

Report on the Hand, Foot and Mouth Disease Outbreak in Fuyang City, Anhui Province and the Prevention and Control in China

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Report prepared by
the Chinese Center for Disease Control and Prevention
the Office of the World Health Organization in China



List of Acronyms

CDC	Center for Disease Control and Prevention
EV71	Enterovirus 71
HFMD	Hand, foot and mouth disease
ICU	Intensive Care Unit
IHR(2005)	The International Health Regulations (2005)
MOH	Ministry of Health
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
WHO	World Health Organization

Contributors

Chinese CDC staff conducted the outbreak investigation, performed the data analysis and drafted the document. WHO staff helped reviewing the data and contributed to the revision of the manuscript.

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Executive Summary

In late March 2008, a hospital clinician was alarmed by the occurrence of 3 consecutive deaths of pre-school children presented with severe pneumonia and rapid deterioration in Fuyang City, Anhui Province. Up until mid-April, 15 children have died of similar severe illness.

Through an investigation conducted by local and national experts, the disease was confirmed on April 23 as hand, foot and mouth disease (HFMD) caused by enterovirus 71 (EV71) based on epidemiological, clinical, laboratory and pathological evidence. Retrospective case investigation revealed that a simultaneous outbreak had occurred in the same area with children presenting skin rashes and blisters over hand, foot, and mouth.

Anhui is an inland province located in the central part of Southeastern China. Fuyang City is located in the Northwest region of Anhui Province and has a total population of 9.76 million. The city covers a total area of 9,700 km² with one of the highest population densities in Mainland China (1,000 per square km). In Fuyang City, from March 1 to May 9, there have been 6,049 reported cases of HFMD of which 353 were severe and 22 were fatal (case fatality rate 0.4%). Retrospective case-finding identified 302 cases that occurred between March 1 and April 22, and revealed that the first case occurred as early as March 10. The number of cases according to date of onset began to increase in early April, and peaked on April 28. The number of reported HFMD cases in Fuyang City decreased after May 5.

Among the 6,049 reported cases in Fuyang City the gender ratio was 1.9:1. The age range varied between 28 days to 18 years of age, with 78% of the cases being 3 years of age or younger. All districts/counties in Fuyang City reported HFMD cases, with more than half the cases concentrated in 3 districts (Yingzhou, Yingdong and Yingquan). Epidemiological investigation revealed no contact between the 22 fatal cases, but environmental investigation of the cases' households revealed poor hygienic and sanitary conditions among these families.

The clinical symptoms of the mild HFMD cases are those typical for the disease: rashes on hands and feet, mouth and buttocks, fever and general malaise. All fatal cases presented an acute onset of fever and influenza-like-illness without catarrhal syndrome. The cases' condition rapidly deteriorated, developing tachypnea, cyanosis, and some presented seizures. All fatal cases died of serious complications such as neurogenic pulmonary oedema due to EV-71 infection.

Testing initial cases for a variety of diseases, including seasonal and avian influenza A/H5N1 and SARS did not reveal any conclusive results. Subsequently, additional testing by Chinese Center for Disease Control and Prevention (CDC) was performed and several

expert consultations were conducted. On April 23, a variety of specimens such as pharyngeal swabs, lung puncture fluid, lung tissues, and blood from 5 out of 12 fatal cases (42%), tested EV71 nucleic acid positive by RT-PCR. EV71 genotype C4 viruses were isolated from specimens of both mild and fatal cases. These sequences from mild and fatal cases exhibited high homogeneity. Isolated EV71 virus strain gene sequences were uploaded to GenBank on May 7.

From January 1 to May 9, 2008, 61,459 HFMD cases and 36 deaths were reported through the disease reporting system in Mainland China. The number of reported cases increased sharply after the disease became notifiable on May 2, and with cases being reported from nearly all provinces. The 5 provinces with the highest number of reported cases are Guangdong (11,374), Anhui (9,235), Zhejiang (6,134), Shandong (4,566) and Henan (3,230).

Because of the change in reporting policy and increased awareness of the general public about the disease, it is expected that there will be an increase in the number of reported HFMD cases in the upcoming weeks and months from Anhui Province and the rest of China.

Non-polio enteroviruses are common and exist worldwide. Although infection often has no symptoms and goes unnoticed, these viruses are also associated with occasional outbreaks in which a larger-than-usual number of patients develop clinical disease, sometimes with fatal consequences.

The initial high case fatality rate of the Fuyang City outbreak, 2.9% (18/610) from March 1 to April 23, was likely attributed to the following factors: rapid disease progression, late clinical presentation, and limited local medical capacities. Although there is no specific treatment for enterovirus infections and a vaccine is not currently available, once the aetiology of the disease was known and early treatment was provided to the severe patients, the case fatality rate decreased considerably to 0.07% (4/5439) from April 24 to May 9, due to enhanced surveillance and implementation of prevention and control measures.

There have been a number of outbreaks of EV71 HFMD in the Asia-Pacific region since 1997. In China, outbreaks have been reported in Taiwan Province in 1998 (>100,000 cases and 78 deaths) and in Shandong Province in 2007 (38,606 cases and 14 deaths).

The Government of China has shown its strong technical and political commitment to control the disease in Anhui and other provinces. In addition to enhanced surveillance, training was provided to clinicians and public health workers to improve the treatment success rate by increasing early identification and treatment of severe HFMD patients. Guidelines were written to enable early admission of severe cases to the hospital, and critical cases to the paediatric ICU. After that, the case fatality rate has decreased substantially. In addition, to prevent HFMD, the Ministry of Health started a nationwide health campaign, stressing the need for personal hygiene, in particular hand washing

practices.

In the future, China is devoted towards enhancing the above-mentioned measures for the prevention and control of HFMD in China. As part of the efforts to implement the International Health Regulations, IHR(2005), China will further strengthen the early warning system by immediate notification of clustering of clinically abnormal and severe cases, as well as increasing international collaboration and information exchange.

Section 1 - Investigation of HFMD Outbreak in Fuyang City, Anhui Province

I. Background

Anhui is an inland province located in the central part of Southeastern China, (29°41'~34°38'N, 114°54'~119°37'E). Two rivers, Yangtze and Huhe, run through the province, which covers an area of 139,600 km². Anhui Province is geographically composed of flatlands with a subtropical climate and has an average annual rainfall accumulation of about 900mm. Fuyang City is located in the Northwest region of Anhui Province and has jurisdiction over 8 counties (district, city) and 172 municipalities. The total population is 9.76 million, including approximately 1.5 million migrant workers that work outside of the city. The city covers a total area of 9,700 km² with one of the highest population densities in Mainland China.

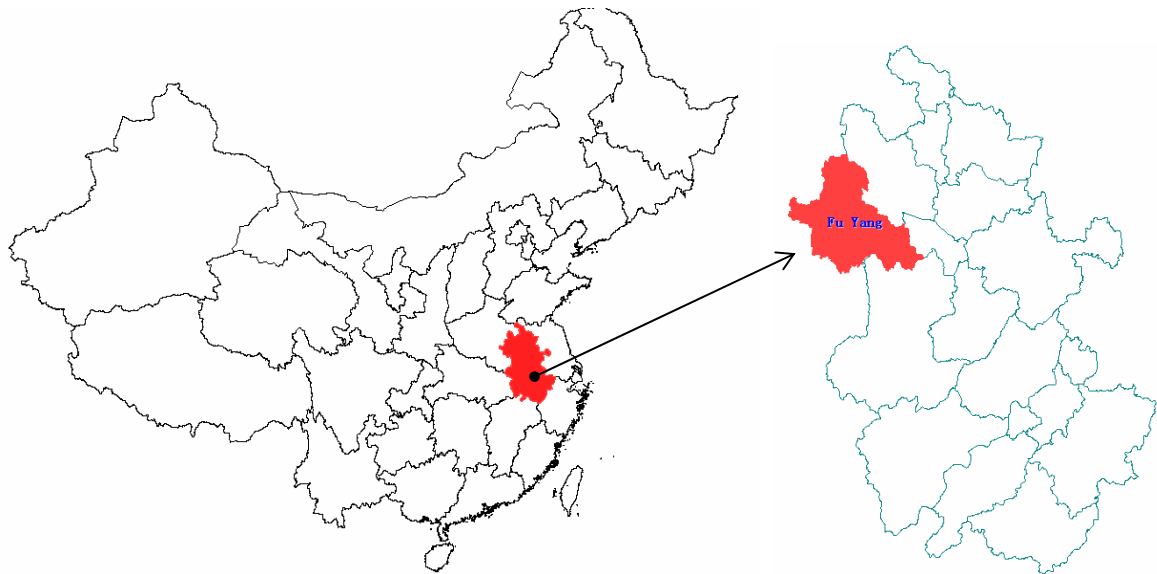


Figure 1. Geographic location of Fuyang City, Anhui Province in China.

II. Outbreak identification and investigation – chronology of events

1. Outbreak identification and reporting

From March 27 to 29 of 2008, 3 infants with severe pneumonia were admitted to the paediatric unit of Fuyang First People's Hospital. All 3 cases died despite medical treatment. These abnormal circumstances alarmed the health-care staff and were reported to the Fuyang Health Bureau.

2. Anhui provincial health department organized investigation

After receiving the report on March 31, Anhui Provincial Health Bureau subsequently dispatched 3 expert groups that included epidemiologists, clinicians and laboratory experts to conduct a field investigation. However, the etiology could not be confirmed at the time, and on April 15, the Anhui Health Bureau asked for assistance from the Ministry of Health (MOH).

3. MOH expert groups assist investigation and control

After receiving the report on April 15, MOH immediately dispatched an expert team comprised of epidemiologists, laboratory experts, clinicians and pathologists. The group arrived in Fuyang City on the morning of April 16 to assist with the epidemiological investigation and with the implementation of prevention and control measures. Afterwards, more experts were sent to Fuyang City to participate in the outbreak investigation and prevention and control.

4. Detection, reporting and treatment of severe cases

Since April 17, based on the main clinical manifestations of early fatal cases, a case definition for severe case screening was formulated and continuously revised in order to detect severe cases at an early stage and increase treatment effectiveness. All health-care facilities in the jurisdiction area were requested to evaluate the admitted suspect cases.

Severe cases are defined as having two of following clinical manifestations:

1. Continuous high fever.
2. Weakness, vomiting, irritability, etc.
3. Abnormal White Blood Cell count (WBC).
4. High blood glucose level.
5. Poor blood circulation of limbs.

All detected severe cases should be admitted for further monitoring and receive in-patient treatment. All the severe cases detected by these criteria were subjected to further investigation and analysis.

5. Laboratory testing and autopsy findings

From April 19 to 21, Chinese CDC performed Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) tests on samples from 12 fatal cases and 11 mild HFMD cases. Five of the fatal cases and 8 of the mild cases tested positive for EV71. Gene sequencing of samples from fatal and mild cases strongly exhibited homogeneity. Findings of the autopsies conducted on three fatal cases strongly suggest viral infection.

6. Etiology confirmation and outbreak information dissemination

On April 22, Chinese CDC organized an expert group composed of epidemiological, clinical, laboratory and pathology experts to review the existing evidence. The experts concluded that enterovirus 71 (EV71) was the main pathogen of the HFMD outbreak in Fuyang City, Anhui Province.

On April 23, MOH confirmed the experts' findings and recommendations. On the same day, Anhui Health Bureau disseminated the Fuyang City EV71 outbreak information on its website.

7. Surveillance and review of HFMD

Based on the results of the epidemiological investigation and etiology study, Fuyang City started HFMD case surveillance reporting on April 22, requesting all township and county or higher level healthcare facilities to report cases on a daily basis. Each day, surveillance output is reported through the submission of reporting forms. Since May 2, the web-based national disease surveillance and information management system also includes HFMD.

HFMD was not previously categorized as a notifiable infectious disease. In order to assess the local HFMD situation prior to the reclassification of HFMD, the MOH expert team conducted a HFMD retrospective review of data from all health care facilities in the jurisdiction area and were able to identify 302 unreported cases. The HFMD case inclusion criteria were as follows:

Any child under the age of 7 that sought medical care in Fuyang City between March 1 and April 21, 2008 which showed the following symptoms:

- Skin rash or blisters on hand, foot, or buttock, *and* fever, *in the absence of* measles, rubella, chicken pox and other febrile eruption diseases
- Skin rash or blisters on hand, foot, or buttock, *and* ulcers on the mouth or mucous membrane, *in the absence of* drug-related rash or allergy.

III. Investigation Results of Outbreak in Fuyang City

1. Characteristics of the outbreak

From March 1 to May 9, 2008, there were 6,049 HFMD cases reported in Fuyang City, of which 3,023 were hospitalized, 353 were severe and 22 were fatal. Hospitalized cases accounted for 50% of cases, and severe cases accounted for 6%. The incidence rate¹ was 69.6/100,000; while the case fatality rate was 0.4%. The 6,049 reported HFMD cases include 302 HFMD cases that occurred from March 1 to April 22 and were identified through retrospective investigation.

A. Descriptive analysis of reported cases

1) Epidemiological data

The gender ratio of the 6,049 reported cases in Fuyang City was 1.9:1 with 3,938 male cases and 2,111 female cases. The age range of the reported cases in Fuyang City varied between 28 days to 18 years of age; while the highest number of cases was found in children 3 years of age or younger (4,708 cases, 78% of all cases). (See Table 1).

Table 1. HFMD cases by age group and gender from March 1 to May 9, 2008 in Fuyang City

Age group (years)	Male		Female		Total	
	No. of cases	Incidence rate (‰)	No. of cases	Incidence rate (‰)	No. of cases	Incidence rate (‰)
0-	450	7.05	265	4.49	715	5.82
1-	1083	17.85	578	10.36	1661	14.27
2-	964	16.26	505	9.27	1469	12.91
3-	579	9.85	284	5.26	863	7.65
4-	366	6.20	166	3.06	532	4.69
5-	225	3.76	126	2.29	351	3.06
6-	102	1.78	67	1.66	169	1.73
7-	50	1.50	33	1.49	83	1.49
8-	42	0.88	18	0.57	60	0.76
9-	19	0.33	10	0.26	29	0.30
10-	15	0.04	22	0.07	37	0.05
11-15	40	0.07	33	0.07	73	0.07
16-20	1	0.00	2	0.01	3	0.00
20-	0.00	0.00	0.00	0.00	0.00	0.00
Unknown	2	-	2	-	4	-
Total	3938	0.91	2111	0.52	6049	0.70

All districts/counties of Fuyang City have reported cases with the highest number of cases in Yingzhou, Yingdong and Yingquan districts. The total number of cases reported by these

¹ HFMD cases reported by routine and enhanced surveillance system during the period, divided by the total population in Fuyang city

districts accounted for 56% (3,288 cases) of the total number of reported cases in Fuyang City. The incidence rates were also high in these three mentioned districts. (See Figure 2).

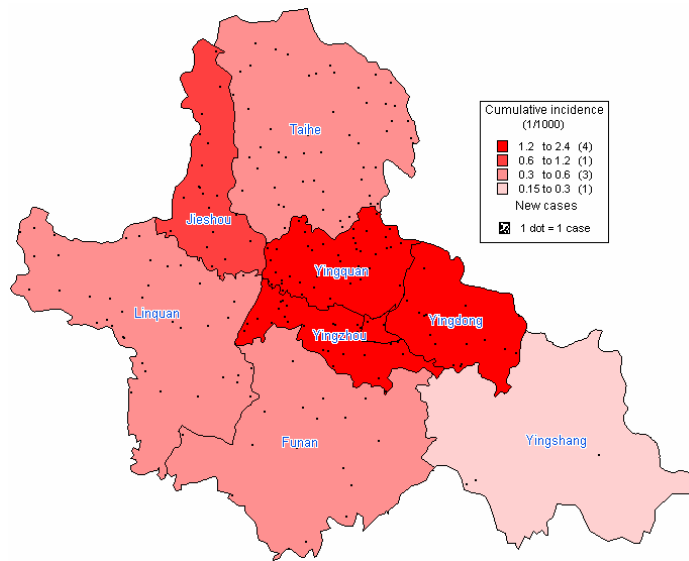


Figure 2. Incidence rate by districts/counties of Fuyang City, from March 1 and May 9, 2008

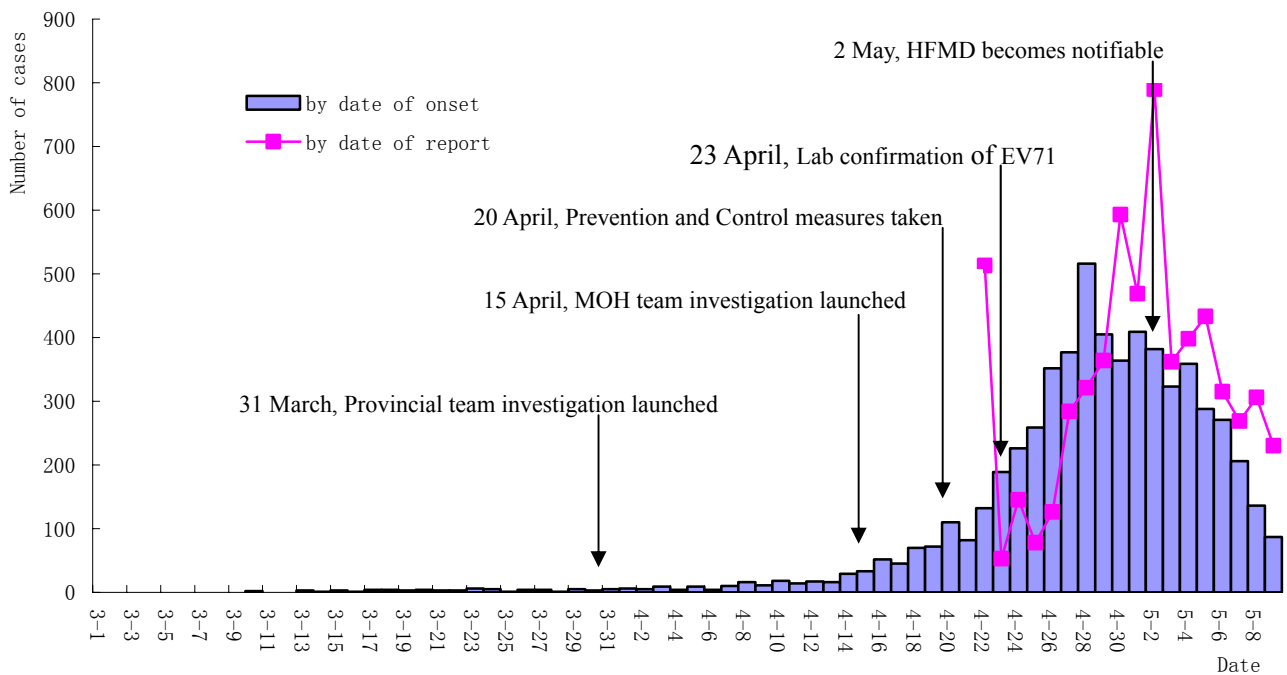


Figure3. The number of HFMD cases by date of onset and date of reporting from March 1 to May 9, 2008 in Fuyang City

Figure 3 shows the distribution of the number of HFMD cases by date of onset and date of reporting between March 1 and May 9, 2008 in Fuyang City. Although the first case of HFMD occurred on March 10, the number of cases by date of onset only began to increase in early April with a rapid increase between April 16 and April 28. After April 28, the number of cases by date of onset decreased while the number of reported cases by date of reporting continued increasing until May 5 after which it decreased as well. Figure 4 shows

the total number of hospitalizations and discharges of HFMD cases per day between April 25 and May 7 in Fuyang City. The daily number of hospitalizations of HFMD cases, which had been increasing since April 29, has been decreasing since May 7.

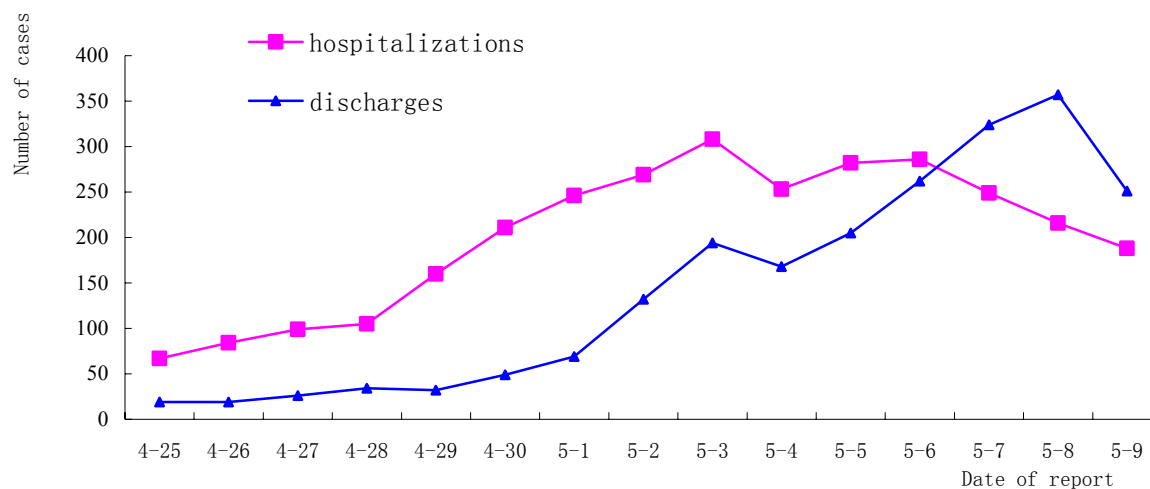


Figure 4. Daily number of hospitalizations and discharges of HFMD cases from April 25 to May 9 in Fuyang City.

2) Clinical symptoms

The clinical symptoms of 65 HFMD cases hospitalized in Fuyang No.2 Hospital were analyzed. The main clinical symptoms included rash, fever, general malaise, cough, and vomiting. Rashes (vesicular lesions/ulcers) were mostly localized on hands and feet (99%), mouth (80%) and buttocks (42%). Some cases had rashes around the anus, on their face or all over their bodies. (See Table 2). Routine blood tests were conducted on blood specimens collected from 39 of the 65 HFMD cases studied. The obvious abnormality reported was an elevated White Blood Cell count (WBC) in 15 (39%) of the samples tested.

Table 2. Clinical symptoms of hospitalized HFMD cases in Fuyang No.2 hospital (n=65).

Clinical symptom	Number of cases	Proportion (%)
Rash	65	100
Fever	46	70.8
General malaise	20	30.8
Coughing	12	18.5
Vomiting	8	12.3
Nasal discharge	6	9.2
Convulsion	4	6.2
Nasal occlusion	2	3.1
Diarrhea	2	3.1
Stiff neck	2	3.1
Pharyngalgia	1	1.5
Myoclonic twitching	1	1.5



Figure 5. Comparison of HFMD critical case prior (left) and after (right) medical treatment was provided at Fuyang No.2 hospital.



Figure 6. The rash of HFMD cases (on hand and foot)

B. Descriptive analysis of the initial fatal cases

1) Epidemiological data

As of May 9, there have been 8 consecutive days without any fatalities reported by Fuyang City (See Figure 7). For the 22 fatal cases reported to date in Fuyang City, the gender distribution was 1:1, and age ranged between 3 months and 3 years. The number of fatal cases in age groups 0-, 1-, 2-, 3- was 6, 8, 7, 1, which accounted for 28%, 36%, 31% and 5% of cases, respectively. Fatal cases were reported in 5 districts and counties: Yinzhou (9, 41%), Yingquan (6, 27%), Funan (4, 18%), Linqun (2, 9%) and Yindong (1, 5%). The majority of fatal cases occurred in rural areas. Figure 5 shows the distribution over time according to date of onset of the fatal cases reported in Fuyang City between March 23 to April 29.

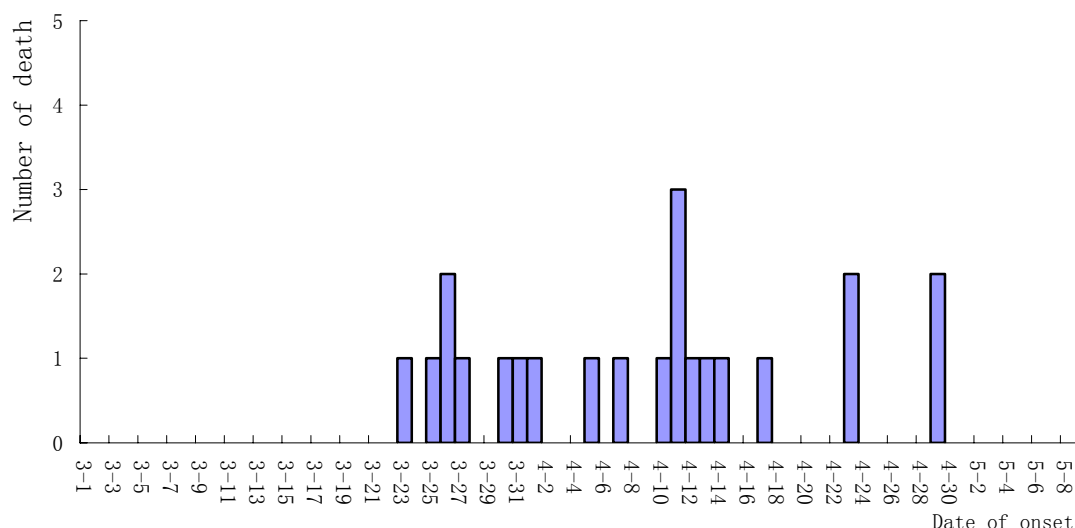


Figure 7. Fatal cases (n=22) by date of onset from March 23 to April 29 in Fuyang City.

2) Clinical symptoms

Data from 15 out of 22 fatal cases were analyzed. All cases were infants and had an acute onset of fever and influenza-like illness without catarrhal syndrome. Following general treatment guidelines for infectious respiratory diseases, local village or private doctors treated the patients with antibiotics without visible results. The condition of the cases deteriorated, developing tachypnea, cyanosis, and some presented seizures with foaming at the mouth of white or pink color. (See Table 3). Most hospitalized cases were preliminary diagnosed as severe pneumonia. Despite proactive medical procedures taken, the severe cases deteriorated rapidly and died. The mean duration between onset of symptoms and the hospitalization was 2 days; between hospitalization and time of death, 10 hours; and between onset of symptoms and time of death, 3 days. Further information on clinical conditions of the patients and their treatment will be discussed in an upcoming report.

Table 3. Clinical symptoms of fatal HFMD cases in Fuyang No.2 hospital (n=15).

Clinical symptom	Number of cases	proportion%
Fever	15	100
Tachypnea	14	93.3
Oral cyanosis	12	80.0
Pink foaming at the mouth	9	60.0
Coughing	7	46.7
Vomiting	8	53.3
Myoclonic twitching	3	20.0
Rash on palm, sole	6	40.0
Nasal discharge	2	13.3
Stiff neck	2	13.3

3) Exposure information

Epidemiological investigation revealed no contact between the 22 fatal cases. All cases were infants who had remained at home during the 2 weeks before the onset of symptoms. One case had been vaccinated within 1 month prior to onset of symptoms. Environmental investigation of the cases' households showed poor hygienic and sanitary conditions. All affected families had their own water well and none reported abnormalities after food consumption. In addition, no livestock die-off was reported by the affected families or in their village.

2. Laboratory testing and autopsy findings

A. Laboratory testing of fatal cases

Between March 31 and April 16, the Anhui CDC tested 53 specimens (including whole blood, blood serum, pharyngeal swab and tissue samples), collected from fatal HFMD cases, and tested negative for the presence of seasonal influenza, avian influenza A/H5N1, Severe Acute Respiratory Syndrome (SARS) .

On April 18, the Institutes of Infectious Diseases and the Viral Diseases Prevention and Control of Chinese CDC received from Anhui CDC the previously collected specimens: pharyngeal swabs, lung puncture fluid, lung tissues, and blood. Laboratory testing for the presence of bacteria and virus was performed immediately on these samples. Specimens from 5 out of 12 fatal cases (42%) tested EV71 nucleic acid positive by RT-PCR. Of these 5 EV71 positive fatal cases, the lung tissue specimen tested EV71 positive for 1 case, and for another case, the intestinal lymph nodes, cerebrospinal fluid, spleen, thymus, kidney, brain, heart and lung specimens were EV71 positive. For the other 3 cases, the pharyngeal swabs were EV71 positive.

Viral isolation was conducted on 6 different types of specimens (including lung tissue, mouth efflux, brain tissue and pharyngeal swab) collected from 3 fatal cases. For all 6 specimens, the nucleotide sequencing and neutral antibody tests revealed the presence of EV71 virus.

B. Autopsy findings

The autopsy on 3 fatal cases performed by the Medical School of Beijing University, found mainly changes in the brain, lung, heart and lymphatic system. There were cases of severe brain oedema; lung congestion/pulmonary oedema, no significant lung inflammation, no significant bleeding; cardiac enlargement; hypertrophy of tonsils, thymus and lymph nodes; spleen enlargement; normal kidney, liver and gastrointestinal organs. The autopsy findings were overall consistent with the clinical manifestations and disease progression and strongly suggest viral infection.

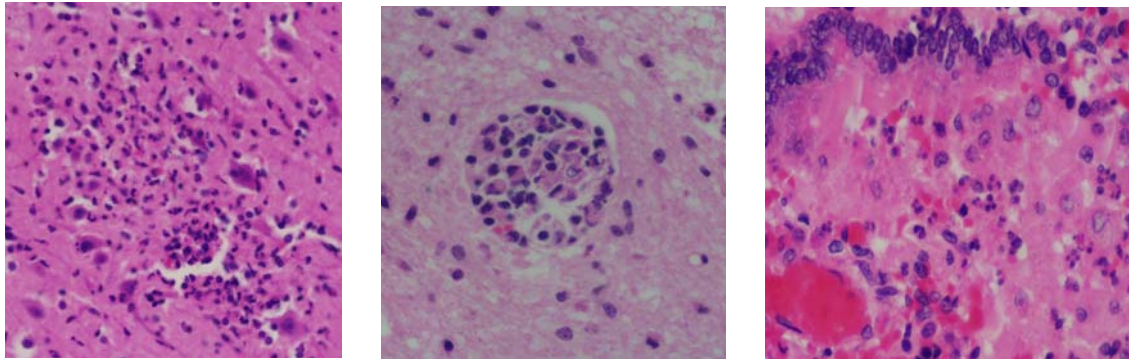


Figure 8. Left: brain tissue; Middle: spinal cord; Right: bronchus.

C. Etiology study of mild HFMD cases

RT-PCR testing for EV71 was performed on 122 different Fuyang city specimens, including pharyngeal and rectal swabs, of which 61 (50%) were EV71 nucleic acid positive. Gene homogeneity was 99.3%-99.97% between the virus strains from mild cases (2 strains were from 2 mild cases) and fatal cases (6 strains were from 3 fatal cases). No neuro-virulence site mutation of the EV71 virus was found among severe and mild cases through bioinformatics analysis. Chinese CDC submitted the gene sequences of 3 virus strains to GenBank on May 7.

Section 2 – Situation Analysis of HFMD in China

I. Current HFMD situation in China

1. HFMD surveillance

Before May 2, HFMD was not categorized as a notifiable disease and reporting of HFMD relied on voluntary reports submitted by clinicians. Since May 2, HFMD has been established as a class “C” notifiable disease, indicating that all clinical and laboratory diagnosed cases are reported through the web-based national disease surveillance and information management system. Standards for the clinical and laboratory diagnosis of HFMD cases can be viewed at the MOH website.²

2. Occurrence of HFMD in China

From January 1 to May 9, 2008, 61,459 HFMD cases were reported through the disease reporting system in Mainland China. The incidence rate was 4.5/100,000, and the number

² Guideline for HFMD prevention and control, 2008 edition

<http://202.96.155.170/publicfiles/business/htmlfiles/mohjbyfkzj/s3577/200805/34775.htm>

of deaths reached 38 (case fatality rate 0.06%).

1) Time distribution

The number of reported cases has been increasing since April 28. After categorizing HFMD as a class “C” notifiable disease, reported cases increased sharply. For HFMD time distribution and date of reporting see Figure 9.

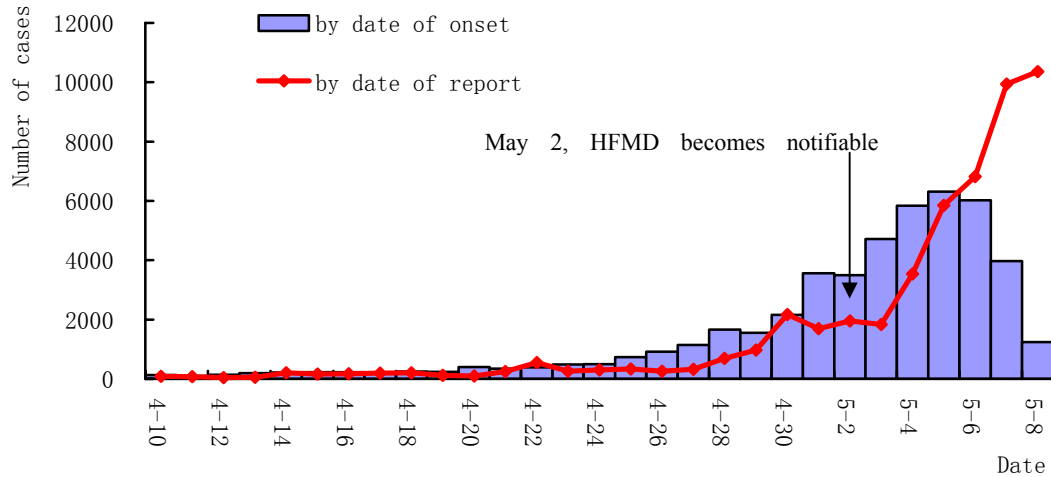


Figure 9. The number of HFMD cases by date of onset and date of reporting from April 10 to May 9, 2008 in China.

2) Geographical distribution

HFMD cases were reported in nearly all provinces in Mainland China. The 5 provinces with the highest number of reported cases are Guangdong (11,374), Anhui (9,235), Zhejiang (6,134), Shandong (4,566) and Henan (3,230).



Figure 10 Incidence rate of HFMD cases by province in China from Jan 1 to May 9, 2008

3) Age distribution

Children under 5 years old accounted for 92% of reported HFMD cases primarily affecting children ages 1 to 3 years old. See Figure 11 for the age distribution of HFMD in China.

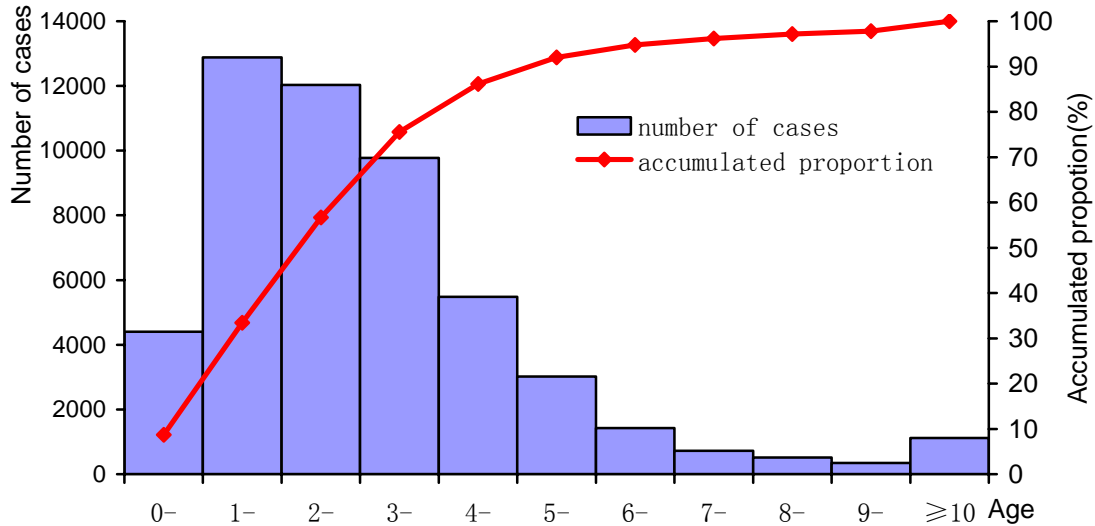


Figure 11. HFMD cases by age in China from January 1 to d May 9, 2008

3. Laboratory surveillance

After the identification of the HFMD outbreak in Fuyang City, Chinese CDC immediately began national-wide targeted laboratory testing on samples from HFMD cases. Up until May 9, 582 cases of samples from 23 provinces were tested positive for HFMD: EV71 accounted for 54.5%, Coxsackie A16 accounted for 17.4%, and other enteroviruses accounted for 28.2%.

II. HFMD and EV71 infection in China before 2008

The first reported case of HFMD in Mainland China occurred in Shanghai in 1981. Since then, cases have been reported in Beijing, Hebei, Tianjin, Fujian, Jilin, Shandong, Hubei, Qinghai and Guangdong. In 1995, the Wuhan Virus Institute isolated the EV71 virus from HFMD patients. In 1998, Shenzhen CDC also isolated the EV71 virus from HFMD patients. There was a HFMD and Herpangina outbreak in Taiwan in 1998 with two outbreak waves occurring in June and October. 129,106 cases were reported from sentinel sites with a total of 405 severe cases and 78 deaths. The majority of cases were children under 5 years of age, and complications included encephalitis, aseptic meningitis, pulmonary oedema/pneumorrhagia, acute flaccid paralysis and myocarditis. In 2007, an HFMD outbreak occurred in Linyi City of Shandong Province with a total of 39,606 cases reported, including 14 deaths. Laboratory testing found the main etiologic pathogen to be EV71

while other detected enteroviruses were Echo3 and/or Coxsackie A16.

In 2007, there were 83,344 HFMD cases identified in Mainland China. The incidence rate was reported as 6.34/100,000 with a total of 17 deaths and case fatality rate of 0.02%. The majority of cases occurred in pre-school children (41% of all cases) or children in childcare centres (52%). Prevalence of HFMD in children under 10 years of age was high, accounting for 97% of total reported cases. The HFMD peak season is from May to October with most cases occurring between June and July (see figure12). However, this may vary since HFMD was not a notifiable disease before 2008. Information on reported cases may be incomplete. Therefore, it is difficult to make an accurate estimation of past HFMD incidence in China.

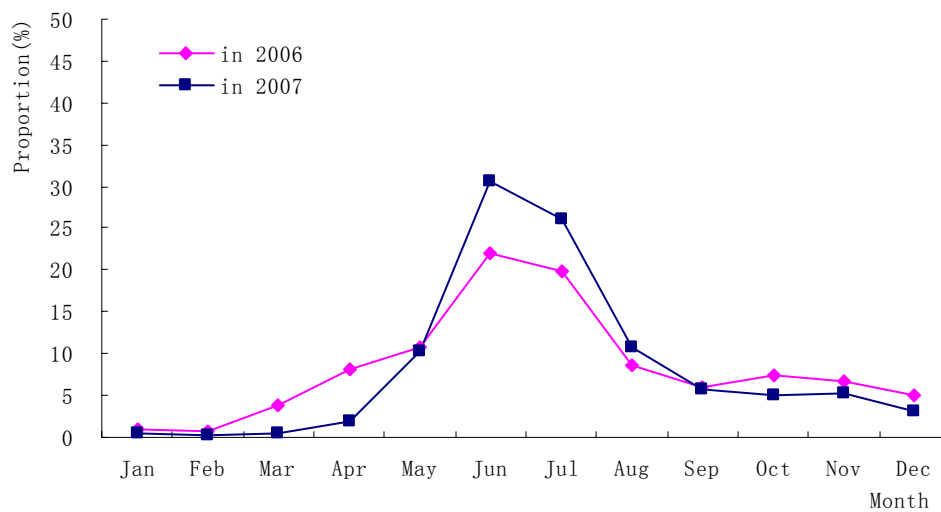


Figure 12 The distribution of HFMD cases by month in 2006 and 2007

Section 3 – Outbreak Response in Fuyang City, Anhui Province and China

I. The main response to the Fuyang City outbreak

1. Strengthening of disease surveillance

A case definition was formulated for the early detection of severe cases and for the reporting, monitoring and treatment of severe cases.

A HFMD reporting protocol was developed, and daily reporting of HFMD is performed at each level of health care facility.

2. Optimization of patient treatment and minimization of case fatalities

This includes the following:

- Designation of specific hospitals for the treatment of EV71-infected patients, who are allocated as follows: mild cases are sent to nearby health care facilities while designated hospitals focus on the treatment of severe cases.
- Establishment or expansion of paediatric Intensive Care Unit (ICU) facilities.
- Organization of training for high-level national and provincial ICU staff.
- Formation of a specialized medical team and 24 hour on-duty service.
- Enhancement of the monitoring and evaluation of severe cases based on clinical symptoms.
- Clinical monitoring for the early detection of severe cases and early provision of interventions to minimize fatalities.

3. Establishment of patient triage system and control of nosocomial infections

Consultation rooms were established for febrile rash cases within fever outpatient clinics or paediatric wards to prevent cross-transmission among other sick children. Medical equipment is required to be sterilized for each patient.

4. Strengthening technical guidance, development of technical training and improvement of health-care workers' professional skills

The national expert team has developed guidelines for the diagnosis and treatment of HFMD cases, a sampling plan and a HFMD prevention and control plan. The national expert team also assisted Anhui CDC in improving the quality of the provincial enterovirus laboratory. National and provincial experts have guided designated hospitals in Fuyang City in establishing paediatric ICU and have trained 350 health-care workers from 16 cities in Anhui Province on clinical diagnosis, ICU treatment, and epidemiological and sampling skills.



Figure13. Dr. Zhu Chen, Chinese Minister of MOH, visiting a HFMD patient at Fuyang No.2 People's Hospital on April 26, 2008.

5. Establishment of full scale prevention and control measures with focus on childcare centres and schools.

- a. Emphasis placed on promoting health education, disseminating information leaflets, and increasing public awareness.
- b. On a daily basis, the teacher in charge is expected to perform a clinical inspection of pupils in the morning, record absenteeism and reason for absence, and report daily to the local CDC. If children present with fever and rash, their parents should be informed immediately and should seek medical care. Subsequently, disinfection of the school building, tables, chairs and personal belongings should be conducted.
- c. Childcare centres are to disinfect toys daily, and tables should be disinfected before and after meals. Before and after class, the classrooms and school building should be ventilated by opening doors and windows for over 30 minutes.
- d. When 3 or more febrile/rash cases are identified per class, it should be reported to the local CDC immediately. The class should be divided or dismissed in order to avoid a possible outbreak situation.

6. Establishment of HFMD medical fee assistance measure

In order to ensure the prompt treatment of HFMD patients, especially severe cases, Fuyang City enacted the HFMD medical fee assistance measure to reimburse medical fees based on the new rural cooperative medical care regulation. This measure also provides free treatment to severe HFMD cases from low income families.

II. Current response measures for HFMD in China

HFMD is a common acute infectious disease that is widespread, and the peak season ranges from May to October. Following the death of many severe HFMD cases in Fuyang City and in order to strengthen HFMD surveillance, prevention and control and to protect the public's health, the Chinese Government enacted the following major outbreak response measures at the national level:

1. Formation of a HFMD taskforce group

On May 3, MOH formed a taskforce group for HFMD prevention and control with Minister Zhu Chen as team leader and deputy ministers Qiang Gao, Xiaowei Ma, Qian Liu as vice team leaders. There are 4 subgroups within this taskforce group: coordination, outbreak prevention and control, medical treatment and information dissemination.

2. Categorization of HFMD as a class "C" notifiable disease, prompt detection and treatment of severe cases and understanding the outbreak situation

Since May 2 2008, MOH categorized HFMD as a class "C" notifiable disease. All health care centres should report HFMD according to the "Law on notifiable infectious diseases prevention and control of the People's People's Republic of China" and "Infectious diseases report management regulation."

3. Strengthening implementation of HFMD prevention and control measures

- a. On April 29, MOH issued the "Notice on the enhancement of HFMD and other enterovirus infectious diseases prevention and control measures." It requested all levels of health departments to emphasize prevention and control of HFMD and other infectious diseases caused by enteroviruses.
- b. Since April 30, several guidelines have been published on the MOH website, including, "Guideline for HFMD medical treatment" and "Guideline for HFMD prevention and control (2008 edition)."

4. Increasing information exchange

Outbreak information was disseminated in a timely manner according to related national and international regulations. Information on the event was reported to WHO when EV71 was found as the causal agent of the outbreak by Chinese CDC on April 23. The gene sequence of isolated EV71 virus strain was submitted to GenBank³ on May 7. Six outbreak

³ The website is <http://www.ncbi.nlm.nih.gov/sites/entrez?db=nucleotide>. The serial numbers are: bankit1092219 EU703812; bankit1092307 EU703813; bankit1092309 EU703814.

information newsletters were also disseminated to Health Departments of Hong Kong, Macau and Taiwan since the beginning of the outbreak.

5. Improvement of health education

Prevention and control measures for HFMD are being promoted through various channels, and early reporting of symptomatic cases is encouraged.

Section 4 – Discussion

I. General background information on HFMD

HFMD is a common infectious disease caused by various enteroviruses, including EV71 and Coxsackie A. The predominant feature of HFMD is high morbidity in infants. HFMD is spread worldwide throughout the year and is transmitted predominantly by fecal-oral transmission, respiratory droplets, contact with case's blister fluid or general close contact with cases.

EV71, a non-polio enterovirus, was first identified in 1969. It is reported that the clinical manifestations of EV71 infection varies from classical HFMD symptoms to herpangina, aseptic meningitis and encephalitis. Fifty to 80% of cases are asymptomatic or have mild flu-like symptoms. A few cases have severe nervous system damage that may result in death. The case fatality rate of severe cases is 10%-25%. No enterovirus vaccine is currently available. And because EV71 have a high asymptomatic infection rate, and can survive for long periods of time in the environment or sewage, it is a challenge to prevent and control.

II. HFMD outbreak in Fuyang City due to EV71 infection.

The HFMD outbreak in Fuyang City, Anhui Province that started in late March 2008 was caused by EV71 infection. Severe cases in Fuyang City are similar in terms of clinical manifestations and coincide with the population distribution, clinical manifestation and pathological findings of severe cases in the 1998 Taiwan outbreak and 2007 Shandong outbreak of EV71. Currently, testing of samples from Fuyang City cases reveal that the main etiologic pathogen is EV71. EV71 nucleic acid was identified in severe and mild cases in Fuyang City, and the viral nucleotide sequence was highly homogeneous.

III. Analysis of risk factors for high mortality rate in the initial phase of the outbreak

The case fatality rate for HFMD in Fuyang City, Anhui Province varied over time. Initially, from March 1 to April 23, it was 3% (18/610) and subsequently decreased to 0.07% (4/5439) from April 24 to May 9.

The initial high case fatality rate of the Fuyang City outbreak was likely attributable to the following factors:

- a. According to the investigation of fatal cases, in the early clinical phase most cases had mild symptoms and were either treated as usual by rural doctors and private clinics or did not seek medical care. Most cases suddenly deteriorated in the first 2 or 3 days of clinical treatment with the situation worsening by the time of hospitalization, often already past the optimal time for treatment. The average time interval between hospitalization and time of death was only 10 hours.
- b. Sixty percent of severe cases had no rash and therefore increased the difficulty for clinical doctors to diagnose enterovirus infection.
- c. The proportion of severe cases caused by EV71 is higher and more likely to result in rapid disease progression and central nervous system damage with severe complications such as brainstem encephalitis, neurogenic pulmonary oedema, etc.
- d. Mild cases normally did not seek medical care, and were therefore more difficult to detect and report. Underestimation of the number of mild cases based on hospital registration and disease reporting is possible.
- e. The precarious socioeconomic status of some of the affected families may have resulted in a delay of presenting the patient to the hospital.

Based on the field investigation, no geographical clustering of HFMD cases was found around the severe cases in the initial stage of the outbreak while those severe cases and deaths occurred in Fuyang city. Further investigation of this is needed.

IV. Risk assessment

1. Risk of individual infection

Everyone is at risk of infection, but not everyone who is infected becomes ill. Young children under 5 years old are most susceptible. The clinical manifestation of most cases is mild. Since enteroviruses are omnipresent, it is likely for adults and older children to have immunity. The main transmission route for enterovirus 71 is via respiratory droplets, contact with fluid in the blisters or contact with infected faeces. The risk of transmission

can be minimized by avoiding contact with known infected individuals or activities that are of risk and by improving personal hygiene.

2. Risk of transmission

HFMD is a relatively common disease even outside of Fuyang City and other areas of China. There have been a number of outbreaks of EV71 HFMD in the Asia-Pacific region since 1997. Outbreaks have been reported in Bulgaria (1975), Malaysia (1997), Australia (1999) and Singapore (2000) among other areas in the region⁴. In China, an outbreak of HFMD due to EV71 was reported in Taiwan Province in 1998 with a total number of 129,106 cases of HFMD and Herpangina, of which 405 cases were severely ill and 78 cases were fatal⁵. Last year, Shandong Province experienced a HFMD outbreak with more than 40,000 cases and 14 deaths. This year, the number of EV71 cases has increased in Singapore⁶ and Vietnam⁷ while the disease has also been reported in Malaysia⁸.

HFMD caused by EV71 is very common and not an emerging infectious disease. The public health impact of HFMD is not more serious than other common childhood diseases such as measles, Japanese encephalitis, epidemic meningitis, infectious diarrhea and pneumonia. According to the Chinese Ministry of Health it is not necessary to take public health measures regarding travel restrictions and quarantine in order to prevent the spread of the disease. WHO does not recommend restricting travel and trade to affected countries or regions but emphasizes improving personal hygiene for disease prevention.

V. Future work plan

1. Intensify the monitoring and control of EV71 infection

The Chinese government recognized the containment of HFMD as a high priority. The local governments are conducting a large-scale health education and public health promotion campaign to improve personal hygiene and ameliorate environmental sanitation. The Chinese MOH will continue to collect data on the clinical diagnosis and treatment of severe EV71 cases from Fuyang City and Anhui Province, evaluate existing control measures and strategies, update the technical guidelines and promptly organize training for paediatric doctors and public health workers in order to provide guidance on HFMD prevention and control in China.

Chinese CDC will further improve the technical capacity of its public health laboratory

⁴ http://www.who.int/csr/don/2008_05_07/en/index.html

⁵ <http://www.cdc.gov/ncidod/EID/vol9no3/02-0285.htm>

⁶ <http://www.sgdi.gov.sg/>

⁷ <http://www.thanhniennews.com/healthy/?catid=8&newsid=38319>

⁸ <http://thestar.com.my/news/story.asp?file=/2008/4/24/nation/21045923&sec=nation>

network for enterovirus identification and monitoring in order to identify the enterovirus strains circulating in endemic areas and to analyze the molecular epidemiological characteristics of different strains and assess their clinical severity.

2. Improve and enhance the public health event surveillance and early warning system

MOH will reinforce the legislation for communicable disease surveillance and public health event reporting and improve the early warning and response for public health emergencies as part of an effort to implement the International Health Regulations, IHR (2005)⁹. The International Health Regulations (2005) are an international legal instrument which is legally binding for all WHO Member States. The purpose and scope of the IHR (2005) are to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade.

Recently, the Ministry of Health requested all doctors and public health workers to report deaths and clusters of severe cases of unknown cause immediately to the local health department. Subsequently, the local health department should promptly report these cases to MOH.

3. Strengthen international cooperation and information exchange

The Chinese government will share information on the HFMD outbreak and experience of containment and clinical treatment with WHO and other countries. Furthermore, the government plans to increase international cooperation to strengthen scientific research of enterovirus infection.

⁹ http://www.who.int/topics/international_health_regulations/en/