



Scientific Committee on Enteric Infections and Foodborne Diseases

Update on Situation of Enterovirus Infection

Purpose

This paper provides an update on the situation of enterovirus (EV) infections, excluding polio and those enteroviruses that exclusively cause respiratory disease or conjunctivitis, and describes the public health actions for the prevention and control of the disease.

Background

2. Enteroviruses (EVs) are a genus of small, non-enveloped positive-sense single-stranded RNA viruses under the family *Picornaviridae*. They are classified into 12 species according to the molecular and antigenic properties of their viral capsid protein (VP1): enterovirus-A to H and EV-J. EVs have also previously been classified into four named groups: polioviruses (PV), coxsackieviruses A (CA), coxsackieviruses B (CB), and echoviruses (E), with subsequent newly described viruses being named with a system of consecutive numbers: EV68, EV69, EV70, EV71, etc. Both naming systems are commonly used and can be mapped with each other. For example, CA16 and EV71 belong to species EV-A; CA9 belongs to EV-B; PV1 to 3 belong to EV-C; and EV68 and EV70 belong to EV-D.

3. EV71 could be further genotyped through molecular analysis of VP1 and VP4 gene sequences.¹ Based on these, EV71 could be divided into three genotypes: A, B, and C. Genotypes B and C are each further divided into five subgenotypes: B1 to B5 and C1 to C5 respectively.^{2,3} Genotyping is important in exploring the phylogenetic relationships of EV71 circulating in different geographic locations or in different periods in the same location.



Clinical features

4. EVs may cause a range of clinical syndromes (Table 1).⁴⁻⁶

Table 1 Common syndromes caused by non-polio enteroviruses^{4,5,7-9}

Syndromes	Serotypes most often implicated
Hand, foot and mouth disease	CA16 & EV71 CA4, 5, 6, 9 & 10 CB265
Herpangina	CA2, 466, 8 & 10 Probably CB3
Aseptic meningitis / Encephalitis / Meningoencephalitis	EV71 CA2, 4, 6, 7 & 9 CB165 E4, 6, 7, 9, 11 & 16
Poliomyelitis-like paralysis	EV71 CA7 E4, 6 and 9
Myopericarditis	CA4 & 16 CB165 E9
Epidemic pleurodynia (Bornholm disease)	CB166
Acute haemorrhagic conjunctivitis	EV70 CA24 & CA24 variant
Respiratory disease	EV68 CA21 & 24 CB1 & 365 E4, 8, 9, 11 & 20

5. The most common syndrome caused by enteroviruses is hand, foot and mouth disease (HFMD), which is characterised by fever, sores in the mouth and a rash with blisters on hands, feet and also buttock. HFMD is caused by a few serotypes of enteroviruses, most frequently coxsackievirus A16 (CA16) and enterovirus 71 (EV71). Other viruses associated with the syndrome are CA4, 5, 6, 9, and 10 and coxsackievirus B (CB) 2 to 5.^{6,10} HFMD caused by different EV serotypes may have slightly different clinical presentations. For instance, CA6 has atypical presentation compared with other EVs, with more widespread rash, larger blisters and subsequent skin peeling and/or nail shedding.¹¹

6. Most EV infections, including HFMD are mild and resolve in seven to 10 days.¹² However, some EV infections may cause more serious diseases, such as aseptic meningitis, encephalitis, poliomyelitis-like paralysis and myocarditis. For example, studies have shown that CA6 infection may have more severe complications⁹, and EV71 infection in particular has been associated with large HFMD outbreaks with severe and fatal complications.¹²

7. Immunity to enterovirus infection is serotype-specific. Once a person has had an infection with a specific enterovirus, he or she will usually become immune to that particular virus for life. Yet, he or she is still susceptible to infection with other strains of enteroviruses. Infants, children, and adolescents are thus more prone to infection and illness from enteroviruses because in general they do not have immunity to them (except in infants less than six months of age with maternal-source antibodies).^{13,14}

Outbreak potential

8. EV is also known to cause outbreaks in child care centres, kindergartens and primary schools, resulting in significant absenteeism and economic loss.¹⁵ Outbreaks of HFMD occur every few years in different parts of the world, but in recent years these have occurred more often in Asia.¹² Countries/regions in Asia with outbreaks of HFMD documented over the past decade include: mainland China^{9,16-22}, Hong Kong²³, Taiwan²⁴⁻²⁷, Singapore^{28,29}, Republic of Korea^{30,31}, Thailand³², Vietnam³³, Cambodia³⁴ and Japan^{10,35-37}. In addition, the EV71 infection is of particular concern as it more likely associates with severe outcomes (like viral meningitis, encephalitis, meningoencephalitis, poliomyelitis-like paralysis) and even death.

Mode of transmission

9. EV infections are transmitted through stools of infected persons (faecal-oral route), respiratory secretions (nose and throat discharges and saliva via direct person-to-person contact, droplets or fomites) and fluid from blisters (direct contact). The illness is contagious during the acute stage and sometimes for a longer duration afterwards, as faecal shedding of virus may continue for several weeks after symptoms have subsided.

Management of patients

10. Currently there is no specific treatment for EV infection. Some symptomatic treatment could be provided to relieve fever and pain from oral ulcers. Patients should also be alerted of the symptoms of serious complications such as

persistent high fever, decrease in alertness or deterioration in general conditions and advised to seek medical attention promptly. Sick children should stay away from school or gatherings till all vesicles have dried up to avoid spreading and outbreak of the disease.

11. There is no effective vaccine or chemoprophylaxis available on the market for EV infection. Maintaining high standards of personal and environmental hygiene are the mainstay of prevention of the disease.

Epidemiology

12. The EV infection activity in Hong Kong is mainly monitored through various surveillance systems, namely:

- Voluntary reporting of HFMD/herpangina institutional outbreaks;
- Sentinel surveillance on HFMD;
- Statutorily notification of EV71 infections;
- Voluntary reporting of severe paediatric enterovirus infections (SE) (other than EV71 and poliovirus); and
- Hospital admission episodes of HFMD cases in public hospitals.

13. Over the past ten years, EV infection occurs all year round, with higher activity during summer, in Hong Kong. As reflected by various surveillance systems, EV infection mainly affects children and causes outbreaks in child care centres/kindergartens, primary schools and secondary schools.

14. Laboratory diagnosis has changed gradually from primarily viral culture to PCR since 2010 and the sensitivity of enterovirus detection and ability for serotype determination was enhanced. It is necessary to take this factor into account when interpreting the data.

Institutional outbreaks

15. From 2005 to March 2015, a total of 3,379 HFMD/herpangina institutional outbreaks affected more than 21,000 persons were recorded. The number of HFMD/herpangina institutional outbreaks accounted for about 42% of all outbreaks recorded by the Centre for Health Protection (CHP) of the Department of Health (DH). Majority of the outbreaks occurred in child care centres/kindergartens (61.5%), followed by primary schools (20.7%) and secondary schools (12.7%) (Figure 1). The size of outbreaks was generally small with a median of four persons (ranged from two to 65 persons).

16. Seasonal pattern of enterovirus activity is observed that the activity usually starts to increase in May, peaks in June/July, and returns to baseline in August. A smaller peak may occur in winter (Figure 2). Higher number of HFMD/herpangina institutional outbreaks occurred about every two to three years (Figure 1). An exceptionally high number of HFMD/herpangina institutional outbreaks were recorded in 2010 and 2013 with 851 and 779 outbreaks respectively and over 5,000 persons were affected in both years. Such cyclical high activity was also observed in other places such as Taiwan³⁸, Malaysia³⁹ and Japan⁴⁰.

Figure 1 Number of HFMD/herpangina outbreaks and number of persons affected, 2005 to March 2015

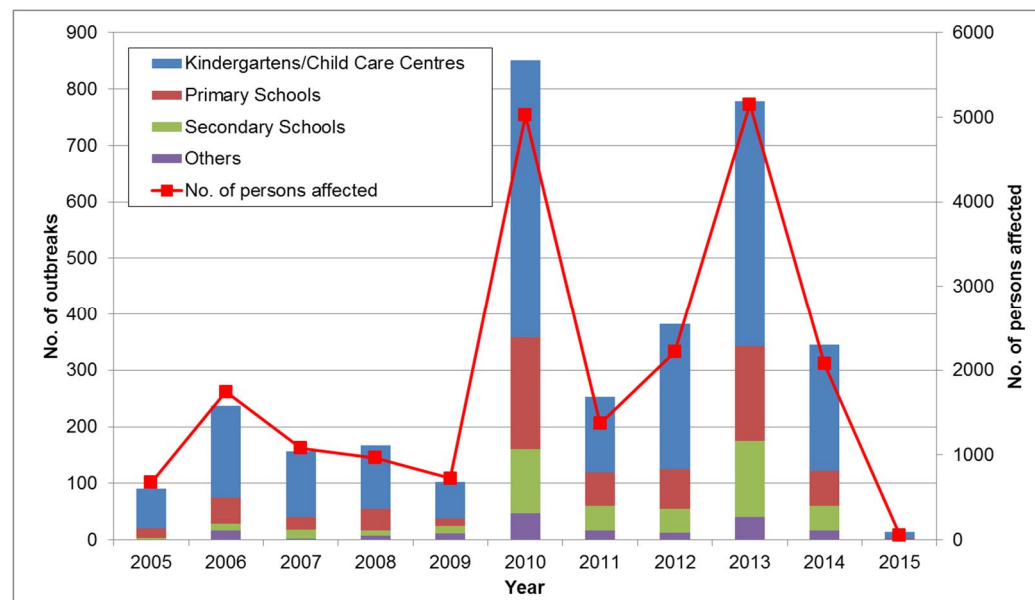
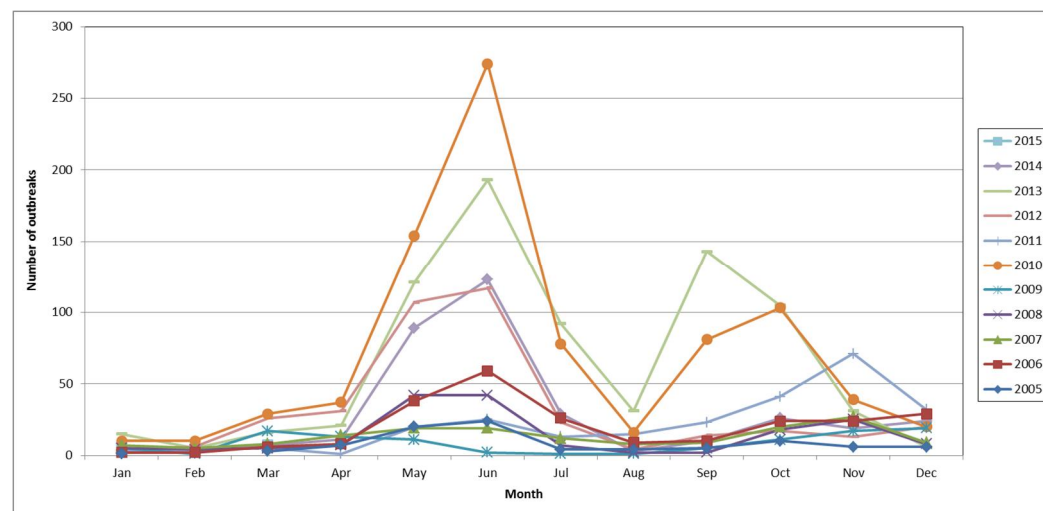


Figure 2 Seasonal pattern of HFMD/herpangina outbreaks, 2005 to March 2015



EV serotypes among laboratory-confirmed HFMD/herpangina institutional outbreaks

17. Based on the outbreaks with laboratory confirmation (21.9% of the total), CA16 and EV71 were the most common EV serotypes identified to be associated with local HFMD/herpangina institutional outbreaks from 2008 to 2014 except for year 2010 and 2013. CA6 and CA16 were the predominant serotypes in 2010, while CA6 was the single predominant strain in 2013 (Table 2).

Table 2 Distribution of EV serotypes in laboratory-confirmed HFMD institutional outbreaks from 2008 to March 2015

Year	CA1	CA2	CA4	CA5	CA6	CA10	CA12	CA16	CB4 & CB5	E	EV71	Mixed	Other / untyped EV
2008	0 0.0%	0 0.0%	<u>5</u> <u>11.6%</u>	0 0.0%	0 0.0%	1 2.3%	0 0.0%	<u>6</u> <u>14.0%</u>	0 0.0%	0 0.0%	<u>20</u> <u>46.5%</u>	2 4.7%	9 20.9%
2009	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1 3.5%	0 0.0%	<u>14</u> <u>48.3%</u>	0 0.0%	0 0.0%	<u>4</u> <u>13.8%</u>	0 0.0%	10 34.5%
2010	0 0.0%	0 0.0%	13 5.9%	1 0.5%	<u>61</u> <u>27.9%</u>	4 1.8%	1 0.5%	<u>25</u> <u>11.4%</u>	2 0.9%	3 1.4%	11 5.0%	2 0.9%	96 43.8%
2011	1 1.6%	1 1.6%	1 1.6%	1 1.6%	<u>10</u> <u>15.9%</u>	3 4.8%	0 0.0%	<u>13</u> <u>20.6%</u>	0 0.0%	0 0.0%	<u>13</u> <u>20.6%</u>	1 1.6%	19 30.2%
2012	0 0.0%	5 6.6%	<u>8</u> <u>10.5%</u>	0 0.0%	<u>16</u> <u>21.1%</u>	0 0.0%	0 0.0%	<u>26</u> <u>34.2%</u>	0 0.0%	0 0.0%	<u>11</u> <u>14.5%</u>	1 1.3%	9 11.8%
2013	0 0.0%	0 0.0%	0 0.0%	0 0.0%	<u>106</u> <u>71.1%</u>	7 4.7%	0 0.0%	3 2.0%	1 0.7%	2 1.3%	5 3.4%	2 1.3%	23 15.4%
2014	0 0.0%	0 0.0%	<u>7</u> <u>13.2%</u>	0 0.0%	<u>7</u> <u>13.2%</u>	5 9.4%	0 0.0%	<u>16</u> <u>30.2%</u>	0 0.0%	0 0.0%	<u>6</u> <u>11.3%</u>	0 0.0%	12 22.6%
2015*	0 0.0%	0 0.0%	0 0.0%	0 0.0%	<u>1</u> <u>50%</u>	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1 50%

*Figures as of March 2015

18. CA6-associated HFMD/herpangina outbreaks or increase in the proportion of CA6 isolates have also been reported worldwide over the past few years, for example, in the US in 2012⁴¹, and in other Asian countries/areas, including Japan (2009 and 2011)^{10,37}, Guangzhou and southern China (2010 to 2013)^{8,18,42}, Thailand (2012)³² and Beijing (2013)⁴³.

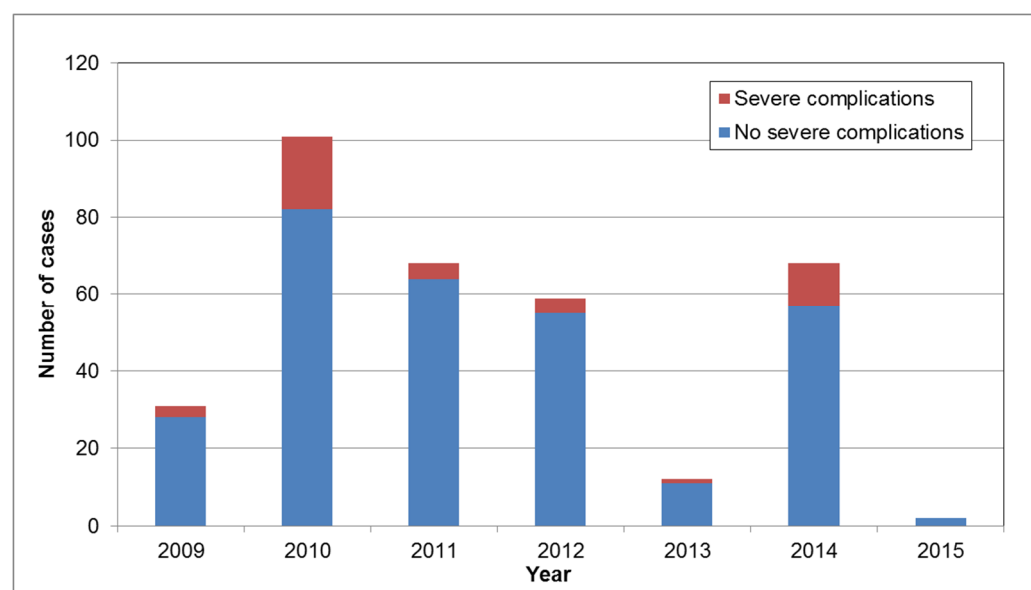
Sentinel Surveillance

19. The sentinel surveillance data also showed similar seasonal and cyclical patterns of EV activity. There were also very high level of EV activity recorded in 2010 and 2013. Besides, seasonal patterns were also observed and the activity usually started to increase in May, peaked in June/July and returned to baseline in August and a smaller peak occurred in winter.

EV71 infection

20. Enterovirus 71 infection has been made notifiable since 2009. A total of 341 cases of EV71 infection were recorded from 2009 to March 2015. The annual number of EV71 case recorded ranged from two to 101 (Figure 4). The male-to-female ratio was 1.5:1 and their ages ranged from 14 days to 43 years old (median: two years). A total of 248 EV71 cases required hospitalisation with a median length of stay of three days (range: discharged on the same day of admission to 90 days). Forty two cases (12.3%) developed severe complications (e.g. meningitis, encephalitis, meningoencephalitis, acute flaccid paralysis, myocarditis and radiculomyelitis). Three fatal cases were recorded in 2009, 2011 and 2014. The overall case fatality rate for reported EV71 in the past six years was 0.9%. Besides, the annual proportion of EV71 infections with severe complications ranged from 0.0% to 18.8% from 2009 to March 2015, while the overall complication rate in the same period was 12.3%. This rate is comparable to that in other countries/areas.^{44,45}

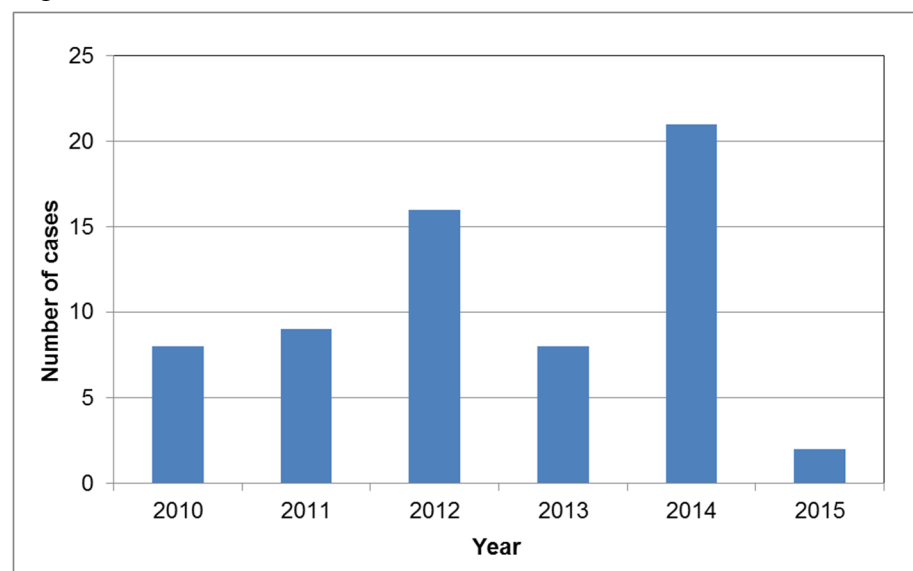
Figure 4 Number of EV71 cases recorded from 2009 to March 2015



Severe paediatric enterovirus infection (SE)^a

21. There were 64 cases of SE (other than EV71 and poliovirus) recorded from 2010 to March 2015. The annual number of SE cases recorded ranged from two to 21 (Figure 5). The male-to-female ratio was 1.6:1. The patients' age ranged from nine days to 12 years (median: four months). All were inpatients with a median length of stay of seven days (range: one day to 40 days). The patients were complicated with meningitis (75.0%), encephalitis (14.1%), meningoencephalitis (3.1%), cerebellar ataxia (3.1%), myocarditis (3.1%) and pneumonia (1.6%). Two fatal cases (3.1%), affecting a nine-month-old boy and a four-year-old boy, were recorded in 2012. Both of them enjoyed good past health.

Figure 5 Number of SE infections recorded from 2010 to March 2015



EV serotypes among SE infections

22. The distribution of EV serotypes among SE infections also showed a

^aReporting criteria for severe paediatric enterovirus infection (other than EV71 and poliovirus)

An individual fulfilling both the clinical criteria AND laboratory criteria should be reported to Centre for Health Protection for further investigation.

Clinical Criteria

1. Children ≤ 12 years old on date of admission; AND

2. A person presented with the following condition: Meningitis; OR Encephalitis; OR Acute flaccid paralysis; OR Other central nervous system complication (e.g. cerebellar ataxia); OR Myocarditis/pericarditis; OR Pulmonary edema or hemorrhage OR Death

Laboratory Criteria

Any one of the following:

- Isolation of enterovirus (other than EV71 and poliovirus) from a clinical specimen
- Detection of enterovirus (other than EV71 and poliovirus) by PCR from a clinical specimen

distinct pattern over the past few years. As shown in Table 3, among the SE infections from 2010 to March 2015, the proportions of coxsackievirus B (CB) and echovirus were both higher than that of coxsackievirus A (CA). 95.5% of CB-associated SE infections were aged less than one (Table 4). On the other hand, the proportion of CB and echovirus among HFMD/herpangina institutional outbreaks were extremely low.

23. As for coxsackievirus A, CA16 had not been reported among SE cases. On the other hand, CA6 was associated with SE infections in 2010 and 2013, which were the two years with higher HFMD activity with CA6 predominance among the strains identified in institutional outbreaks.

Table 3 Distribution of EV serotypes among SE infections from 2010 to March 2015

EV serotypes associated with SE infections	2010	2011	2012	2013	2014	2015*	Total for the serotype (%)
Coxsackievirus A							
CA2	0	1	2	0	0	0	3 (4.7%)
CA6	3	0	0	2	0	0	5 (7.8%)
CA10	0	0	0	1	0	0	1 (1.6%)
Coxsackievirus B							
CB1	0	7	0	0	0	0	7 (10.9%)
CB3	0	0	3	0	0	0	3 (4.7%)
CB4	1	0	2	0	0	0	3 (4.7%)
CB5	0	0	1	1	7	0	9 (14.1%)
Echovirus							
E6	0	0	1	0	3	0	4 (6.2%)
E9	0	0	0	1	0	0	1 (1.6%)
E15	0	0	0	0	1	0	1 (1.6%)
E18	0	0	1	0	0	0	1 (1.6%)
E25	0	0	3	0	1	0	4 (6.2%)
E30	0	0	3	2	0	0	5 (7.8%)
Untyped	4	1	0	1	9	2	17 (26.5%)
Total for the year (%)	8 (12.5%)	9 (14.1%)	16 (25.0%)	8 (12.5%)	21 (32.8%)	2 (3.1%)	64 (100%)

*Figures as of March 2015

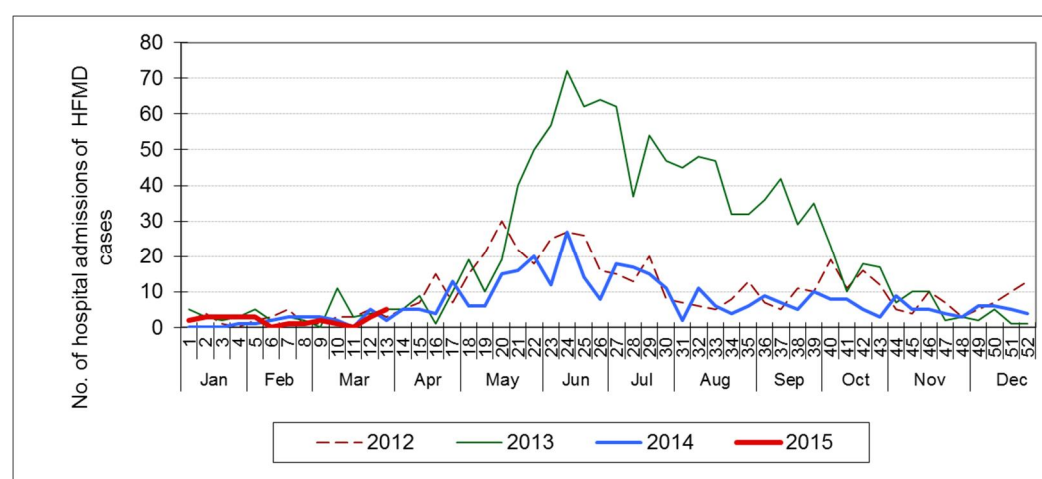
Table 4 Proportion of infants aged less than 1 among SE infections by EV serotypes 2010 to March 2015

EV serotypes	No. of SE cases aged < 1 year (No. of SE cases aged 0 to 12)	Proportion of cases aged < 1 year
CA	4 (10)	40.0%
CB	21 (22)	95.5%
E	5 (16)	31.3%
Untyped	9 (16)	56.3%
All serotypes	39 (64)	60.9%

Hospital admission episodes of HFMD cases in public hospitals

24. Hospital admission episodes of HFMD cases in public hospitals also had seasonal variation that the number started to increase in May, peaked in June/July and returned to baseline in August. High number of hospital admission of HFMD cases was observed in 2013 (Figure 6).

Figure 6 Hospital admission episodes of HFMD cases in public hospitals, 2012 to March 2015



Prevention and control of enterovirus infection

Surveillance

25. Surveillance system for EV infections has been in place in Hong Kong. The system includes several components that capture a spectrum of EV infections at community level and hospital level in different population groups and settings,

which complement each other so as to provide a more comprehensive picture of the situation of EV infections in Hong Kong. The different components of the surveillance system are:

- a. Sentinel surveillance
 - for the detection of HFMD cases at general outpatient clinics (GOPC), general practitioners (GP) clinics, child care centres/kindergartens (CCC/KG) and Accident & Emergency Departments (AED) of public hospitals;
- b. Voluntary reporting of HFMD/herpangina institutional outbreaks;
- c. Statutory notification of EV71 infections and voluntary reporting of other severe paediatric enterovirus infections (SE), which may or may not have presented with HFMD/herpangina; and
- d. Hospital admission episodes of HFMD cases in public hospitals.

26. Monitoring of enterovirus activity in neighboring area is indispensable as it provides information for the prediction of the trend of EV activity in Hong Kong.

27. The Annex shows the findings of surveillance of the EV activity in 2014. With close monitoring of the disease activity, timely and appropriate risk communication to the public can be taken place.

Outbreak investigation and control

28. Early detection of HFMD/herpangina institutional outbreaks with prompt implementation of control measures is expected to limit the spread of the disease. Upon receiving notifications, CHP conducts epidemiology investigation and implements control measures to contain the outbreaks.

Pre-primary institution inspection

29. To monitor and strengthen the implementation of infection control and preventive measures among the institutions, the Pre-primary Institutions Inspection Team of CHP conducts unscheduled visits to child care centres and kindergartens to:

- a. Monitor the procedure of disinfection of items used and the proper disposal of contaminated clothing and other types of waste;
- b. Provide information on personal protective gear and advice on their proper usage, maintenance and disposal after use;
- c. Provide the latest information and guidelines on prevention of communicable diseases; and

- d. Give appropriate advice on any necessary improvement in the preventive measures for the control of communicable diseases.

Public education and community engagement

Health Education

30. The Central Health Education Unit of CHP has developed a designated website and has prepared a series of health education materials (e.g. leaflets, posters and television announcements) to remind public to maintain vigilance against HFMD.

Guidelines

31. The Infection Control Branch of CHP has published the guideline on "Prevention of Communicable Diseases in Schools/Kindergartens/Kindergartens-cum-Child Care Centres/Child Care Centres" to provide useful practical information for prevention of communicable diseases including HFMD.

Risk communication

32. When surge in HFMD activity is predicted, CHP will issue letters to doctors, private hospitals, schools and CCC/KGs to remind them to remain vigilant against the disease. Another round of letters will be sent to schools and CCC/KGs in late August before the new school year starts in September.

33. To further enhance risk communication, the weekly online publication "EV SCAN" was issued during the peak of the epidemics. Other means to increase public awareness of HFMD included issuing press releases for large scale outbreaks or severe infections associated with enterovirus, and broadcasting TV announcements to call on the public to maintain high standards of hand hygiene and stay vigilant against communicable diseases.

Vaccine

34. Development of an EV71 vaccine has been underway in view of EV71's potential of causing large outbreaks and the severity of complications. Phase III trials of an inactivated EV71 vaccine have been completed in China.⁴⁶ The vaccine consists of an inactivated subgenotype C4 virus that is currently prevalent in mainland China. Whether local application is advisable when it is available on the market remains to be seen.

Way forward

35. It might be worthwhile to review the communicable disease surveillance system and develop a more comprehensive, integrated and cost effective strategy. It is also important to keep abreast of the latest development of vaccine and to consider assessment of the local applicability when it is available.

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Surveillance findings of enterovirus infection activity in Hong Kong in 2014

In 2014, the overall HFMD activity in Hong Kong was moderate compared with the high activity in 2013. An increase in HFMD activity in 2014 was first detected in early May according to the statistics collected from sentinel surveillance based at GP clinics (Figure 7) and child care centres/kindergartens (Figure 8). The activity peaked in early June, began to decline in late June, and returned to baseline in August. A second, much smaller activity peak then appeared in late October to early November for a few weeks, as shown by the HFMD consultation rates at sentinel GP clinics (Figure 7) and the number of reported HFMD/herpangina institutional outbreaks (Figure 9). The HFMD activities depicted in the other components of the surveillance system also showed a similar pattern.

Figure 7 HFMD consultation rate among sentinel GP clinics by week
from 2012 to 2014

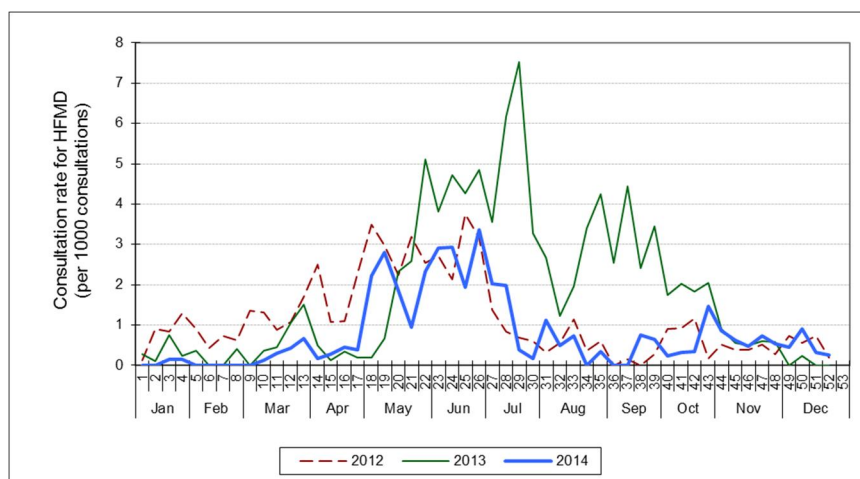


Figure 8 Proportion of CCC/KGs with reported HFMD cases by week

from 2012 to 2014

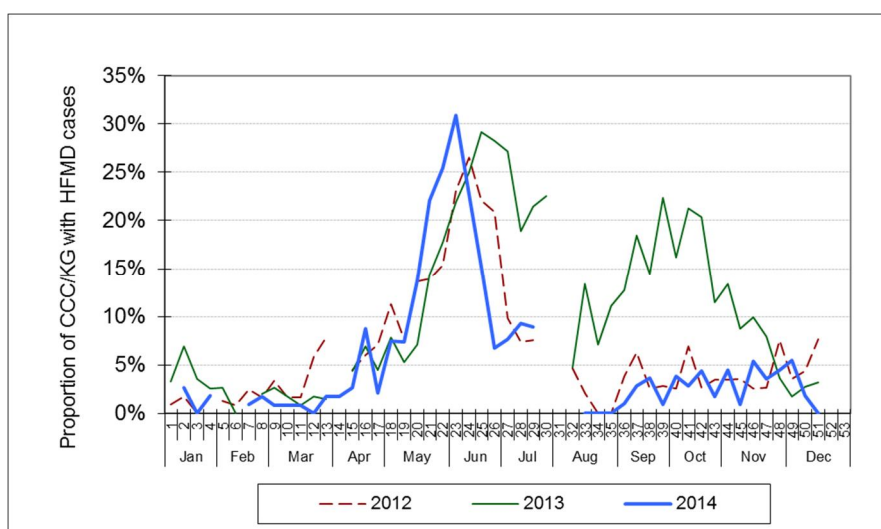
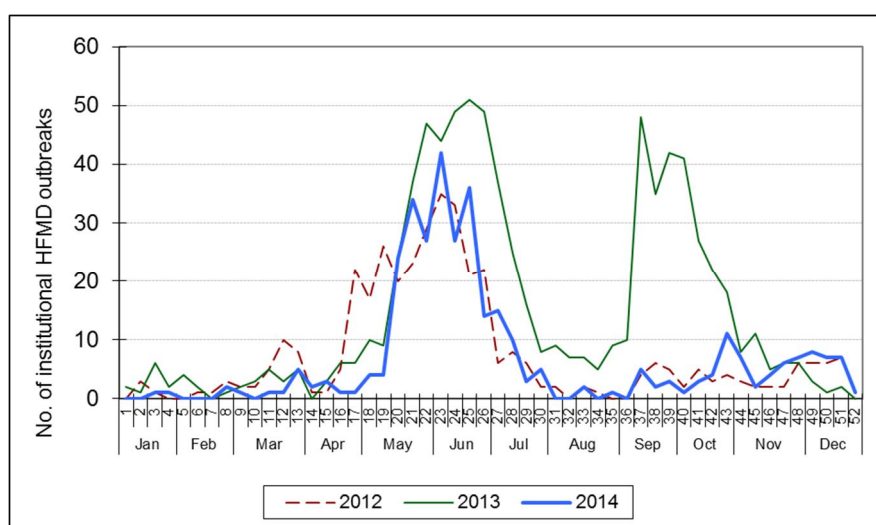


Figure 9 Number of HFMD/herpangina institutional outbreaks by week reported to CHP, 2012 to 2014



The rise in HFMD activity in 2014 was earlier than that in 2013 by about two weeks as shown by several surveillance components such as GP clinics (Figure 7). The return to baseline level of the first peak also occurred earlier than that in 2013, and the second peak in 2014 was much smaller in magnitude compared with 2013.

In 2014, a total of 346 HFMD/herpangina institutional outbreaks, in which only 2.6% were herpangina outbreaks, were recorded (382 and 779 outbreaks in 2012 and 2013 respectively). About 2,000 persons were affected. The sizes

(number of persons affected) of most outbreaks were small, with 64.2% of outbreaks having fewer than or equal to five persons affected (range of number of persons affected: two to 52; median: four). The institution with 52 affected persons was a children's residential home. Two CCC/KGs had been advised by CHP to suspend classes for two weeks following HFMD outbreaks associated with EV71 infection.

EV71 infections and other severe paediatric enterovirus infections (SE)

Although the HFMD activity in 2014 seemed to be lower compared with that in 2013, the number of case-based notifications/reports of EV infections (which may or may not have presented with HFMD) was higher than that in 2013. In 2014, a total of 68 EV71 infections (Figure 10) and 21 severe paediatric enterovirus infections (other than EV71 and poliovirus) (SE) were reported (Figure 11). The number of EV71 cases in 2014 was higher than those in 2012 and 2013, while the number of SE cases in 2014 was the highest since 2010. EV71 was associated with one death, while SE infections did not have any associated death in 2014.

Figure 10 Number of EV71 notifications by sex from 2009 to 2014

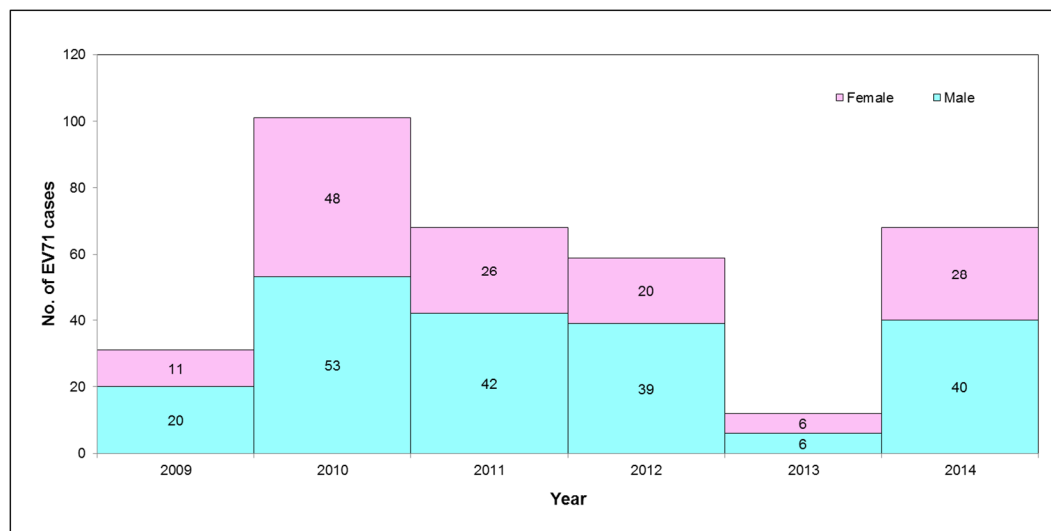
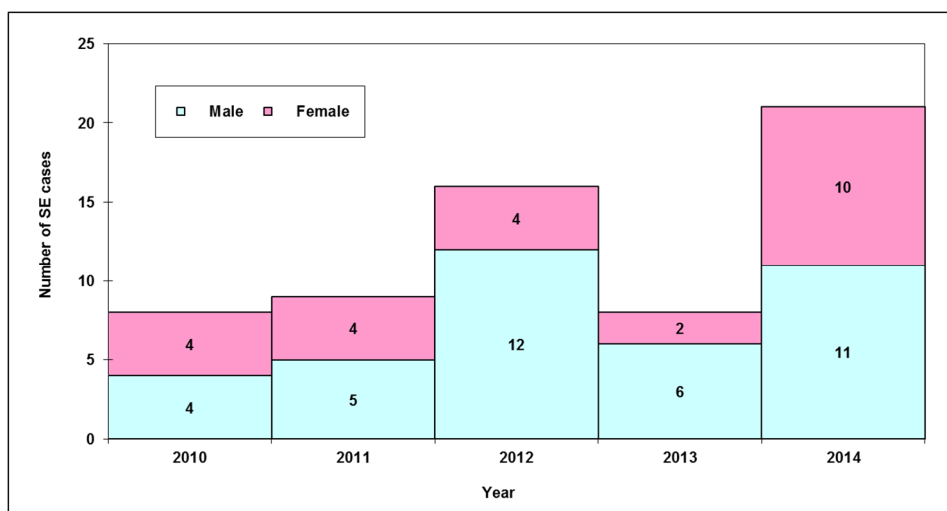


Figure 11 Number of SE infections reported to CHP by sex from 2010 to 2014



Among those 68 **EV71 cases** notified in 2014, the male-to-female ratio of the affected was 1.4:1 and their ages ranged from three months to 18 years (median: 2.7 years). Sixty-two cases (91.2%) required hospitalisation with a median stay of three days (range: discharged on the day of admission ó 50 days). Eleven cases (16.2%) developed severe complications including encephalitis (five cases), poliomyelitis-like paralysis (three cases), meningitis (two cases), and meningoencephalitis (one case). The fatal EV71 case involved a two-year-old girl with severe complication of encephalitis.

As for **SE infections**, among those 21 cases in 2014, the male-to-female ratio was 1.1:1, and their ages ranged from 20 days to 11 years (median: three months). The diagnoses included meningitis (16 cases), encephalitis (three cases), meningoencephalitis and cerebellar ataxia (one case each). All required hospitalisation with a median stay of seven days (range: three ó 40 days). The enteroviruses involved were: CB5 (seven cases), E6 (three cases), E15 (one case) and E25 (one case). The remaining cases were untyped enterovirus other than poliovirus and EV71.

EV serotypes among laboratory-confirmed HFMD/herpangina institutional outbreaks

In 2014, 53 (15.3%) HFMD/herpangina institutional outbreaks had causative agents confirmed by laboratory. Among them, the majority were associated with CA16 (30.2%), followed by CA4 (13.2%), CA6 (13.2%), EV71 (11.3%), and CA10 (9.4%). CA6, the most common strain associated with HFMD outbreaks in 2013 (71.1% of laboratory-confirmed outbreaks in 2013), was associated with about 13% of laboratory-confirmed outbreaks in 2014.

Enterovirus activity in neighboring areas

Guangdong Province

Surveillance data showed that in 2014, the HFMD activity in Guangdong Province was much higher than those in previous years. The number of HFMD disease started to increase in end March and reached a peak in May, with the peak about twice as high as that in 2013. The rise in activity and the peak both appeared one month earlier than 2013. The activity returned to baseline in September but a smaller peak reappeared in October.

Outbreaks of HFMD in Mainland China over the past few years were mainly caused by EV71 and CA16 with differing ratios in different regions and at different times in the same region.⁴⁷⁻⁴⁹ Sporadic cases associated with other coxsackieviruses, such as CA4, CA5, CA6, CA10 and CB2 to CB5, were occasionally reported.^{50,51} CA6 has also been identified as the predominant serotype associated with an HFMD epidemic from 2010 to 2013.^{8,18,42} A study performed phylogenetic analysis of CA6 isolates collected in Guangzhou from 2010 to 2012, and concluded that the CA6 strain were similar to those found in Shanghai in 2011 and 2012, Shenzhen in 2011, Japan in 2011, France in 2010, Thailand in 2012 and Israel in 2012 and 2013.⁸ It has been suggested that this cluster of circulating CVA6 strain had emerged as a new and major cause during a continuing HFMD epidemic in the region.⁸

For EV71, subgenotype C4 has been the sole viral genetic lineage circulating in mainland China since 1998. The large HFMD outbreaks with severe

neurological complications that have occurred since 2007 in Mainland China are mainly due to subgenotype C4a of EV71.⁵²

Taiwan

In Taiwan, the enteroviral activity in 2014 started to increase in late March; reached a peak in late April; started to decrease in early June; and returned to baseline in early October. The predominant circulating EV serotypes in 2014 in Taiwan were CA10, CA2, and CA5.³⁸ There were six severe enterovirus infections in 2014 as of November 3, each associated with EV71, CA2, CA5, CA16, CB5, and E11 respectively.³⁸

Unlike that in Mainland China where C4 subgenotype of EV71 has been the predominant circulating endemic viruses since 1998, EV71 has cyclically caused epidemics in Taiwan with different predominant genotypes since the same year: in 1998 (genotype C2), 2000 - 2001 (B4), 2005 (C4), 2008 (B5), and 2012 (B5).

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