological Surveillance of Infectious Diseases (NESID). Herpangina has been classified as a Category IV infectious disease under the Infectious Diseases Control Law since April 1999. Approximately 3,000 pediatric sentinel clinics report weekly cases by gender and age group to local government health centers and, through prefectural municipalities, the central infectious disease surveillance center (Infectious Diseases Surveillance Center, National Institutes of Infectious Diseases). Herpangina was reclassified as a Category V infectious disease subsequent to the implementation of the revised Infectious Diseases Control Law in November 2003. Reporting is based on clinical diagnoses by physicians of "sudden onset with high fever" and "vesicles, ulcer and redness around the uvula". Approximately 10% of pediatric sentinel clinics serve as infectious agent's surveillance sentinels for herpangina, while prefectural and municipal public health institutes (PHIs) conduct pathogen laboratory testing and report positive cases to the central infectious disease surveillance center.

**Incidence:** Annual case counts from 1982-2004 (Fig. 1) reveal that 1984 experienced the largest number of cases with 204,555 (97.51 cases per sentinel), followed by 70,000-120,000 cases per year until 1998. After the enactment of the Infectious Diseases Control Law, annual cases have increased to 100,000-150,000, although cases per sentinel have remained similar to figures prior to the enactment at 30-50, indicating the occurrence of epidemics of similar magnitudes.

Weekly reported cases from the most recent six seasons are shown in Fig. 2. After the standard epidemic level of 1.0 case per sentinel clinic is exceeded during weeks 22-23 every year (end of May- beginning of June), cases increase rapidly and peak during weeks 27-29 (July). Post-peak decreases to less than 1.0 per sentinel usually occurred between weeks 31-38 (August-September), although in some years this decrease was not seen until autumn. However, as compared with HFMD (see IASR 25:224-225, 2004) the occurrence of herpangina clearly concentrated in the summer.

The age of cases has not changed appreciably over the last 20 years; 70% of cases were 1-4 years of age (Fig. 3). In looking at each age group after 1998, children 1 year of age accounted for the largest number of cases (22-25%), while the proportion of cases decreased with increasing age among those older than 2 years; cases were few among those older than 6 years. The proportion of cases 0 years of age has been decreasing, and is thought to be associated with the decreasing number of births as similarly seen for chickenpox and exanthem subitum.

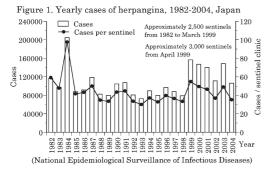
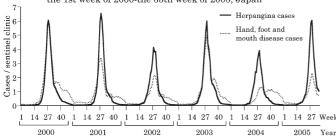
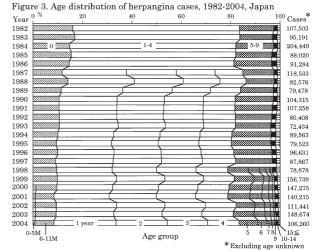


Figure 2. Weekly cases of herpangina and hand, foot and mouth disease, the 1st week of 2000-the 35th week of 2005. Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before September  $8,\,2005$ )



(National Epidemiological Surveillance of Infectious Diseases)

Table 1. Virus isolation/detection from herpangina cases, 1997-2004, Japan

Virus	Repo	rts of	isolati	on/de	tection	from	herpa	ngina	cases	Total	
virus	1997	1998	1999	2000	2001	2002	2003	2004	Total	reports*	2005
CA2	93	26	69	18	77	1	36	73	393	757 (52)	5
CA3	3	38	1	2	-	11	-	-	55	90 (61)	-
CA4	101	75	189	64	91	127	84	246	977	1,588 (62)	5
CA5	71	32	17	21	50	9	3	2	205	310 (66)	3
CA6	8	46	112	56	29	59	57	18	385	673 (57)	148
CA8	1	5	6	5	72	5	1	-	95	151 (63)	-
CA10	61	85	26	119	16	14	216	2	539	977 (55)	20
CA12	1	11	-	-	2	1	30	3	48	70 (69)	-
CA16	1	17	8	1	8	7	5	6	53	2,065 (3)	2
Other CA	-	4	3	12	7	-	5	5	36	541 (7)	4
EV71	4	2	3	10	1		14	4	38	1,639 (2)	1
CB	39	40	69	41	55	44	24	45	357	4,940 (7)	7
Echo	20	97	33	29	20	42	28	13	282	14,440 (2)	2
Other entero	4	1	4	1	3	1	4	3	21	918 (2)	-
Entero subtotal	407	479	540	379	431	321	507	420	3,484	29,159 (12)	197
Adeno	30	54	31	37	30	18	32	20	252	17,657 (1)	12
HSV	17	29	22	37	20	12	22	20	179	2,047 (9)	6
Othes	12	7	19	7	11	3	3	5	67	73,849 (0)	4
Total	466	569	612	460	492	354	564	465	3,982	122,712 (3)	219

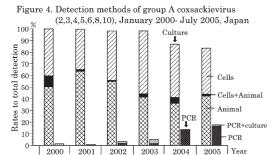
<sup>\*</sup>Reports during 1997-2004, ( ): Percentage of the reports on isolation from herpangina cases to those from the total cases, Data based on the reports received before September 9, 2005

According to results of a questionnaire survey by the study group on severe enterovirus infections (response rate: 2000&2001 - 41%, 2002 - 32%), the number of cases of herpangina that clinically worsened during the course of illness and required hospitalization was 309 in 2000, 294 in 2001, and 200 in 2002 (see IASR 25:226-227, 2004). The occurrence of complications among patients with herpangina and HFMD should be monitored.

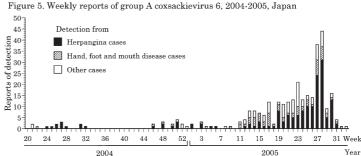
Virus isolations/detections: The principal etiologic agent of herpangina is group A coxsackievirus (CA). CA is most often isolated from nasopharyngeal swabs, followed by stool samples. The most common CA serotypes detected in herpangina cases during 1997-2004 (Table 1) were CA4, CA10, CA2, CA6, and CA5, in the descending order of frequency. CA4 was most prevalent in 1997, 1999, 2001, 2002 and 2004, as was CA10 in 1998, 2000, and 2003. Changes in circulating serotypes from year to year, a characteristic of enteroviruses, was observed during 1982-1996 (see IASR 17:212-213, 1996; 21:212-213, 2000; and http://idsc.nih.go.jp/iasr/virus/graph/ev-1a.html). A few enteroviruses such as CA16, enterovirus 71, group B coxsackievirus, and echovirus, as well as non-enteroviruses such as adenovirus and herpes simplex virus, were detected.

Virus identification method: Utilization of animals (e.g. suckling mice, especially newborn mice), a more sensitive method of CA virus isolation than cultured cells, has accounted for more than 50% of CA virus isolation reports. However, since the addition of PCR as a reporting item for virus detection in 2000, the proportion of CA detections by PCR has been increasing every year (Fig. 4). This increase stems from the fact that virus isolation involves time and labor, with fewer PHIs using suckling mice. Although pan-entero primers are utilized for detection of enteroviruses by PCR, pathogen confirmation should be performed by virus isolation, the gold standard. Recently, nucleotide sequence analysis has been increasingly used for serotyping virus isolates. However, because various difficulties with nucleic acid analysis have been identified, neutralization or complement fixation (CF) assays are the preferred methods of serotype testing, with genetic analysis used as a supplementary method at the present time (see p. 237 of this issue). In addition, enteroviruses other than CA have been reported that are difficult to identify with antiserum prepared for enterovirus identification and distributed to PHIs (see p. 238 of this issue). Cases in which viruses are difficult to isolate or identify should be referred to NIID, Department of Virology II, Laboratory II.

Trend in 2005: Weekly reports of herpangina exceeded 1.0 per sentinel in week 23 (June 6-12) as seen every year, and peaked at 6.0 per sentinel in week 28 (July 18-24), equivalent to the peak in 2000 and the second highest figure next to 2001. As of week 35 (August 29-September 4), 1.02 cases per sentinel were reported (Fig. 2). Most of the viruses detected were CA6 (148 cases), followed by CA10 (20 cases) (Table 1, as of September 9). Although there were few reports of CA6 in the summer of 2004, CA6 detections were reported in the winter (Fig. 5) and subsequently increased after week 11 of 2005 (March 14-20), not only from cases of herpangina but also from those with HFMD, upper respiratory inflammation, and fever (see p. 238 of this issue and IASR 26:178&222, 2005). The number of reports of CA6 isolation from 26 PHIs in 2005 has already surpassed figures from each of the years during 2000-2004.



(Infectious Agents Surveillance Report: Data based on the reports received before August 19, 2005)



(Infectious Agents Surveillance Report: Data based on the reports received before September 9, 2005)

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases

#### Vol. 26 No. 10 October 2005 Infectious Agents Surveillance Report

http://idsc.nih.go.jp/iasr/

National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division. Ministry of Health, Labour and Welfare

Current methods for laboratory diagnosis of hepatitis E	263
Detection of hepatitis E virus G3 from frozen deer meat involved in	
hepatitis E outbreak and a survey for HEV infection among wild	
deer, 2003–Hyogo	264
A case of hepatitis E virus G3 infection due to consumption of wild	
boar meat, March 2005–Fukuoka	265
An outbreak of hepatitis E virus G4 infection, September 2004	
-Hokkaido	266
Genetic analysis of hepatitis E virus G3 detected from three of four	
sporadic cases of hepatitis E in June 2005–Mie	267
Incidence of hepatitis E virus infection among animals in Japan	269

Selection of the 2005/06 season influenza HA vaccine strains in
Japan270
Two cases of leptospirosis presumably infected by rodents, May-
June 2005–Okinawa
A brucellosis case due to Brucella melitensis infected during
a travel to Syria, June 2005273
An outbreak of EHEC O157:H7 infection among participants of
a community event, June 2005–Toyama274
An outbreak of food poisoning due to diarrhegenic Escherichia coli
caused by springwater at a camp site, July 2005–Fukuoka City
and Oita 275

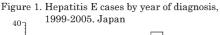
#### <THE TOPIC OF THIS MONTH> Hepatitis E as of August 2005, Japan

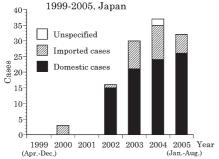
Hepatitis E is an acute hepatitis caused by infection with hepatitis E virus (HEV), which belongs to the family Hepeviridae, genus Hepevirus. Hepatitis E shares many clinical characteristics with hepatitis A, including typical symptoms such as jaundice and the absence of chronic infection. However, the case-fatality rate is reportedly higher than that of hepatitis A, with 20% fatality among pregnant women. In developing countries, fecal-oral infection with viruses excreted in feces of infected patients commonly occurs, resulting in sporadic cases or outbreaks. However, large-scale outbreaks have occasionally been reported due to contaminated drinking water. On the other hand, in Japan and other countries, HEV infection has been identified in different animal species, leading to the recognition of hepatitis E as a zoonotic infectious disease (see IASR 193-194, 2005).

There are four known HEV genotypes (G1-G4). G1 mainly circulates within human populations in developing countries. G2 has been reported in epidemics in Mexico, Namibia, and Nigeria, but has not been seen in recent epidemics. G3 and G4 infect both humans and animals. Only one HEV serotype is thought to exist.

In Japan, reporting of hepatitis E was mandatory within 7 days after diagnosis by a physician as an "acute viral hepatitis" (category IV notifiable infectious disease), under the National Epidemiological Surveillance of Infectious Diseases (NESID) based on the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (the Infectious Diseases Control Law, implemented in April 1999). Subsequently, in accordance with the law amendment in November 2003, "hepatitis E" became an independent category IV notifiable infectious disease, with notification being required immediately after diagnosis.

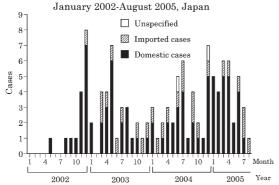
Yearly and monthly incidence: Since April 1999, 118 cases reported as hepatitis E and confirmed as HEV infection have been recorded: 0 in 1999 (day of diagnosis during April-December), 3 in 2000, 0 in 2001, 16 in 2002, 30 in 2003, 37 in 2004, and 32 in 2005 (day of diagnosis during January-August) (reports as of September 8, 2005). Reports of cases presumed to have been infected in Japan (domestic cases) have increased sharply after 2002 (Fig. 1). At the same time, cases presumed to have been





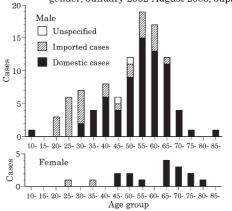
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before September 8, 2005)

Figure 2. Hepatitis E cases by month of diagnosis,



(National Epidemiological Surveillance of Infectious Disease Data based on the reports received before September 8, 2005) infected outside Japan (imported cases) have also increased since 2003. The increase in reports may reflect the fact that laboratory confirmation of infection through HEV gene detection by RT-PCR and IgM antibody detection by ELISA has recently become possible (see p. 263 of this issue). Dates of diagnosis by month are shown in Fig. 2. Seasonality has not been apparent. Hepatitis E was diagnosed within 10, 19, and 28 days of initial examination in 25%, 50%, and 75% of reported cases, highlighting the considerable time required in order to make the diagnosis.

> Figure 3. Age distribution of hepatitis E cases by gender, January 2002-August 2005, Japan



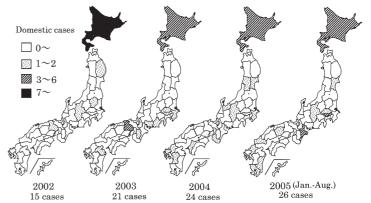
(National Enidemiological Surveillance of Infectious Disease: Data based on the reports received before September 8, 2005)

Table 1. Hepatitis E cases in Japan by suspected region of infection, 1999-2005

region of infection, 155	2000
Inside Japan	86
Outside Japan	30
China	12
India	6
Nepal	2
Thailand	1
Myanmar	1
Bangladesh	1
Pakistan	1
Southeast Asia	1
Afghanistan	1
Two or more countries	4
Unspecified	2
Total	118

(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before September 8, 2005)

Figure 4. Hepatitis E cases by prefecture, 2002-2005, Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before September 8, 2005)

Age and gender: Males overwhelmingly outnumbered females among both domestic and imported cases (101 total male cases: 71 domestic, 28 imported, 2 unknown; 17 total female cases: 15 domestic, 2 imported). Most of the domestic cases were of middle or advanced ages, with peaks in the latter 50's for males and the latter 60's for females, while imported cases were mainly in their 20's to early 30's (Fig. 3).

The laboratory diagnostic methods and genotypes: Of the 118 cases reported between April 1999 and August 2005, 33 cases were diagnosed by gene detection and 102 by antibody detection (figures include cases diagnosed by both methods). Virus genotypes were reported for 17 cases (including those determined after the initial report); G3 was detected in 12 domestic cases and 1 imported case (presumed to have acquired infection in Thailand), while G4 was detected in 4 domestic cases.

Presumed region of infection: Distribution of domestic cases by prefecture is shown in Fig. 4. During 2002-August 2005, cases were reported in 30 different prefectures. Cases from Hokkaido occur every year and account for about one third of all cases nationwide. The presumed areas of infection among imported cases were mainly in Asia, with China being the most identified followed by India (Table 1).

Foodborne infection: Of 86 domestic cases diagnosed during April 1999-August 2005, 16 were suspected to have been infected through pork liver consumption, 13 through wild boar liver and meat consumption, and seven by raw deer meat consumption. Recently reported foodborne outbreaks are described below.

- 1) In Hyogo Prefecture, four of eight members from five families who consumed frozen raw deer meat became ill in April 2003; HEV-IgM antibody and HEV genes were detected from acute-phase serum. The nucleotide sequences of HEV G3 detected in leftover wild deer meat were nearly identical to those from the cases (see p. 264 of this issue).
- 2) In Fukuoka Prefecture, one of 11 persons who ate wild boar meat developed disease in March 2005, with HEV G3 genetic sequences from serum of cases matching those detected in leftover wild boar meat (see p. 265 of this issue).
- 3) In Hokkaido, a patient developed illness in September 2004 and subsequently died of fulminant hepatitis the following month. Investigation and laboratory tests revealed that three of 14 family members and relatives who ate at a restaurant with the case, in addition one of nine individuals from a separate group that ate at the same restaurant, were confirmed to have been infected. Although food items were suspected as the source of the outbreak, no virus-contaminated food items could be implicated (see p. 266 of this issue). HEV G4 was detected in one case.
- 4) In Mie Prefecture, four sporadic cases were notified in late June 2005. Two strains of HEV G3 detected from three cases demonstrated high homology by phylogenetic analysis. Although consumption of undercooked meat was suspected as the cause, a common source of infection was not identified (see p. 267 of this issue).

HEV infections among animals (see p. 269 of this issue): HEV infection in pigs has been found at high frequencies in both developing and developed countries. In Japan, HEV genes have been detected in significant proportions from serum and feces of pigs 2-3 months of age. In addition, it is known that HEV is widely distributed among wild boars throughout the country. In contrast, while HEV has been detected in deer meat in Hyogo Prefecture, investigations have revealed no other HEV genetically-positive deer, with very few antibody-positive deer, in other prefectures.

Prevention of HEV infection: Given the fact that it has become evident that recent cases of HEV infection have been due to consumption of raw animal liver and meat, the Ministry of Health, Labour and Welfare has published a "Case study of hepatitis E virus infection through consumption of meat (hepatitis E Q&A)" on its homepage to promote awareness of HEV (Notice by the Inspection and Safety Division, Department of Food Safety, Pharmaceutical and Food Safety Bureau, November 29, 2004: http://www.mhlw.go.jp/topics/syokuchu/kanren/kanshi/041129-1.html). It is important to inform hunters, meat handlers and consumers to avoid eating raw meat or organs of pigs or other wild animals, and to consume these food items only after thorough cooking.

Furthermore, similar to the prevention of hepatitis A, it is important to pay attention to drinking water sources and to avoid eating undercooked food when traveling to endemic areas. Vaccines for hepatitis E are currently under development.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases

## <u>IASR</u>

#### Vol. 26 No. 11 November 2005 Infectious Agents Surveillance Report

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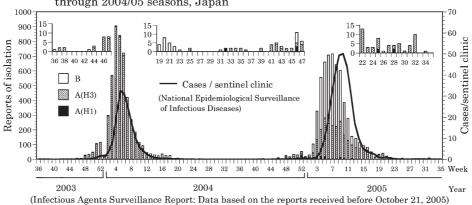
National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Analysis of influenza virus isolates in 2004/05 season in Japan Estimation of the excess mortality during 2004/05 influenza- epidemic season in Japan	
Influenza encephalopathy cases during 2003/04 season in Japan	
A summary of telephone consultations of citizens for influenza	
during 2004/05 season	296
Isolation of influenza virus types AH3 and B from a mixed	
infection case, March 2005-Yamaguchi	297
Outbreaks of low pathogenic avian influenza type AH5N2	
occurring on chicken farms, June 2005-Ibaraki	298
Estimated demand for influenza vaccine in 2005/06 season in	
Japan-MHLW	300
Influenza control measures in 2005/06 season in Japan-MHLW	301
Isolation of influenza virus type AH3 from a suspected case of	
encephalitis during the non-epidemic period, August 2005	
-Nagoya City	302

Isolation of influenza virus type AH3 from two cases returning from Thailand, August-September 2005–Kobe City	303
Isolation of influenza virus type AH3 in early 2005/06 season,	202
September 2005–Mie	505
A local epidemic of meningitis due to group A coxsackievirus 9,	
July-August 2005–Akita	304
Outbreaks of norovirus infection during non-epidemic period,	
July-August 2005-Sakai City	305
A case of Lyme disease due to a Borrelia valaisiana-related	
species infected abroad, June 2005	306
Detection of Echinococcus multilocularis eggs from dog feces,	
June 2005–Saitama	307
An outbreak of EHEC O26 infection at a nursery school, June-	
August 2005-Sapporo City	308
AIDS and HIV infections in Japan, July-September 2005	

#### <THE TOPIC OF THIS MONTH> 2004/05 influenza season, Japan

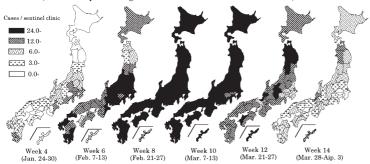
Figure 1. Weekly cases of influenza and isolation of influenza viruses from 2003/04 through 2004/05 seasons, Japan



During the 2004/05 season (September 2004-August 2005), approximately 1,500,000 cases of influenza were reported by sentinel clinics throughout Japan, the largest epidemic in the past 11 seasons, with an estimated total of approximately 17,700,000 cases occurring nationwide. The epidemic was a mixture of influenza B, AH3, and AH1 viruses; the majority was influenza B viruses, most belonging to the Yamagata lineage, a characteristic only observed in Japan.

Incidence of influenza: Under the National Epidemiological Surveillance of Infectious Diseases, clinically diagnosed influenza cases have been reported weekly by approximately 5,000 influenza sentinel clinics nationwide (3,000 - pediatric, 2,000 - internal medicine). Compared to the previous 10 seasons, the peak number of cases per sentinel per week in the 2004/05 season was the third largest after the 1994/95 and 1997/98 seasons (see http://idsc.nih.go.jp/idwr/kanja/weeklygraph/01flu.html). However, because the epidemic period was prolonged, the total number of cases per sentinel during 2004/05 season was 321.5, the largest figure in the past 11 seasons. In 2005, the rise in weekly case counts occurred later than usual, with nationwide activity increasing rapidly after sentinel reporting exceeded 1.0 during week 3. Activity peaked during week 9, then rapidly decreased to less than 1.0 per sentinel during week 19 (Fig. 1). At the prefectural/district level (Fig. 2), early increases in sentinel reporting were seen in the Kanto, Tokai and Hokuriku districts, while late increases were observed in the Hokkaido and Tohoku districts. Although the number of cases per sentinel decreased to less than 0.1 after the nationwide epidemic ended, during weeks 27-30, cases per sentinel exceeded 0.1 for the first time since 1990, reflecting the regional epidemic seen in Okinawa Prefecture (see

Figure 2. Incidence of influenza by prefecture from 4th through 14th weeks of 2005, Japan (National Epidemiological Surveillance of Infectious Diseases)



IASR 26:243-244, 2005). By the national reporting for all cases of "acute encephalitis" initiated in November 2003, 51 cases of influenza encephalopathy were reported during the 2004/05 season (see p. 295 of this issue).

Excess mortality due to influenza: Excess mortality due to influenza during the 2004/05 season, based on the total number of deaths in Japan, was estimated at 15,100 during February-April 2005 (see p. 293 of this issue).

Isolation of influenza viruses: During the 2004/05 season, prefectural and municipal public health institutes (PHIs) nationwide reported a total of 3,348 influenza B virus isolates, 2,513 influenza AH3 isolates, and 184 influenza AH1 isolates (reports as of October 21, 2005, Table 1).

Table 1. Isolation of influenza viruses in seasons 1997/98-2004/05

Subtype	Isolates from specimens collected during September through August next year								
Subtype	1997/98 199			1999/2000 2000/01		2002/03	2003/04	2004/05	
AH1	16	17	4,462 (23)	1,866 ( 25)	3,268 ( 14)	1	5	184	
AH3	6,111 ( 6)	5,153 (34)	2,711 (11)	806 (5)	3,108 ( 21)	5,002 ( 31)	4,739 ( 47)	2,513 ( 32)	
В	146	4,242 ( 5)	10	2,311 ( 107)	1,905 ( 5)	2,567 ( 20)	291 ( 2)	3,348 ( 39)	
A (H subtype unknown)	-	-	-	-	1	1	-	-	
C	2	-	6 (4)	-	10 ( 1)	-	28 (4)	3	
Total	6,275 ( 6)	9,412 ( 39)	7,189 (38)	4,983 ( 137)	8,292 ( 41)	7,571 ( 51)	5,063 ( 53)	6,048 ( 71)	

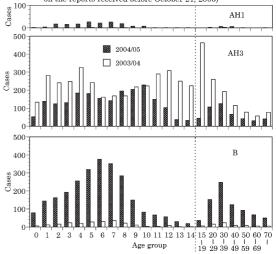
( ):Detection by PCR only, or PCR and antigen detection, not included in the total.

(Infectious Agents Surveillance Report: Data based on the reports received before October 21, 2005)

Influenza AH3 viruses were initially isolated in Aichi and Osaka Prefectures during weeks 36 and 39, of 2004, respectively (see IASR 25:290-291, 2004), and after continuously being isolated in small numbers in many districts, increased sharply during weeks 3-5 in 2005 (Fig. 1). Although the number of isolates decreased after week 6, influenza AH3 viruses were continuously isolated without interruption in Okinawa and other prefectures during the summer. In Nara Prefecture, an outbreak was reported in a facility during July-August (see IASR 26:244-245, 2005). Influenza B viruses were isolated in Yamagata Prefecture during week 42 and in Ibaraki and Hyogo Prefectures during week 46, and increased from week 3 of 2005 simultaneously with influenza AH3 virus. Activity peaked late during week 7 and continued until week 20 (Fig. 1). contrast, although influenza AH1 virus was rarely isolated during the 2002/03 (1 case) and 2003/04 (5 cases) seasons, it was reported in Fukushima and Okayama Prefectures during week 46 of 2004, and continuously isolated from week 48 of 2004 until week 13 of 2005. Influenza AH1 viruses were subsequently isolated during weeks 17, 18, and 19 (1 case each) and weeks 25 and 28 (2 cases each) in different

Influenza AH3 viruses were frequently isolated from cases 12 years of age or younger, while infrequently isolated from those 13 years or older. In contrast, influenza B viruses were isolated with greatest frequency in children 6 years of age among the pediatric population, and individuals in their 30s among adults. Influenza AH1 viruses were mainly isolated from children 2-10 years of age (Fig. 3).

Figure 3. Age distribution of cases with isolation of influenza virus in 2003/04 and 2004/05 seasons, Japan (Infectious Agents Surveillance Report: Data based on the reports received before October 21, 2005)



Antigenic characteristics of 2004/05 isolates and the vaccine strains for 2005/06 season: The antigenicity of influenza AH1 virus was similar to that of A/New Caledonia/20/99, the vaccine strain for the 2004/05 season. Of the influenza AH3 viruses, A/Fujian/411/2002-like strain (the representative strain being A/Wyoming/3/2003, a component of the 2004/05 vaccine), the primary circulating strain from the previous season, was frequently isolated during the first half of the season, while A/California/7/2004-like strains constituted the majority of isolates during the latter half of the season. Of the influenza B viruses, 99% was the Yamagata lineage, with most resembling the B/Shanghai/361/2002 strain, a component of the 2004/05 vaccine (see p. 289 of this issue).

Vaccine strains for the 2005/06 season are as follows: A/New York/55/2004 (influenza AH3 virus), an A/California/7/2004-like strain which replaces A/Wyoming/3/2003; A/New Caledonia/20/99 (influenza AH1 virus); and B/Shanghai/361/2002 (influenza B virus), which belongs to the Yamagata lineage, were continuously selected (see IASR 26:270-272, 2005).

Production of influenza vaccine and influenza vaccine coverage among the elderly: For the 2004/05 season, 20,740,000 vaccine doses were produced and 16,430,000 doses used. The demand for the 2005/06 season has been estimated at approximately 21,500,000 doses (see p. 300 of this issue). The vaccine coverage rate among the elderly (primarily those 65 years of age or older), in compliance with the Preventive Vaccination Law, was 47% for the 2004/05 season (Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

Avian influenza outbreaks: In late June 2005, outbreaks due to low pathogenic A/H5N2 virus occurred among birds in Ibaraki (see p. 298 of this issue) and Saitama Prefectures. Approximately 2,000,000 domestic fowl either died of infection or were slaughtered. No cases of apparent human A/H5N2 infection have been identified in Japan or other countries.

Preparedness for the next influenza pandemic: WHO has issued a global influenza pandemic preparedness plan (see http://www.who.int/csr/resources/publications/influenza/WHO\_CDS\_CSR\_GIP\_2005\_5/en/). The Ministry of Health, Labour, and Welfare has also stepped up pandemic preparedness efforts in Japan by establishing a national taskforce for influenza preparedness planning on October 28, 2005, and is in the process of developing a national influenza action plan.

Because pathogen diagnosis is important in differentiating severe acute respiratory syndrome from influenza, laboratory reports of influenza virus detection from overseas travelers during non-epidemic periods have been increasing (see IASR 24:281-282, 2003 & 25:278-279, 2004). During non-epidemic periods in 2004/05, influenza AH3 virus was isolated from returning travelers from Vietnam (see IASR 26:222, 2005), China (see IASR 26:243, 2005), and Thailand (see p. 303 of this issue) suspected of contracting avian influenza. On the other hand, isolation of influenza AH3 (see p. 302 of this issue) and AH1 viruses from cases with no history of foreign travel received attention during non-epidemic periods in the latter half of the 2004/05 season. The importance of year-round influenza surveillance has become much clearer, while improvements in laboratory testing systems at public health institutes, as well as cooperation from health care providers with specimen collection, are both critically needed.

at public health institutes, as well as cooperation from health care providers with specimen collection, are both critically needed.

Preliminary reports for 2005/06 season: Influenza AH3 virus was isolated in the following prefectures or cities: Mie Prefecture (weeks 36 and 37, see p. 303 of this issue), Nagasaki Prefecture (week 37, primary school outbreak), Kobe City (week 39, a returning traveler from Thailand, see p. 303 of this issue), Okinawa Prefecture (week 42, junior high school outbreak), and Kobe City (week 43). In addition, influenza A/H1N1 was detected by PCR in Tokyo (week 36, primary school outbreak).

On November 7, designated as kickoff day, efforts have begun toward developing an integrated strategy against influenza for this upcoming season (see p. 301 of this issue).

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

#### Vol. 26 No. 12 December 2005 Infectious Agents Surveillance Report

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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

Detection of norovirus genogroup(G) II/4 variants in Japan, prevailing in Europe and US since 2002325	Two
Genetic variation of norovirus GII/4 detected in recent years—Chiba. 327	Two
Genetic analysis of noroviruses detected from sporadic and outbreak	(
cases of gastroenteritis, October 2003-September 2005-Ehime 327	-
Molecular epidemiology of noroviruses, January 2003-March 2005	An
-Kumamoto, Saga and Oita	е
An outbreak of norovirus infection caused by well water, March 2003	An
-Niigata	c
Incidence of outbreaks of norovirus infection in elderly-care facilities	Isol
during 2000/01-2004/05 season-Hokkaido	PF
Prevention and control of norovirus infection in elderly-care facilities	a
-the Health and Welfare Bureau for the Elderly, MHLW332	Two
Development of a rapid diagnostic ELISA kit for norovirus infection. 334	b
Detection of noroviruses from domestic oysters for consuming raw	Sal
during 2001/02-2004/05 season	F
Detection and genotyping of noroviruses from imported shellfish,	An o
June 2004-February 2005	C

Two outbreaks of sapovirus gastroenteritis, May-June 2005	
-Miyazaki33	8
Two outbreaks of sapovirus gastroenteritis and an outbreak of group	
C rotavirus gastroenteritis at primary schools, June 2005	
-Kanagawa33	9
An outbreak of group C rotavirus gastroenteritis during a norovirus	
epidemic, May 2005–Osaka34	0
An outbreak of norovirus food poisoning presumably caused by	
catered "sushi", October 2005-Shiga34	0
Isolation of influenza virus type A/H3N2, October 2005-Hiroshima34	1
PFGE analysis of Salmonella Braenderup isolates suspected of	
a diffuse outbreak, August-November 2005–9 PHIs and NIID34	1
Two child cases with severe Salmonella infection presumably caused	
by red-eared sliders, March-October 2005-Funabashi City34	2
Salmonella IV (O45:g,z51:-) isolated from an infant with diarrhea	
presumably infected from an iguana, February 2004–Chiba34	4
An outbreak of EHEC O157 infection at a swimming school for young	
children, July 2005–Sapporo City34	5

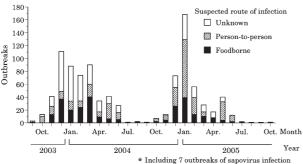
### <THE TOPIC OF THIS MONTH> Outbreaks of norovirus infection, September 2003-October 2005

Norovirus (NV) is the name of a genus of Caliciviridae proposed by the International Committee on Taxonomy of Viruses in 2002. It used to be called small round structured virus (SRSV) or Norwalk-like virus. NV is an RNA virus, being grouped into genogroup (G) I and II. GI has at least 14 and GII 17 different genotypes. A large amount of NV is excreted in stool and vomit and fecal excretion continues for about a week after disappearance of symptoms. It is transmitted by person-to-person infection directly or through fingers and also food poisoning is caused by contamination of food. The major symptoms are diarrhea, vomiting, nausea, and abdominal pain, which last usually for 1-3 days. For aged persons and infants with strong dehydration, such symptomatic treatment as transfusion is applied. Care must be taken for suffocation due to deglutition of vomit.

1. The Statistics of Food Poisoning in Japan: According to the Statistics of Food Poisoning in Japan in 2004, NV food poisoning outbreaks counted at 277, which was the second largest figure by etiological agent after *Campyrobacter* food poisoning. Cases of NV food poisoning numbered 12,537 accounting for 45% of all food poisoning cases. Since 2001, when bacterial food poisoning decreased, it has been standing the first rank (see IASR 24:309-310, 2003 and http://www.mhlw.go.jp/topics/syokuchu/index.html).

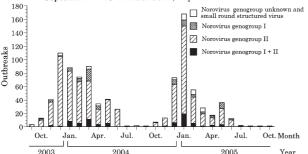
2. Reports of NV detection from outbreaks: Aside from the Statistics of Food Poisoning in Japan, Outbreak Reports from Infectious Agent Surveillance are made by prefectural and municipal public health institutes (PHIs) to the Infectious Disease Surveillance Center, National Institute of Infectious Diseases. In these reports, outbreaks due to person-to-person or

Figure 1. Monthly outbreaks of norovirus infection\* by route of infection, September 2003-October 2005, Japan



\* Including 7 outbreaks of sapovirus infection (Infectious Agents Surveillance Report: Data based on the reports received before October 27, 2005)

Figure 2. Monthly outbreaks of norovirus infection by genogroup, September 2003-October 2005, Japan



(Infectious Agents Surveillance Report: Data based on the reports received before October 27, 2005)

unknown route of transmission of the agent are included. During December 2004-January 2005, outbreaks suspected of person-to-person infection increased suddenly (Fig. 1). During September 2003-October 2005, the virus was detected from cases of food poisoning, gastroenteritis, and food handlers in 959 outbreaks, in 934 of which NV was detected by PCR (GII 744, GI 76 and GI+GII 73 outbreaks) (Table 1). In addition, sapovirus (SV) in 7 outbreaks and rotavirus (RV) in 14 outbreaks were solely detected and in some outbreaks multiple viruses were detected. NV GII-detected outbreaks

Table 1. Outbreaks of viral gastroenteritis and food poisoning reported by public health institutes in Japan. September 2003-October 2005

in Japan, September 2003-October 2005					
Virus detected	Outbreaks				
Norovirus genogroup I (Noro GI)	72				
Norovirus genogroup II (Noro GII)	709				
Norovirus group unknown (Noro NT)	41				
Sapovirus (Sapo)	7				
Small round structured virus (SRSV)	4				
Rotavirus group A (Rota A)	10				
Rotavirus group C	3				
Rotavirus group unknown	1				
Subtotal (Single virus detected)	847				
Noro GI+SRSV	3				
Noro GII+SRSV	15				
Noro GII +Noro NT	19				
Noro GI+Noro GII	69				
Noro GI+NoroGII+SRSV	3				
Noro GI+Sapo	. 1				
Noro GII+Rota A NT	1				
Noro GI+Noro GII+Rota A NT	1				
Subtotal (Two or more virus detected)	112				
Total	959				

(Infectious Agents Surveillance Report: Data based on the reports received before October 27, 2005)

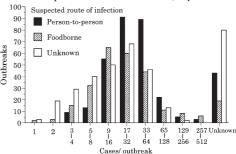
started to increase earlier in the 2003/04 season from November, while in 2004/05, it increased markedly during December 2004-January 2005 and again in May (Fig. 2).

**Scales of outbreaks:** Numbers of cases per outbreak are tabulated for 803 outbreaks in which case numbers were reported (Fig. 3). In outbreaks suspected of person-to-person infection, 17-32 cases were the most frequently involved and in outbreaks suspected of foodborne infection, 9-16 cases.

Places of infection or consumption of incriminated food: The suspected places of outbreaks being suspected of person-to-person infection were homes for the aged (including elderly care facilities), primary schools, hospitals, nursery schools, and welfare facilities in this order of frequency (see Table 2 on p. 325). In 1/3 of the outbreaks occurring at homes for the aged, the route of infection was unknown. Outbreaks with a large number of cases are shown in Table 3. GII was detected from cases of all outbreaks.

**Incriminated foodstuffs:** Of 265 outbreaks suspected of foodborne, incriminated food was recorded in 74 (oyster in 30 and other shellfish in 6 outbreaks). Outbreaks in which NV was detected by PCR from food were only 16 (oyster in 6, well water in 2 outbreaks, and shijimi clams in soy

Figure 3. Outbreak scale of norovirus infection, September 2003-October 2005, Japan



(Infectious Agents Surveillance Report: Data based on the reports received before October 27, 2005)

sauce, tuna fish, and salad etc.); GII in 11, GI in 1 and GI+GII in 2 outbreaks. Methods for detection of NV from incriminated food materials are urgently needed. Besides, other outbreaks due to well water have occurred (see IASR 26:150-151, 2005 and p. 330 of this issue).

- 3. NV detection from children with gastroenteritis: Reports of NV detection from children with gastroenteritis increase from every year-end and outbreaks also increase simultaneously. In 2004 and 2005, reports of NV detection increased in May and June; in 2005 reports came out even in July and August (see Table 4 on p. 325 and p. 327 of this issue). In etiological survey for infectious gastroenteritis, the possible NV infection regardless of season must be kept in mind.
- 4. NV GII/4 prevailing during 2004/05 season: In Europe and US, outbreaks at elderly care facilities and schools occur frequently with NV GII/4 detected in 2002 with mutation in the polymerase-coding region of Lordsdale/93/UK type (2002 type) and 2004 type with further mutation of 2002 type. It has been confirmed that these 2002 and 2004 types were present simultaneously in Japan (see p. 325 of this issue).

Most outbreaks of NV infection occurring at elderly care facilities in Japan during the 2004/05 season were caused by GII/4 NV, as was the case in Europe and US. By analysis of the polymerase-coding region, the principally prevailing viruses were found to be 2004 type and somewhat dissimilar SaitamaU1/97-like virus (see p. 325-327&331 of this issue). In this GII/4 NV, mutation was seen not only in the polymerase-cording region but also in the capsid-coding region (see p. 325-327&331 of this issue).

There used to be few outbreaks due to NV GI, but in the 2004/05 season outbreaks due to GI/3, 8 (see p. 329 of this issue) in the Kyushu district and another due to GI/3 in Ehime Prefecture (see p. 327 of this issue) were reported and future trend seems noteworthy.

5. Conclusion: Correlation between increase in NV detection from domestic oysters and imported shellfish and increase in outbreaks of food poisoning has been seen and such has also been seen in the genotype of detected NV from shellfish and that detected in cases (see p. 335-337 of this issue). It is necessary to keep paying attention to thorough cooking of shellfish (1 min at 85°C)

Since reports of outbreaks of NV infection at elderly care facilities increased suddenly during December 2004-January 2005, Ministry of Health, Labour and Welfare (MHLW) carried out investigation into the actual conditions and compiled the infection control manual in elderly care facilities, requesting report to health centers in compliance with the notice for a requirement on outbreak report in welfare facilities (notice by the Health and Welfare Bureau for the Elderly, MHLW on January 10, 2005) (see p. 332 of this issue).

When NV is not detected in outbreaks, tests for SV and RV are necessary (see p. 338-340 of this issue). Since outbreaks due to multiple viruses have occasionally been seen, usefulness of electron microscopy which allows simultaneous examination of these viruses have been stressed (see p.340 of this issue). To prepare for NV epidemics for not only winter but also other seasons, attention must be paid to infectious agent surveillance data and regular observation for health and strict enforcement of hand washing (see http://www.mhlw.go.jp/topics/syokuchu/kanren/yobou/040204-1.html).

Table 3. Outbreaks of norovirus infection, September 2003-October 2005

No. Period	Suspected route of infection	Place of infection	Suspected	Congumora	Casas*	Genogroup	
No. 1 eriod	(increminated foodstuffs)	(place of preparing food)	cause	Consumers	Cases		
1 Dec. 1-5, 2004	Foodborne (Catered meal)	Business places (Caterer)	Cross	1,275	498	GII	(16 / 26)**
			contamination				
2 May 11-23, 2005	Person-to-person infection	Primary school	Unknown	•••	386	GII	(6/14)
3 Mar. 29-Apr. 1, 2004	Foodborne (Unknown)	Restaurant	Unknown	551	372	GI+GII	(1/9)
4 Jan. 23 <sup>-</sup> , 2004	Foodborne (Unknown)	Business places (Caterer)	Unknown	Unknown	359	GII	(35 / 61)
5 Jan. 5- , 2005	Foodborne (Unknown)	Unknown	Unknown	Unknown	291	GII	(87 / 147)
6 Oct. 24-29, 2003	Person-to-person infection	Kindergarten	Unknown	•••	288	GII	(49 / 59)
7 Mar 1-8, 2004	Person-to-person infection	Primary school	Unknown	•••	282	GII	(5/11)
8 Dec. 19-28, 2004	Foodborne (Unknown)	Hotel	Under	461	260	GII	(22 / 59)
			investigation				
9 Feb. 12-16, 2004	Foodborne (Unknown)	Hotel	Undercooking	1,340	259	GII	(52 / 77)

\*Outbreaks including more than 257 cases, \*\*Positive cases/Examined, ... No information was entered because person-to-person infection was suspected. (Infectious Agents Surveillance Report: Data based on the reports received before October 27, 2005)

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, quarantine stations, and the Research Group for Infectious Enteric Diseases, Japan, have provided the above data.

#### Infectious Disease Surveillance Center, National Institute of Infectious Diseases