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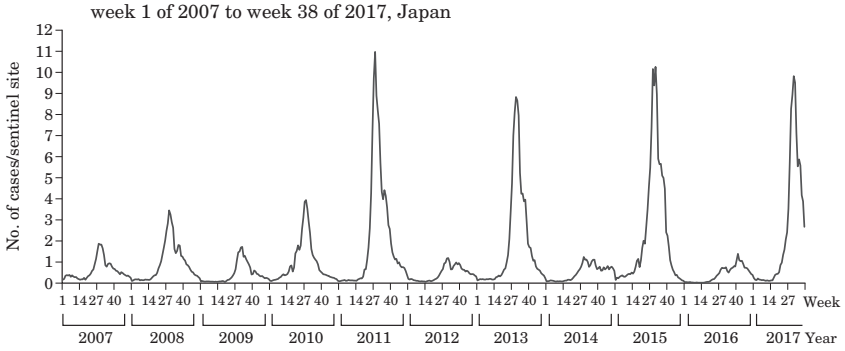
National Institute of Infectious Diseases and
Tuberculosis and Infectious Diseases
Control Division,
Ministry of Health, Labour and Welfare

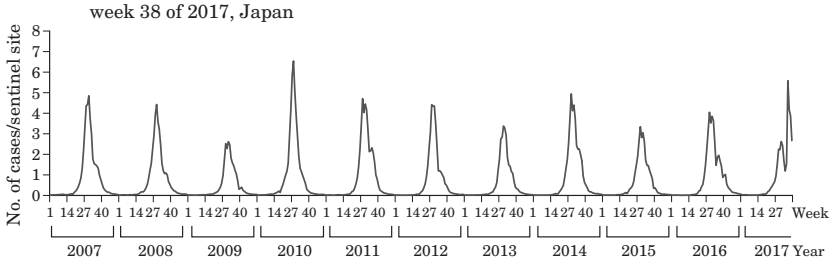
<THE TOPIC OF THIS MONTH>
Hand, foot, and mouth disease and herpangina, 2007 to September 2017 (week 38), Japan

Figure 1. Weekly number of hand, foot, and mouth disease notification per pediatric sentinel, week 1 of 2007 to week 38 of 2017, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of September 27, 2017)

Figure 2. Weekly number of herpangina notification per pediatric sentinel, week 1 of 2007 to week 38 of 2017, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of September 27, 2017)

Hand, foot, and mouth disease (HFMD) and herpangina are pediatric enteroviral diseases that often occur in the summer. Both are category V infectious diseases under the Infectious Diseases Control Law, notifiable based on clinical diagnosis from ~3,000 pediatric sentinel sites. Reporting requires the following clinical manifestations: "2-5mm-sized blisters appearing on the palm, plantar, dorsum of foot or oral mucosa" that "heal without crust formation" for HFMD, and "sudden onset of high fever" and "vesicular rash, ulcers or reddening of the uvula" for herpangina. Causative agents are mostly viruses belonging to *Enterovirus A*.

Trends in notifications of patients and detection of viruses: For both HFMD and herpangina, notifications of patient cases peaked in the summer. For HFMD, large and small epidemic years alternated yearly since 2011 (large epidemic years occurred in 2011, 2013, 2015 and 2017) (Fig. 1). For herpangina, the magnitude of annual fluctuations was smaller (Fig. 2).

Among the reported cases, both for HFMD and herpangina, 90% of the patients were under 5 years of age (Fig. 3 and 4 in p. 192, respectively). As both are monitored via pediatric sentinel sites, the frequency of disease occurrence among adults is unknown. Findings from HFMD surveillance abroad have similarly found that the annualized HFMD incidence among children 6 months-5 years far exceeded those of other age groups, with particularly low levels among those ≥15 years of age (Lancet Infect Dis 14: 308-318, 2014).

Annual trends in detection of *Enterovirus A* by prefectural and municipal public health institutes (PHIs) from 2007-2017 are shown in Fig. 5 in p. 193. From HFMD cases, coxsackievirus (CV) -A6, CV-A16 and enterovirus (EV) -A71 were detected; since 2011, CV-A6 was associated with large scale epidemics (Fig. 1 and 5). While EV-A71 was detected in relatively large numbers in 2010 and 2013, it has not been associated with large epidemics since 2014. From herpangina cases, the following were detected, in descending order of frequency: CV-A4, CV-A6, CV-A10, CV-A2, CV-A5 and CV-A8; the predominant type circulating was found to vary yearly (https://www.niid.go.jp/niid/ja/iasr-sp/510-graphs/4892-iasrgnatsu.html).

For past reports on HFMD and herpangina, please visit the following: HFMD (IASR 33: 55-56, 2012) and herpangina (IASR 26:

(Continued on page 192′)

(THE TOPIC OF THIS MONTH-Continued)

235-236, 2005).

Laboratory diagnosis: Laboratory diagnosis consists of virus isolation and virus genome detection using throat swab or stool specimens during the clinically symptomatic phase. Using multiple cell lines, such as RD cells and Vero cells, has been known to increase virus isolation efficiency for both HFMD and herpangina. As virus isolation efficiency was particularly low for herpangina cases, some PHIs have been conducting virus isolation using suckling mice (see pp. 200 & 202 of this issue).

Recently, for more rapid and simpler methods and to also overcome the low isolation efficiency in cultured cells, viral genome detection directly from clinical specimens has been increasing. For identification of enterovirus type, amplification of the partial sequences of the VP4-VP2 region and/or VP1 regions (e.g., CODEHOP RT-semi-nested PCR) has been used (see Laboratory Manual for HFMD and herpangina). For routine testing, amplification of the VP1 region, where there is high correlation with enterovirus serotypes, is preferable (IASR 30: 12-13, 2009). Since the amendment of the Infectious Diseases Control Law in 2014, quality control and quality assurance for enterovirus laboratory testing have been implemented (see p. 199 of this issue).

Figure 3. Age distribution of hand, foot, and mouth disease cases reported from pediatric sentinel sites, 2007-2016, Japan (National Epidemiological Surveillance of Infectious Diseases)

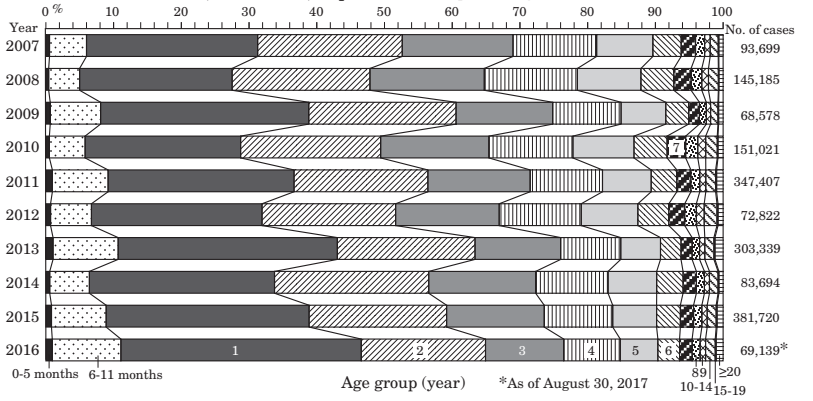
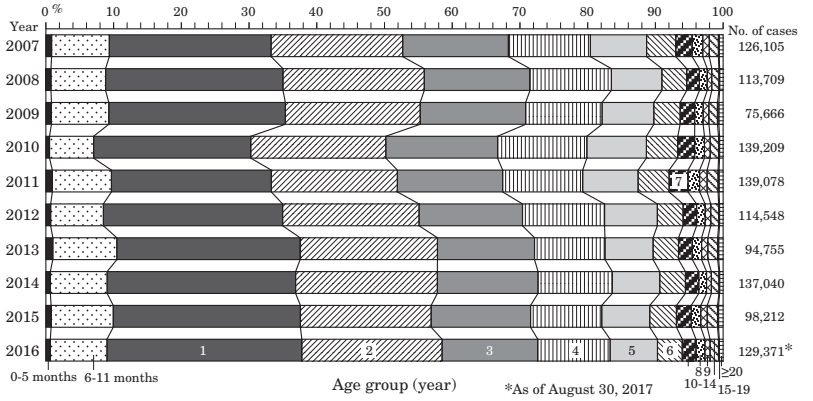


Figure 4. Age distribution of herpangina cases reported from pediatric sentinel sites, 2007-2016, Japan (National Epidemiological Surveillance of Infectious Diseases)



Characteristics of HFMD in recent years and central nervous system complications: Although CV-A6 had been detected mostly from herpangina patients, the virus became increasingly detected from HFMD patients since 2009 (IASR 33: 55-56, 2012), becoming the dominant strain isolated from HFMD patients in large epidemic years during 2011-2017 (Fig. 5 in p. 193) (see pp. 193, 195, 196 & 197 of this issue). HFMD due to CV-A6 has been characterized by atypical manifestations, such as frequently high fever (≥38˚C), extensive blisters in the femoral and gluteal regions and onychomadesis (see p. 198 of this issue). In recent years, atypical HFMD caused by CV-A6 has spread globally, including in Asia.

EV-A71 infection spread among infants in Malaysia, Taiwan, China, Vietnam, Cambodia and other countries in eastern Asia since the late 1990s; it caused complication of central nervous system (CNS) (such as encephalitis, brain stem encephalitis, and paralysis) with severe and often fatal outcomes (see p. 201 of this issue). Fatality has been high when the patients developed neurogenic pulmonary edema or cardiopulmonary failure. From 2008 to 2012, China reported about 7,200,000 HFMD cases; among them, 82,484 were severe and 2,457 were fatal (Lancet Infect Dis 14: 308-318, 2014). Most patients were under 5 years of age, and the fatality was highest among those aged 12-23 months. Ninety percent of the fatal cases were EV-A71 positive. In Japan, severe or fatal HFMD cases have been rare. However, sporadic occurrences have been reported, and during HFMD epidemics associated with EV-A71, CNS complications increased among infants. While CV-A6 is known to cause less CNS complications, as CV-A6 has also been isolated from encephalitis cases (see p. 195 of this issue), the association between CNS complications and enteroviruses other than EV-A71 warrant further investigation (IASR 37: 33-35, 2016).

Prevention and other measures: For both HFMD and herpangina, viral transmission is primarily through droplet or contact. Handwashing and appropriate disposal of body waste is therefore important for preventing spread of infection. Treatment for enterovirus infection is, as a rule, symptomatic. Notably, Asian countries that have experienced large scale epidemics involving cases of severe enterovirus infections have been developing vaccines for preventing disease and severe outcomes. In 2016, China introduced to the market the world's first inactivated EV-A71 vaccine (see p. 203 of this issue).

Concluding remarks: For patients suspected of CNS complications due to enterovirus infection, cerebrospinal fluid is suitable for laboratory diagnosis. However, compared to *Enterovirus B* which are important causes of aseptic meningitis, *Enterovirus A* have a lower detection rate from cerebrospinal fluid. Therefore, when infection of *Enterovirus A* is suspected, testing other samples such as throat swabs and fecal specimens is recommended. Continued laboratory surveillance of enteroviruses and feedback of such information are important.

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, and quarantine stations, have provided the above data.

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＜特集関連情報＞

手足口病およびヘルパンギーナ患者の発生動向とエンテロウイルス検出状況 ── 神奈川県

神奈川県における手足口病患者とヘルパンギーナ患者の発生動向およびエンテロウイルス検出状況について，2017年シーズンと過去9年間（2008～2016年）のデータの解析を行ったので報告する。

1．手足口病患者の発生動向およびウイルス検出状況

2017年の神奈川県域（横浜市，川崎市，相模原市を除く）における手足口病の週別患者報告数は，第24週（6/12～6/18）に定点当たり1.30人となり，第27週（7/3～7/9）に5.15人と警報レベル（一定点当たり5人）を超え，第31週（7/31～8/6）に11.04人とピークを迎えた。過去9年間と比較すると，2015年の12.74（第31週）に次いで大きな流行となっており，2011年以降，2年に1回，流行が起きている（次ページ図1a）。

神奈川県域の病原体定点医療機関から搬入された手足口病患者検体について，ウイルス分離検査（RD-A，A549，VeroおよびVeroE6細胞）およびエンテロウイルス[1-3]の核酸増幅検査を実施した。エンテロウイルス遺伝子が検出されなかった検体では，ヒトパレコウイルス（HPeV）[4]の核酸増幅検査を実施した。2017年は7月末までに81検体の検査依頼があり，現在までにコクサッキーウイルスA（CV-A）6型が55株，HPeV-3が1株，ライノウイルスが1株およびアデノウイルス2型が1株検出されている。このことから今シーズンの手足口病流行の主因ウイルスはCV-A6と考えられた。過去9年間では，流行の大きかった2011年，2013年はCV-A6の検出数が多かったが，2015年はCV-A6とCV-A16の検出数がほぼ同程度検出されており，混合流行により流行規模が拡大したものと推察された（次ページ図2a）。2011年以前は，CV-A16とエンテロウイルスA71（EV-A71）型の流行が主であったが，近年の手足口病の流行にはCV-A6が大きく係わっており，2017年以降もCV-A6の検出動向が注目される。

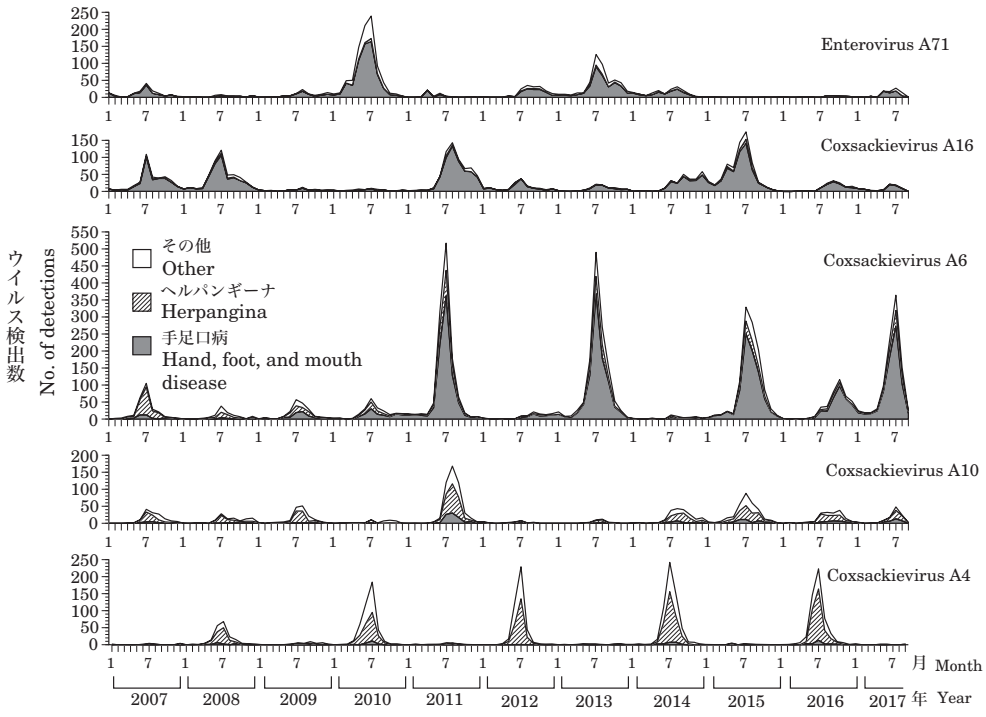
2．ヘルパンギーナ患者の発生動向およびウイルス検出状況

2017年のヘルパンギーナの週別患者報告数は，第28週（7/10～7/16）に定点当たり1.0人を超えたが，第31週（7/31～8/6）の2.24人をピークに減少傾向にあり，流行は例年に比べ小規模であった。過去9年間をみる

（特集つづき）（THE TOPIC OF THIS MONTH-Continued）

図5．エンテロウイルス A71型，コクサッキーウイルスA16型，A6型，A10型，A4型の月別臨床診断名別検出状況，2007年1月～2017年9月

Figure 5. Monthly number of *Enterovirus A* detected, based on reported clinical diagnosis, January 2007 to September 2017, Japan



（病原微生物検出情報：2017年10月3日現在報告数）
(Infectious Agents Surveillance Report: as of October 3, 2017)