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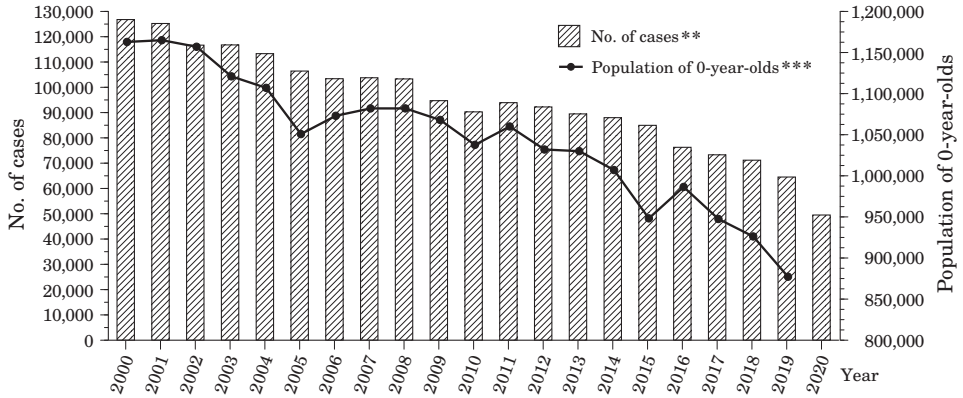
National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare



## <THE TOPIC OF THIS MONTH>
## Exanthema subitum 2000-2020

Figure 1. Yearly number of reported exanthema subitum cases, week 1 of 2000 to week 40 of 2020,* Japan




* as at week 40 of 2020
** National Epidemiological Surveillance of Infectious Diseases/Pediatric Sentinel Sites: as at 7 October 2020
*** Vital Statistics of Japan

Exanthema subitum (ES) is a febrile exanthematous disease in infancy with a generally good prognosis, characterized by a fever that lasts about three days and exanthema with fever reduction. In the acute phase, loose stool/diarrhea, bulging anterior fontanel, eyelid edema, and occipital lymphadenopathy are observed. Mottled exanthema on both sides of the uvula, so-called Nagayama's spots, may appear in the early phase of the disease.

The cause of ES had long been unknown, but in 1988, it was reported for the first time that ES was caused by infection with human herpesvirus 6 (HHV-6). Later, in 1994, human herpesvirus 7 (HHV-7) was also reported to cause ES. ES is designated as a category 5 notifiable disease according to the Infectious Diseases Control Law, and the number of case-patients, by age group, is reported weekly from approximately 3,000 pediatric sentinel sites (Notification criteria: https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-22.html) via the National Epidemiological Surveillance of Infectious Diseases (NESID) system. The epidemiologic situation of ES was summarized based on the information from pediatric sentinel sites. This is the first time ES has been included in the Infectious Agents Surveillance Report (IASR).

**Epidemiological characteristics of ES in Japan**: With the decrease in the population of 0-year-olds, the number of ES cases reported has been decreasing annually (Fig. 1). In 2000, 126,785 cases were reported from pediatric sentinel sites, but the number decreased to 64,519 (provisional data) in 2019. Furthermore, changes were observed in the age distribution, and the percentage of children under 1 year of age decreased over the years, from 77.1% in 2000 to 31.3% in 2020 (Fig. 2).

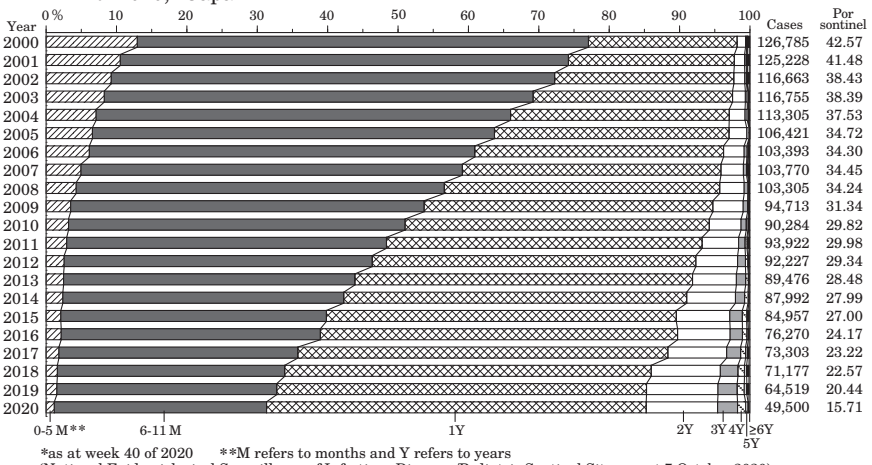
Although there is no apparent trend in the number of ES reports, it is slightly higher in summer than in winter (https://www.niid.go.jp/niid/ja/10/2096-weeklygraph/1651-08subit.html). Since ES is reported based on characteristic clinical symptoms, the causative pathogen is not investigated in many cases. It is possible that the increase in the number of patients in the summer is due to cases of ES-like febrile exanthematous symptoms caused by viruses other than HHV-6 or HHV-7, such as enterovirus infection. ES is regarded as an indicator that pediatric sentinel site reporting is operating in a stable manner because yearly fluctuations in the number of notifications is small. With the coronavirus disease 2019 (COVID-19) epidemic in 2020, reports of other infectious diseases from pediatric sentinel sites decreased, but reports of ES remained constant (https://www.niid.go.jp/niid/images/idsc/idwr/IDWR2020/idwr2020-44.pdf), suggesting that the accuracy of the pediatric sentinel infectious disease surveillance system was maintained at a certain level.

**HHV-6 and HHV-7**: HHV-6 has conventionally been classified into two variants, HHV-6A and HHV-6B, but at the 2012 International Committee on Taxonomy of Viruses, they were reclassified as different species. HHV-6A, HHV-6B, and HHV-7 were all classified into the *Bethaherpesvirus* subfamily in the *Herpesviridae* family; once any of these viruses infect a human, they establish latency in the infected for a lifetime. The age of children infected with HHV-6B is generally lower than that of children infected with HHV-7. If an infant has two episodes of ES, the second ES is often caused by HHV-7. While HHV-6B and HHV-7 have been reported as the cause of ES, the association between HHV-6A and ES remains unclear (see p.214 of this issue). HHV-6B and HHV-7 are thought to be transmitted mainly through saliva. HHV-6B infects T cells through the binding of a membrane protein called glycoprotein H (gH)/gL/gQ1/gQ2 complex expressed on the surface of virions to CD134 (OX40) expressed on the surface of activated T cells (see

(Continued on page 212′)

(THE TOPIC OF THIS MONTH-Continued)

Figure 2. Age distribution of reported exanthema subitum cases, week 1 of 2000 to week 40 of 2020,* Japan




*as at week 40 of 2020 **M refers to months and Y refers to years
(National Epidemiological Surveillance of Infectious Diseases/Pediatric Sentinel Sites: as at 7 October 2020)

Table. Pathogens detected by specimen type in exanthema subitum cases, 2000-2020

| Pathogen detections | No. of detections | (%) | Specimen type* | | | | Median Age (Y) |
|---|---|---|---|---|---|---|---|
| | | | respiratory specimens** | blood | cerebrospinal fluid | other | |
| Human herpes virus 6 (HHV 6) | 853 | 53.3 | 735 | 97 | 17 | 22 | 1 |
| Human herpes virus 7 (HHV 7) | 122 | 7.6 | 108 | 14 | 0 | 2 | 1 |
| Rhinovirus | 92 | 5.8 | 89 | 0 | 0 | 5 | 1 |
| Cytomegalovirus (CMV) | 48 | 3.0 | 47 | 1 | 0 | 0 | 1 |
| Enterovirus - not typed | 38 | 2.4 | 38 | 0 | 0 | 0 | 1 |
| Adenovirus 2 | 33 | 2.1 | 29 | 0 | 0 | 6 | 1 |
| Coxsackievirus A9 | 33 | 2.1 | 33 | 0 | 0 | 1 | 1.5 |
| Adenovirus - not typed | 29 | 1.8 | 26 | 1 | 0 | 2 | 1 |
| Respiratory syncytial virus (RSV) | 21 | 1.3 | 21 | 0 | 0 | 0 | 1 |
| Epstein-Barr virus (EBV) | 19 | 1.2 | 17 | 1 | 0 | 1 | 1 |
| Coxsackievirus A6 | 19 | 1.2 | 17 | 1 | 0 | 2 | 1 |
| Echovirus 9 | 18 | 1.1 | 16 | 0 | 0 | 2 | 1 |
| Echovirus 18 | 16 | 1.0 | 16 | 0 | 0 | 0 | 1 |
| Total | 1,599 | − | 1,192 | 115 | 17 | 43 | 1 |

Pathogens with fewer than 15 detections and negative results are not listed.
*A case may have had the same pathogen detected from more than one specimen type
**sputum/tracheal aspirate or throat swab
(Infectious Agents Surveillance System: as at 24 September 2020)

p.216 of this issue). HHV-6A or HHV-6B is integrated into the genome in some humans (chromosomally integrated HHV-6; ciHHV-6), which can be dominantly inherited from parent to offspring (see p.220 of this issue). A disease associated with HHV-6B other than ES is drug-induced hypersensitivity syndrome (DIHS), one of the severe drug eruptions with multiple organ dysfunction. With DIHS, HHV-6B may be reactivated 2-3 weeks after the disease onset (see p.218 of this issue). In addition, among patients who have undergone hematopoietic stem cell transplantation, it has been reported that HHV-6B that had remained in latent form may be reactivated, leading to encephalitis (see p.213 of this issue).

**Laboratory test for ES**: ES generally has a good prognosis, and HHV-6B and HHV-7 viral gene amplification tests and serology tests for these viruses are not covered by the national health insurance system. Once infected with HHV-6B or HHV-7, the viruses are continuously excreted in the saliva; thus, the presence of viral genes in saliva or pharyngeal swab specimens cannot be used for the diagnosis of ES. Virological diagnosis of ES caused by HHV-6B or HHV-7 requires confirmation of virus isolation from peripheral blood mononuclear cells, detection of viral genes in plasma/serum free of cellular components, or a significant increase in the antibody titers against HHV-6B or HHV-7 between paired sera collected in the acute and convalescent phases.

Virological tests are performed at some public health institutes (PHIs) for patients who are clinically suspected of having ES (see p.215 of this issue). Based on reports from the PHIs to the Infectious Agents Surveillance System, the pathogens detected in patients clinically diagnosed as ES, along with the specimen type, are presented (Table). HHV-6 was the most frequently detected pathogen, followed by HHV-7. In addition, pathogens, such as enterovirus, that cause so-called viral exanthem have also been detected. This indicates that some patients diagnosed with ES include ES-like patients caused by pathogens other than HHV-6B or HHV-7.

**Future perspectives**: ES is often accompanied by febrile seizures, and in rare cases, has been reported to be associated with encephalitis/encephalopathy, thrombocytopenic purpura, and fulminant hepatitis. It is necessary to clarify the epidemiological characteristics of ES patients in Japan, and thereafter, to consider the testing system for HHV-6B and HHV-7 and the need for future vaccine development, along with the approach to implementing vaccination.

*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 Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.*

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