



An Enterovirus Outbreak Associated with Probable Rhombencephalitis in a Nursery, Tak Province, Thailand, 2017

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Abstract

On 4 Sep 2017, the Bureau of Epidemiology received a notification from Tak Provincial Health Office on an outbreak of hand, foot and mouth disease (HFMD) at a nursery following one death at the provincial hospital. An investigation was carried out to confirm the diagnosis and identify source of infection. Active case finding was performed in the nursery, index case's house and community. Medical records were reviewed, and children, teachers and household members of the index case were interviewed. Confirmed cases were defined as children or teachers in the nursery, household members and neighbors of the index case who was found to have enterovirus from fresh stool or nasopharyngeal/throat swab by polymerase chain reaction. Total 30 cases were identified, including nine confirmed, one probable (index case) and 20 suspected cases. The overall attack rate was 51.7% and case fatality proportion was 3.3%. There were 26% of enterovirus 71, 13% of coxsackie B4 identified from fresh stool samples of symptomatic cases. Neither samples from asymptomatic close contact or nasopharyngeal/throat swab was positive. No residual chlorine in the supplied water at the nursery was detected. We recommended hand washing with soap, wash the toys more than once a week, chlorinate the water to more than 0.5 ppm and increase awareness of enterovirus infection to early detect the outbreak.

Keywords: Hand, foot and mouth disease, enterovirus, rhombencephalitis, nursery

Introduction

Enteroviruses are ribonucleic acid (RNA) viruses of the family Picornaviridae.^{1,2} They are non-enveloped viruses that resist pH 3-10, lipid, ether, chloroform and alcohol. They can be inactivated by temperatures above 50°C, ionizing radiation, formaldehyde and phenol. While enteroviruses are transmitted mainly via the fecal-oral route, it can also be spread by respiratory secretion.³ At present, no specific treatment is available for an enteroviral infection.⁴

Enteroviruses can cause various clinical manifestations from asymptomatic (50-80%) to respiratory tract infections, hand, foot and mouth disease (HFMD), herpangina, acute gastroenteritis.

Severe neurological complications can occur with aseptic meningitis or encephalitis such as rhombencephalitis, especially after enterovirus serotype 71 (EV71) infection^{5,6,7}.

EV71 has been reported as the causative agent in several outbreaks of HFMD in Asia during 1997-2008.⁸⁻¹⁴ In Thailand, EV71 was first isolated during 1998 and as it can cause severe manifestation, a surveillance system for EV71 was established in the Bureau of Epidemiology (BOE) by including HFMD as a notifiable disease since 2001⁶. In addition, severe cases of HFMD who need admission in hospital or fatal cases must be fully investigated and isolated for EV71. On 31 Aug 2017, one suspected enterovirus infection

who visited Bantak Hospital was referred and died at Somdejphrajaotaksin Maharaj Hospital. Subsequently, an outbreak of HFMD was detected at a nursery and this event was notified to BOE on 4 Sep 2017. Thus, officers from BOE, Office of Disease Prevention and Control 2 and provincial health office jointly investigated the event during 5-12 Sep 2017. Our objectives were to confirm an outbreak of enterovirus infection, describe epidemiological characteristics of the outbreak, identify the source of infection and provide recommendations to control the outbreak.

Methods

A descriptive study was performed. The situation of HFMD in Thailand during 2012-2016 was retrieved from the national surveillance data in BOE. The HFMD situation in Bantak District, especially in Thong Fah Subdistrict, during 8 Aug-8 Sep 2017 was also assessed in the hospital database by international classification of diseases (ICD) 10 codes of B08.4 (HFMD), B08.5 (Herpangina), B08.8 (Other specified viral infections characterized by skin and mucous membrane lesions), G04 (Encephalitis) and J81 (Pulmonary edema).

Moreover, medical records of the index case in Bantak Hospital and Somdejphrajaotaksin Maharaj Hospital were reviewed for clinical manifestations, disease progression and laboratory findings. Children and teachers at the nursery, and the index case's household members were interviewed for demographic information, clinical manifestation, vaccination, travel history, behavior, sanitation and activities. Active case finding was performed at the nursery and index case's house using a modified investigation form.

The index case was the dead case who was suspected of enterovirus infection on 31 Aug 2017 and led to the investigation. Household members were the index case's family members who had an epidemiological linkage with the index case. Neighbors were people who lived in the neighborhood around 500 meters radius of the index case's house and shared activities with the index case. Contacts were anyone who had shared activities with the index case at home or nursery.

Suspected enterovirus cases were defined as children or teachers in the nursery, household and neighbors of the index case who had at least one of following symptoms during 8 Aug to 8 Sep 2017: rash/vesicles on at least one site of palm, oral cavity, sole or buttock; or upper respiratory infection (URI) symptoms of cough, runny nose or sore throat. Probable cases were

suspected cases with severe neurological or cardiopulmonary symptoms, yet with no enterovirus found by polymerase chain reaction (PCR). Confirmed cases were suspected cases who had enterovirus in fresh stool or nasopharyngeal/throat swab specimen tested by PCR for enterovirus.

Fresh stool specimens were collected from all suspected cases, and close contacts of the index case in household and classroom. The stool specimens were stored under four degrees Celsius during transportation and tested by PCR for *enterovirus* spp. The nasopharyngeal/throat swab specimens were also collected from suspected cases who had any symptoms within seven days of onset, transported by viral transport media and tested by PCR for *enterovirus* spp. All specimens were sent and tested at the National Institute of Health, Thailand.

The possible risk factors of enterovirus infection were analyzed by odds ratio (OR) and 95% confidence interval (CI) using Epi Info version 7.2.1.0¹⁵.

In addition, an environmental study was conducted at the nursery and index case's house by a walk-through survey and discussion with teachers in the nursery and household members.

Results

Situation of HFMD in Bantak District and Thailand

Reports of HFMD in BOE¹⁶ were retrieved on 19 Oct 2017, and HFMD reports from Bantak District Hospital in Tak Province were accessed on 6 Sep 2017. The situation of HFMD in Bantak District was similar to the national reports by months during 2012-2017, with the peak in June and July. There were 1-3 deaths per year (Figures 1 and 2).

Investigation of Index Case

The index case lived in Bantak District, Tak Province. She was three years old, with complete vaccination from the national program and no underlying diseases. Prior to her disease onset, she did not go anywhere, except attending classroom 2 at a nursery in Thong Fah Subdistrict. She started to be sick on 29 Aug 2017 and was treated at home by her parents, presenting with fever and chills, headache, myoclonus at extremities, abdominal pain, nausea and vomiting. On 31 Aug 2017, she was treated at Bantak District Hospital and referred to Somdejphrajaotaksin Maharaj Hospital where she was admitted. At night, as she developed vesicles at palms and soles, physician diagnosed as HFMD and gave supportive treatment.

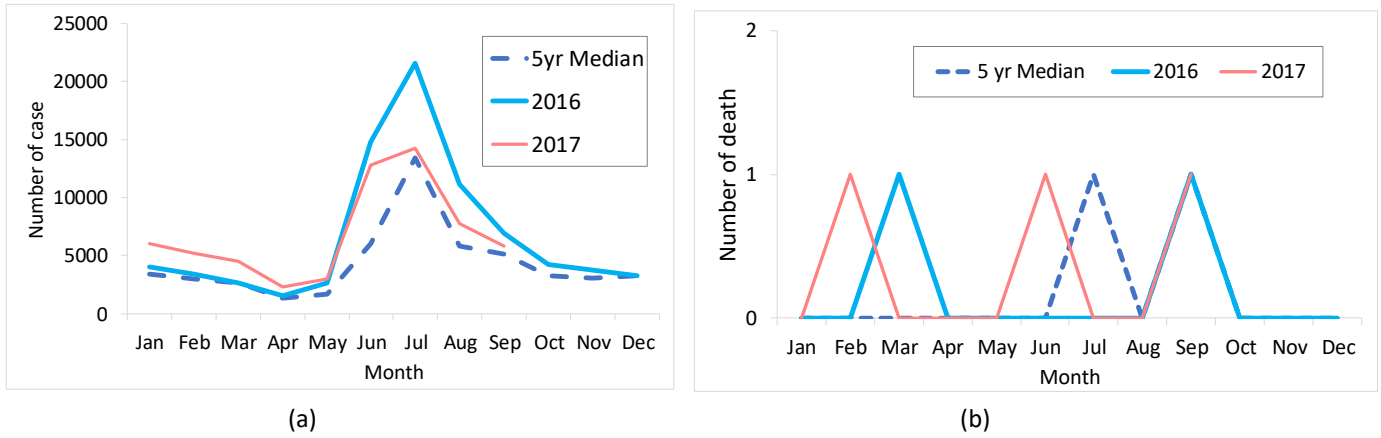


Figure 1. Cases (a) and deaths (b) of hand, foot and mouth disease by months reported to the national disease surveillance system in Bureau of Epidemiology, 1 Jan 2012-19 Oct 2017

On 2 Sep 2017, she suddenly developed dyspnea, tachycardia, hyperglycemia, pink frothy sputum and cardiac arrest, and died. Her chest x-ray finding showed cardiomegaly with patchy infiltration in both lungs. Although the *enterovirus* spp. was not detected by PCR in the stool specimen collected on 2 Sep 2017, her final diagnosis by a pediatrician at the hospital was EV71 infection with HFMD.

Active Case Finding

In the nursery, the children were divided into three classrooms by age groups, with two teachers per classroom. All six teachers and 40 (88.9%) out of 45 children were screened, and 25 suspected cases were identified. Among 12 household members and neighbors, four suspected cases were detected. However, there was no other case in the community. By reviewing ICD10 code at Bantak Hospital, three

suspected cases were found. However, they were not linked with the index case.

Out of total 29 suspected cases, 23 fresh stool samples and nine nasopharyngeal/throat swab samples were collected to test for enterovirus. In addition, nine fresh stool samples were collected from asymptomatic household contacts. There were 26.1% (6/23) of EV71, and 13.0% (3/23) of coxsackie B4 confirmed from fresh stool specimens of the suspected cases. Neither fresh stool nor nasopharyngeal/throat swabs from asymptomatic close contact was positive for enterovirus infection (Figure 3).

Epidemiological Characteristics

There were 30 cases identified in this study, including six EV71, three coxsackie B4, one probable case (index case) and 20 suspected cases. The case fatality proportion was 3.3% (1/30).

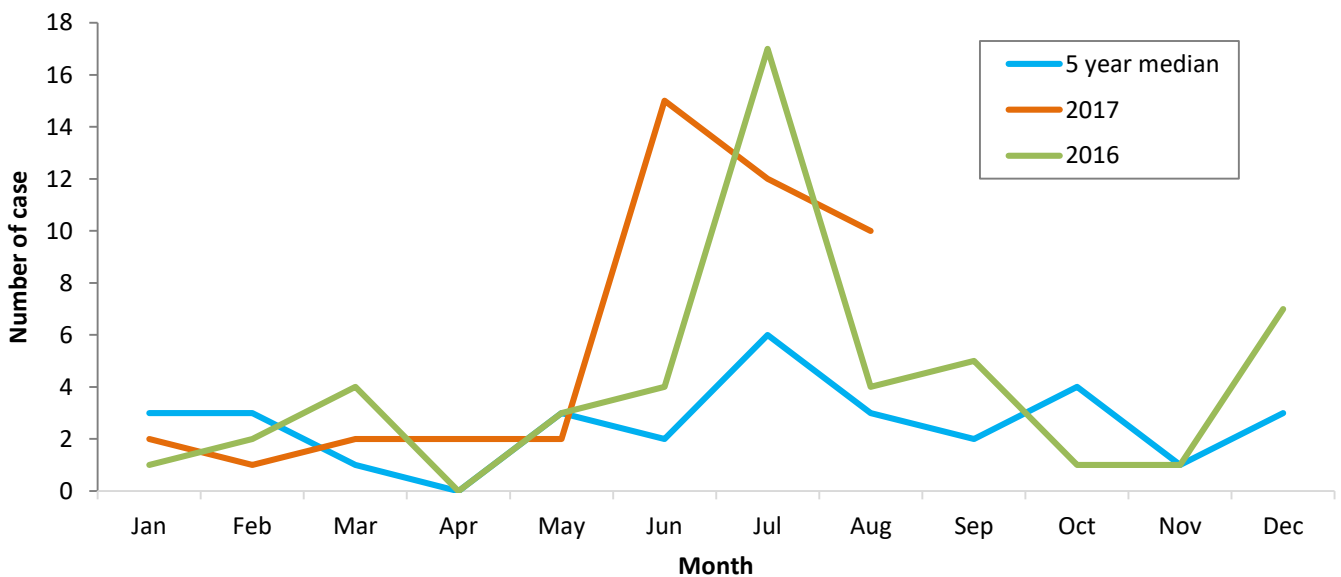
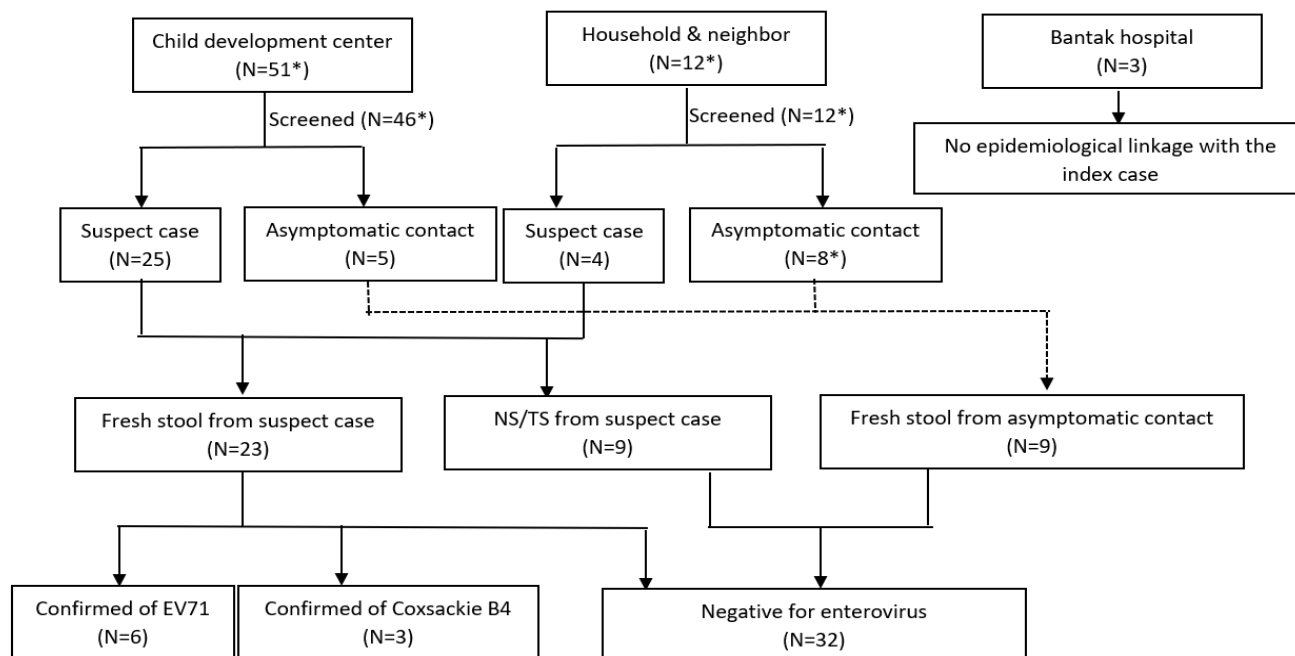


Figure 2. Hand, foot and mouth cases by months identified in Bantak District, Tak Province, Thailand, 1 Jan 2012-6 Sep 2017



* One case was counted as both a student in the nursery and a neighbor.

Figure 3. Active case finding from hand, foot and mouth outbreak in Bantak District, Tak Province, Thailand, 2 Aug-18 Sep 2017

Clinical manifestations of cases were URI symptoms 83.3% (25/30), vesicle/rash 46.7% (14/30) and fever 50.0% (15/30). One third (36.7%) of cases had URI symptoms only. Cardiopulmonary and neurological symptoms were only found in the dead case. All EV71 cases had vesicle/rash (6/6). However, coxsackie B4 cases had URI symptoms (100%), and vesicle/rash (33.3%) (Figure 4).

Upper respiratory symptoms = 25 Vesicle/rash = 14

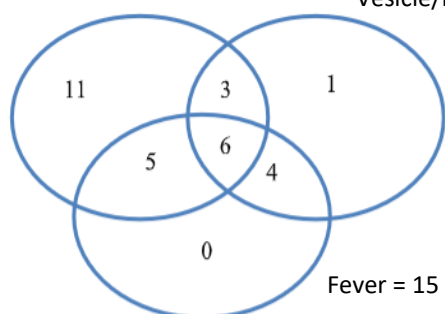


Figure 4. Distribution of enterovirus cases by clinical manifestations in Bantak District, Tak Province, Thailand, 2 Aug-18 Sep 2017

The first case in the index case's house had oral ulcer on 8 Aug 2017, yet we could not collect his fresh stool specimen for testing. The first case at the nursery developed fever, vesicle and URI symptoms in classroom 2 on 16 Aug 2017, and subsequently, the infection spread in the nursery with seven more cases. Therefore, the nursery was closed during 24 Aug-10 Sep 2017 to disinfect the contaminated surface by 1% sodium hypochlorite at least 15 minutes and dry the non-washable items under the sun (Figure 5).

The overall attack rate was 51.7% (30/58). The specific attack rate was higher in males (53.3%, 16/30) and children aged 2-5 years old (67.5%, 27/42). The specific attack rate in the classrooms was 72.7% (10/19) for classroom 1, followed by 70.0% (7/10) for classroom 2 and, 52.6% (10/19) for classroom 3 (Table 1). The median age was three years and six months (range 8 months to 60 years). Children aged 2-5 years old had odds of getting the infection for 7.8 times compared with adults over 15 years (95% CI = 1.9-31.8).

Environmental Results

In general, the nursery was observed to be in good sanitation. There were three classrooms: classrooms 1 and 2 were closely located while classroom 3 was in another building. Density of the classrooms included 4.9, 3.3 and 2.8 m²/person. The residual chlorine in drinking water and water supply was 0.5 ppm and zero respectively. There were four toilets for girls, four toilets for boys and one common washing room.

Interview with teachers revealed that all children had their own drinking glasses. Children washed hands with soap before and after lunch, and after using toilet, yet they used the same towel. They usually washed toys once a week. Alcohol gel was provided by the local public health team as an outbreak response.

The index case lived only with her parents. Although they used the serving spoons for meals, they shared the drinking glass. She played with only one neighbor who was also attending in the same nursery. She went to the nursery with the private vehicle in routine.

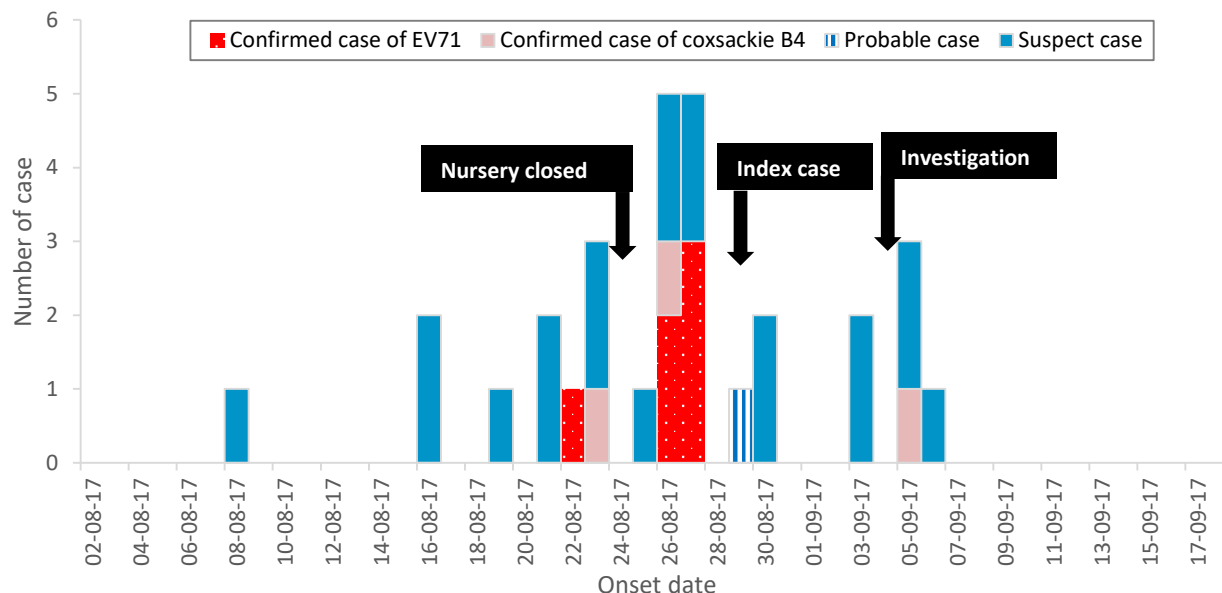


Figure 5. Enterovirus cases by dates of onset in Bantak District, Tak Province, Thailand, 2 Aug-18 Sep 2017

Table 1. Specific attack rates by gender, age and place of an enterovirus outbreak in Bantak District, Tak Province, Thailand, 2 Aug-18 Sep 2017

Characteristic	Total	Number of case	Attack rate (%)
Gender			
Male	30	16	53.3
Female	28	14	50.0
Age (year)			
Child (2-5)	42	27	64.3
Adult (>15)	16	3	18.8
Place			
Nursery	47*	26*	55.3
Index case's house	12*	5*	41.7
Total	58	30	51.7

Discussions

This event was considered as an enterovirus outbreak, as 26.1% of the sampled cases were found to be with EV71 and 13.0% were with coxsackie B4 infection. This implied that multiple species were circulating in the area. This outbreak occurred in August 2017, the rainy season of Thailand, which was consistent with the fact that enteroviral infections appear to peak in the rainy and cold seasons.¹⁷ Our study found that the children aged 2-5 years old posed a higher risk for getting infected with enteroviruses compared to adults, which was consistent with the prior reports¹⁸.

A sensitive case definition, ranged from vesicle or rash to URI, neurological and cardiopulmonary symptoms, was used in this outbreak. As enterovirus infection can demonstrate a wide range of clinical presentations,³ cases with mere URI symptoms were also included as suspected enterovirus infection. A study by Christy SS and Christine ML remarked that the most common pathogens of respiratory tract infection were rhinovirus and enterovirus, accounting for 25.4%¹⁹.

HFMD outbreaks from EV71 are commonly reported in Thailand. An annual report of Thai National Institute of Health during 2016 showed that 19% of HFMD samples were found to have enterovirus and EV71 was found in 32% of the positive samples.²⁰ Moreover, there were reports of patients developed rhombencephalitis after experiencing several days of HFMD, herpangina or febrile illness. Some developed cardiopulmonary failure and died rapidly despite intensive management.^{21,22} In this event, although six EV71 cases and two coxsackie B4 cases at the nursery developed illness prior to the index case, all cases were mild and went to private clinics. Hence, the outbreak at the nursery was unnoticeable by teachers and health care workers. However, a previous study reported that patients with coxsackie B infection were likely to have a higher hospital admission rate and central nervous system involvement while the most common serotypes were coxsackie A16 and B3.²³

Rhombencephalitis refers to inflammation of the brainstem and cerebellum. It is a recognized complication of enteroviral infection and patient may

progress rapidly from intact mental status to death, experiencing in sympathetic overstimulation associated with tachycardia, hyperglycemia and pulmonary edema due to pulmonary vasoconstriction.^{6,24} The index case was classified as a probable case of enterovirus infection due to her clinical manifestations compatible with enterovirus rhombencephalitis as well as epidemiological linkage with the confirmed cases at the nursery. However, the virological etiology of the index case remained unclear as a stool sample was obtained prior to death, instead of throat swab. In the early stage of EV infection like this case, the testing results of rectal swab could be less sensitive²⁵ while the throat swab samples could provide a higher positive rate²⁶.

The World Health Organization has recommended intravenous immunoglobulin (IVIG) in patients with encephalitis and acute flaccid paralysis. Although the use of IVIG has not yet been supported with evidences from randomized clinical trials,²⁷ anecdotal experiences in Asia suggested that if IVIG administered early, it could limit disease progression to affect autonomic nervous system and subsequent pulmonary edema. In Thailand during 2012, two EV71 cases with neurologic involvement were treated with IVIG and both survived.²⁸ However, in 2015, there was a cluster of echovirus 6 infections with an encephalitis death, to whom IVIG was not administered.²⁹ According to the national guidelines, administration of IVIG is recommended in the acute phase of Kawasaki disease, severe Guillain-Barré syndrome and myasthenia crisis while application in other indications depends on the physician's judgment and patients must bear the related expenses.³⁰

Limitations

There was no specimen available to confirm etiology in the dead case such as pair serum for enterovirus, cerebrospinal fluid for PCR (sensitivity 76-100%)²⁵, or brain or heart necropsy.

In term of behavioral risk for disease transmission, the information was acquired by interviewing the teachers since the nursery was closed during the investigation. In addition, recall bias on information from parents might exist for clinical illness of their children. Since behavioral risk factors were difficult to be ascertained in toddlers, the analytic study was not performed.

Conclusion and Recommendations

Almost all enterovirus cases found in this outbreak were children. The pathogens were identified as EV71 and coxsackie B4. To control these pathogens, sanitation is crucial¹⁹. To reduce incidence, control measures should be intensified. Firstly, since alcohol

gels cannot inactivate the enterovirus,¹ washing hand with soap at least 20 seconds before and after eating, and after using the toilet should be emphasized³¹. Furthermore, as children with HFMD might have drooling due to painful swallowing, toys should be washed every day to control this disease. Chlorinating the water supply in Tong Fha Subdistrict should be carried out through collaboration with Provincial Waterworks Authority to ensure the residual chlorine level at 0.5 ppm for inactivation of enterovirus³². Lastly, serotypes of enterovirus should be isolated to increase awareness on HFMD with neurological complications and administration of IVIG should be considered.

Control Measures and Follow up

The local surveillance and rapid response team provided health education to teachers, household members and villagers about the disease, personal hygiene and hand washing. Isolation of sick children were recommended if their parents could not take them back to home immediately.

Following the recommendations by the investigation team on 6 Sep 2017, screening and control measures were monitored at the nursery until 22 Sep 2017 when no more ill children were detected. For sanitation, the children washed their hands with soap under supervision of the teachers and they had their own towels. The drinking glasses were cleaned and non-washable items (nap mats, toys, books) were dried under the sun to disinfect every day.

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Suggested Citation

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