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研究報告の 概要	<p>2008年3月後半、阜陽市(安徽省)で一人の病院臨床医が、重篤な肺炎と症状の悪化が急に進む未就学児症例が連続して3例発症したことによって、危険性を察知した。4月中旬までに、15人の小児が同様の重篤な疾患で死亡した。現地および国の専門家によって行われた疫学、臨床、検査及び病理のエビデンスに基づき、その疾患はエンテロウイルス 71(EV71)が引き起こす手足口病(HFMD)であることが4月23日に確認された。回顧的な症例調査により、小児が手、足及び口に皮膚発疹と水泡を示し、同じエリアで同じ時期に大流行していることが明らかになった。</p> <p>阜陽市では、3月1日から5月9日の間に6,049例のHFMDが報告され、353例が重篤、そして22例が死亡した(致死率0.4%)。回顧的な症例所見により、3月1日から4月22日の間に302例の発生が確認され、第1症例は早くも3月10日に発生したことが明らかになった。発症日を基にした患者数は、4月初めに増加し始め、4月28日にピークに達した。阜陽市で報告されたHFMD症例数は、5月5日以後減少した。阜陽市で報告された6,049症例中、性比は1.9:1であった。年齢範囲は生後28日から18歳であり、3歳以下が78%を占めた。阜陽市の全ての地区/郡は、HFMD症例を報告し、3つの地区(Yingzhou, YingdongとYingquan)に半分以上の症例が集中した。疫学的な調査において、22の致死症例の間に接触はみられなかったが、症例の家庭の環境的調査でこれらの家庭内の低い衛生状態が明らかになった。</p> <p>2008年1月1日から5月9日までの61,459のHFMD症例と36例の死亡は、中国本土の疾患報告制度を通して報告された。5月2日に届出が必要になった後、報告症例数は急激に増加し、ほとんどすべての行政区から報告された。最も多く症例を報告した行政区は、広東(11,374)、安徽(9,235)、浙江(6,134)、山東(4,566)と河南(3,230)であった。</p> <p>非ポリオエンテロウイルスは、ありふれたウイルスで世界中に存在する。感染は多くの場合症状を示さず、気づかれませんが、これらウイルスは、時折通常より多くの患者に臨床的症状が現れ、時々死亡を伴う。1997年以降、アジア太平洋地域でEV71 HFMDの多くの大流行があった。中国では、大流行が、1998年に台湾省(100,000以上の症例、78例の死亡)で、2007年に山東省(38,606症例、14例の死亡)であった。</p>					使用上の注意記載状況・その他参考事項等
	<p>報告企業の意見</p> <p>中国の阜陽市(安徽省)でエンテロウイルス 71による手足口病が大流行し、中国全土でも手足口病が流行しているとの報告である。 本剤の原料血漿は国内献血血漿のみであり、中国からは輸入していない。 また、万一原料血漿にエンテロウイルスが混入したとしても、EMC及びCPVをモデルウイルスとしたウイルスバリデーション試験成績から、製造工程において十分に不活化・除去されると考えている。</p>					

7

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

May 2008



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.

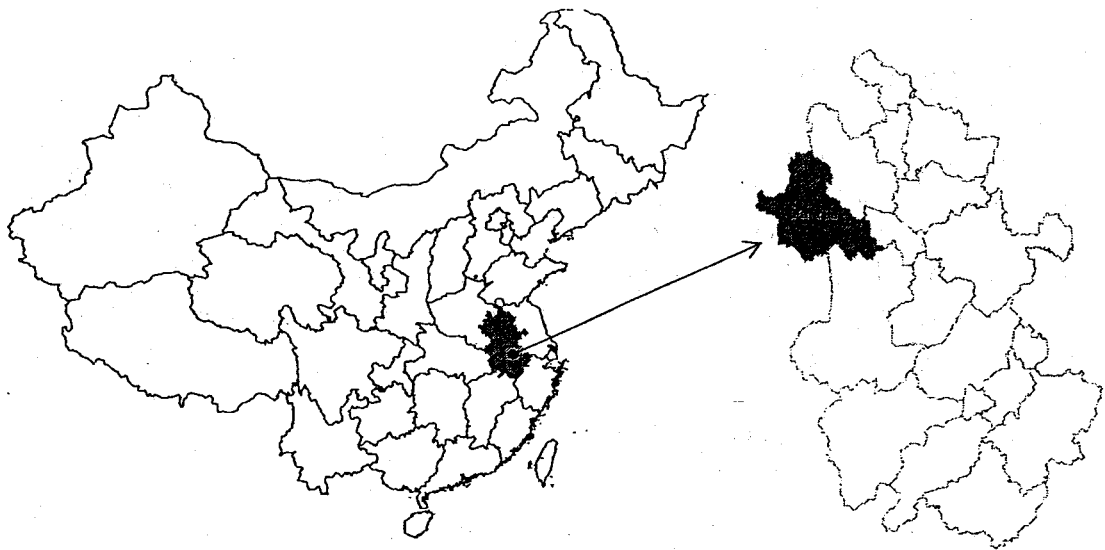


Figure 1. Geographic location of Fuyang City, Anhui Province in China.

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).

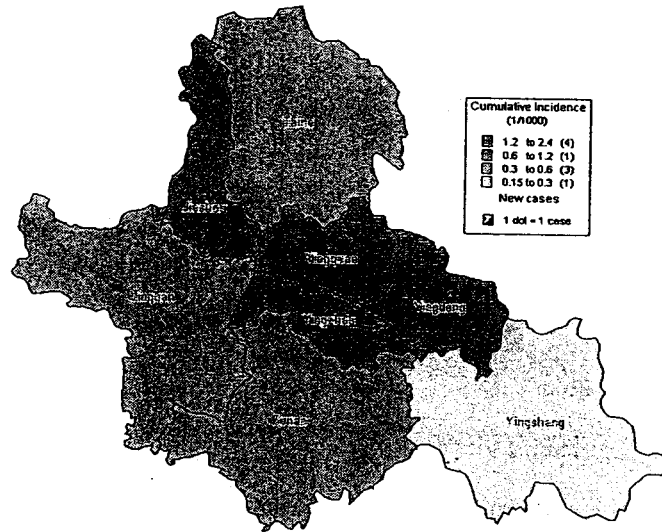


Figure 2. Incidence rate by districts/counties of Fuyang City, from March 1 and May 9, 2008

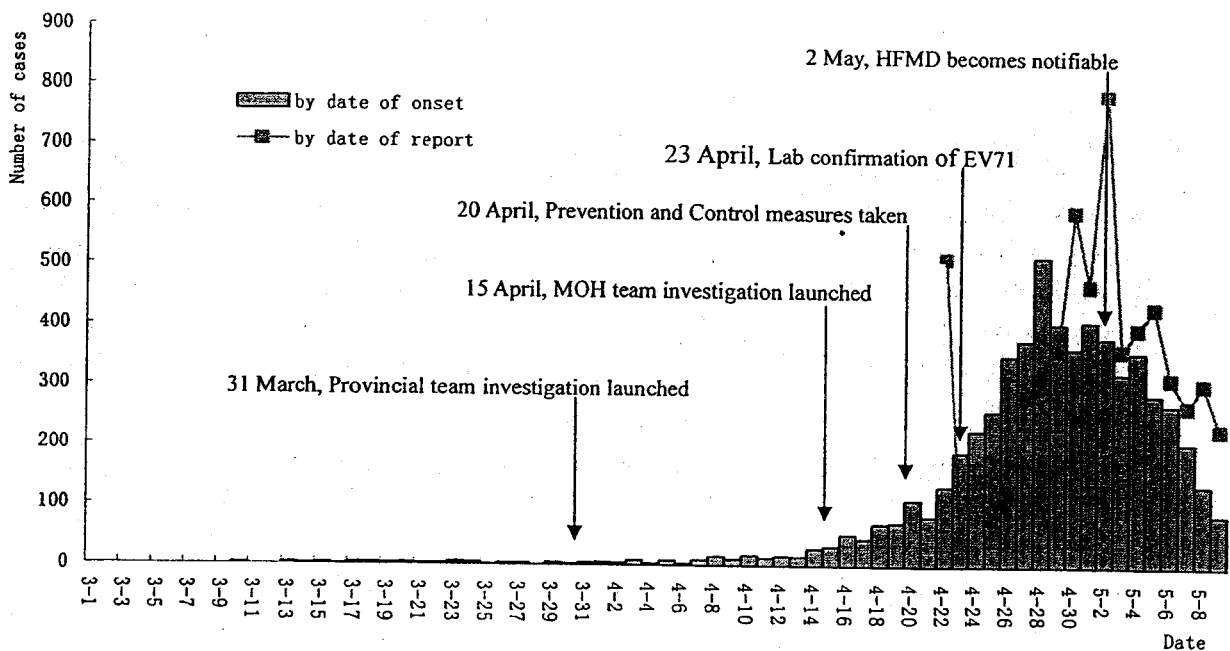


Figure 3. The number of HFMD cases by date of onset and date of reporting from March 1 to May 9, 2008 in Fuyang City

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.

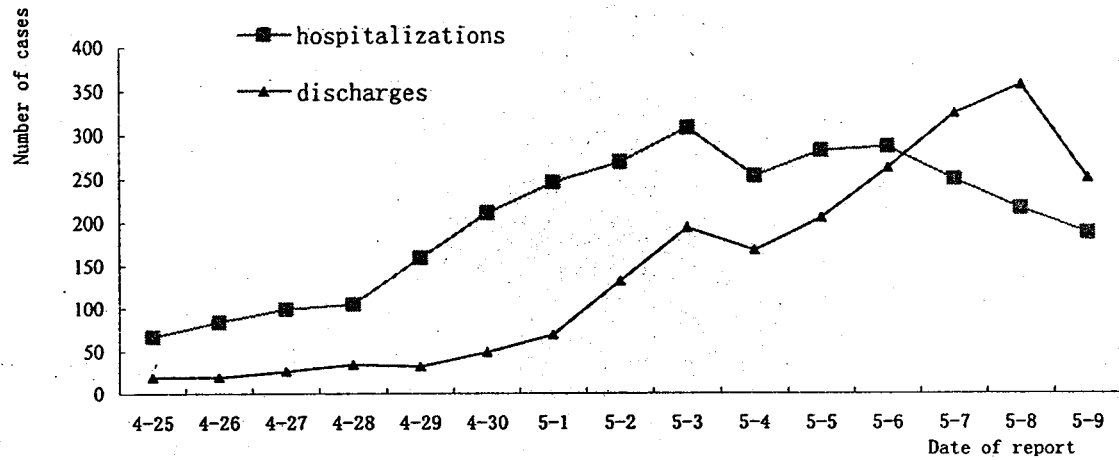


Figure 4. Daily number of hospitalizations and discharges of HFMD cases from April 25 to May 9 in Fuyang City.

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.

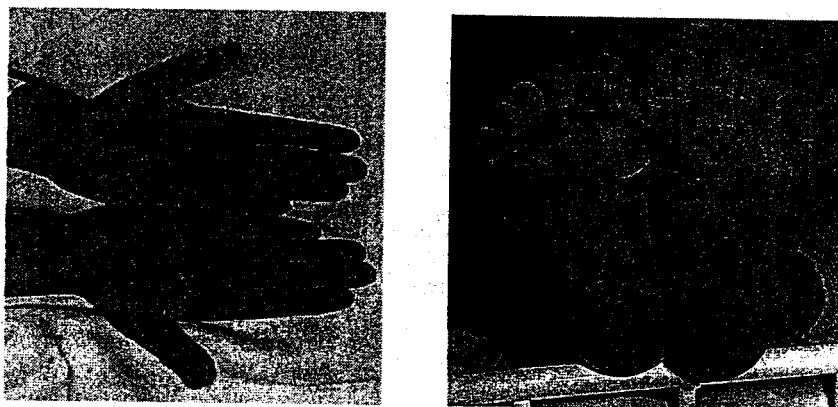


Figure 6. The rash of HFMD cases (on hand and foot)

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.

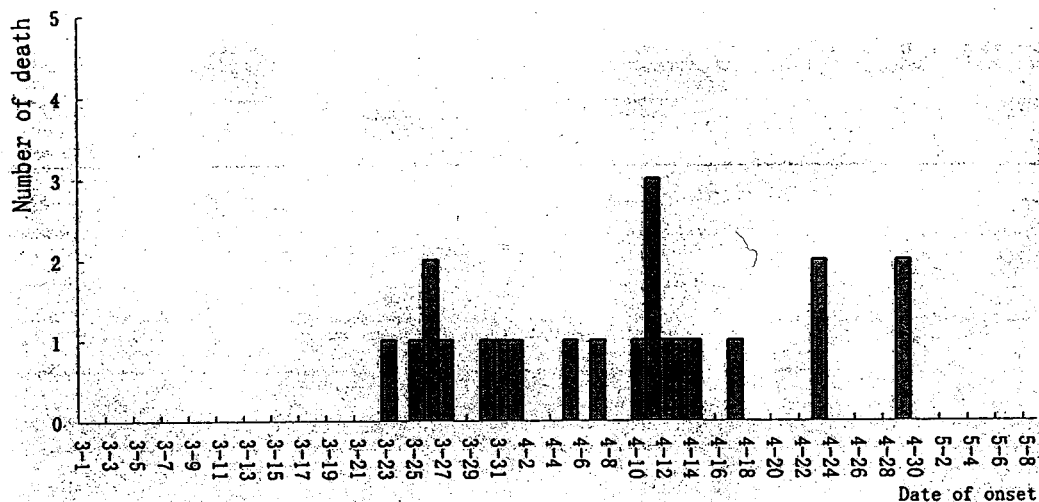


Figure 7. Fatal cases (n=22) by date of onset from March 23 to April 29 in Fuyang City.

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.