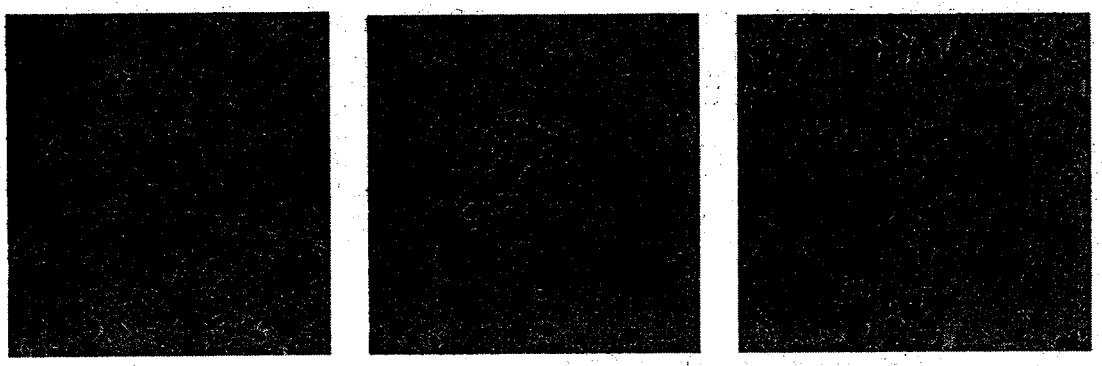

Figure 8. Left: brain tissue; Middle: spinal cord; Right: bronchus.

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.

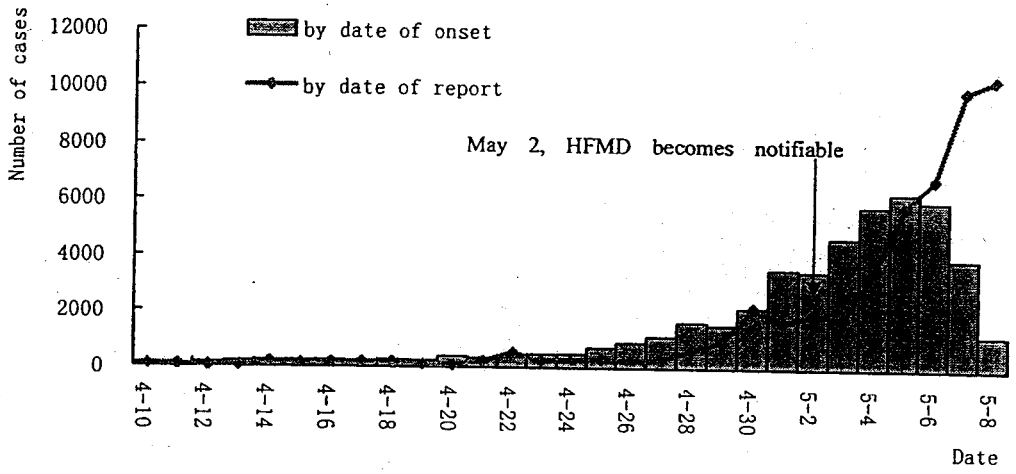

Figure 9. The number of HFMD cases by date of onset and date of reporting from April 10 to May 9, 2008 in China.

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).

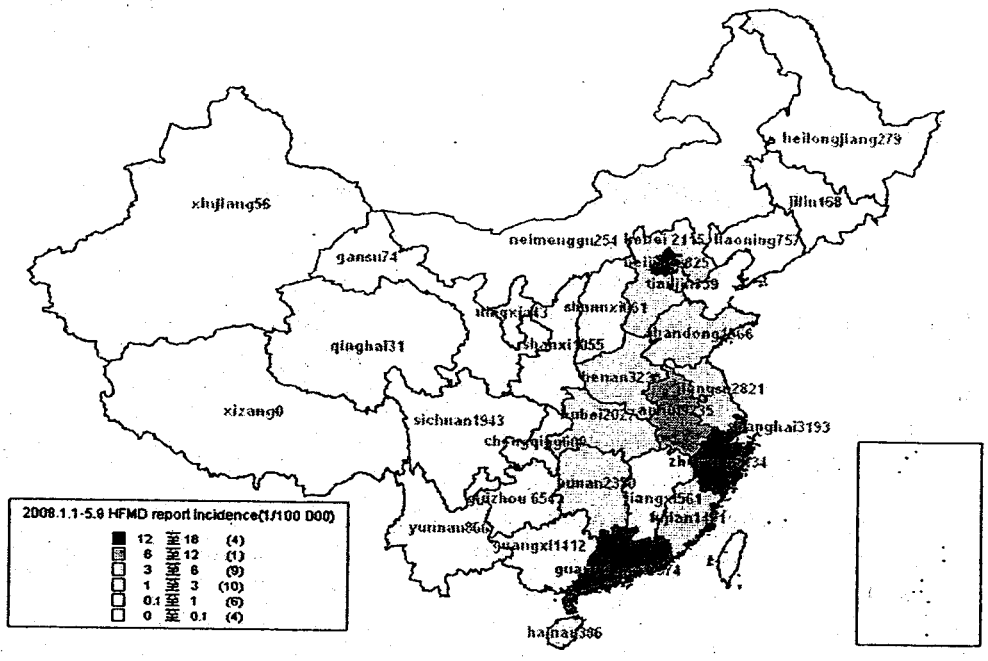

Figure 10 Incidence rate of HFMD cases by province in China from Jan 1 to May 9,2008

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.

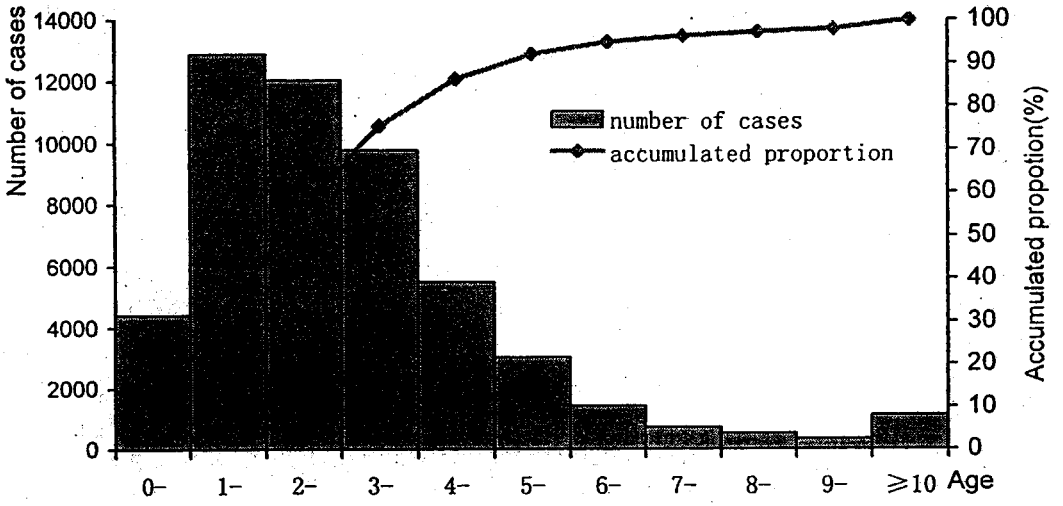

Figure 11. HFMD cases by age in China from January 1 to d May 9, 2008

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/pneumorrahagia, 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.

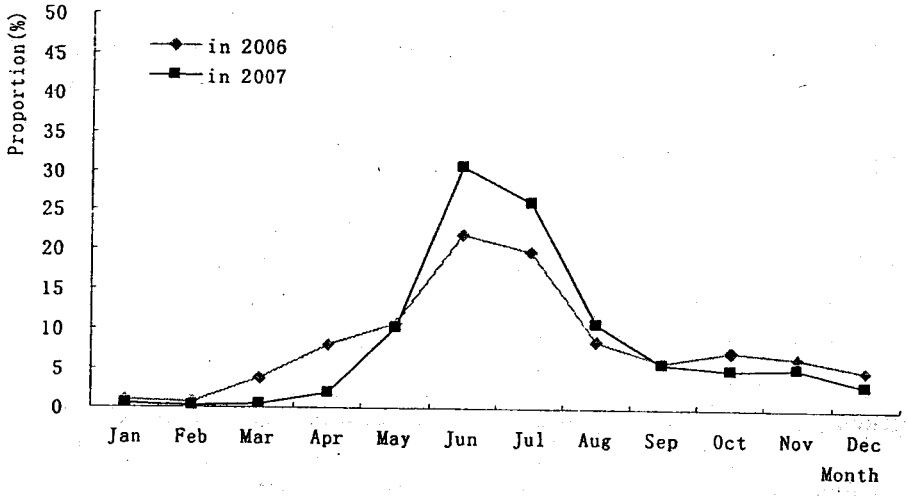

Figure 12 The distribution of HFMD cases by month in 2006 and 2007

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.

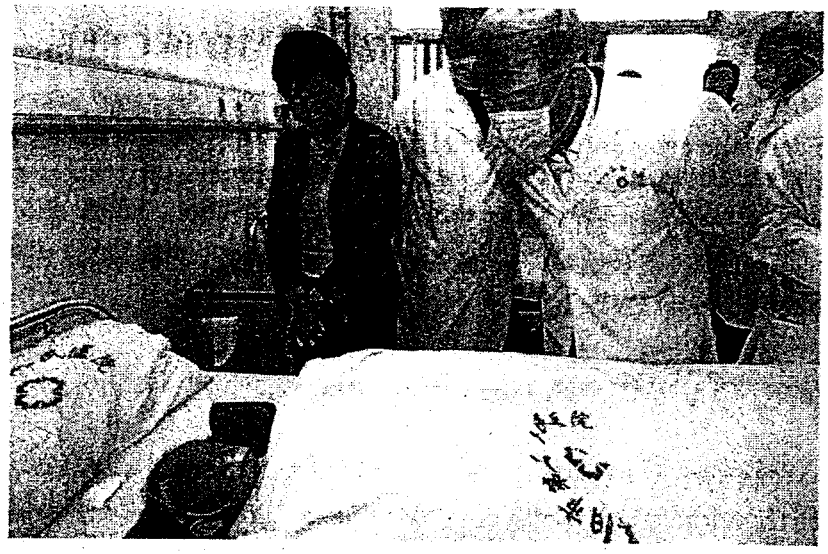

Figure13. Dr. Zhu Chen, Chinese Minister of MOH, visiting a HFMD patient at Fuyang No.2 People's Hospital on April 26, 2008.

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 Minster 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 GenBank[3] 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 ifentified in 1969. It is reported that the clinical manifestations of EV71 infection varies from classical HFMD symptoms to herpangaina, 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 region[4]. 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 fatal[5]. 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 Singapore[6] and Vietnam[7] while the disease has also been reported in Malaysia[8].

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

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[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/

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医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 2008年4月7日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	乾燥濃縮人アンチトロンビンⅢ		研究報告の公表状況	Blood 110 (11, Part 1): p853A NOV 16 2007 The risk of transfusion-transmitted babesiosis due to Babesia microti in Connecticut	公表国 米国	
販売名（企業名）	アンスロビンP-ベーリング（CSLベーリング株式会社）					

研究報告の概要

問題点（米国コネチカット州における Babesia microti によるバベシア症の輸血感染の危険性）

Babesia microti(Bm)はダニ媒介で感染して赤血球内に寄生し、米国のネブラスカ州と中東部以北では風土病である。

本来 Bm はダニ媒介の疾患だが、輸血により少なくとも 50 例の感染報告がある。症状は、発熱、溶血性貧血と血小板減少症で、輸血後 2-8 週で発症する。

コネチカット州での輸血による Bm 感染の危険性を評価するため、2004-2007 年に収集されたドナーとレシピエントの保存検体を試験した。慢性的に輸血を受けている人達から、輸血後 1,3,6,12 ヵ月後に採取され凍結された全血と血清と、関連するドナーの血清を検体とした。

全てのレシピエントの検体で、IFA を用いて Bm に対する抗体を測定した。

レシピエントの検体の IFA が陽性の場合、血液感染を特定するため対応するドナーの血清を Bm 抗体のスクリーニングを実施した。血清反応陽性のレシピエントの保存 DNA は Bm の real-time PCR でも評価された。筆者らは赤血球または血小板を輸血による Bm が 1 件の感染例を特定した。

鎌状赤血球貧血患者の検体 1 件を除いて全ての検体は Bm が陰性であった。その患者は 24 ヶ月で 45 回の赤血球輸血を受けていた。この検体は 2 施設のラボで血清反応陽性が再現された。血清反応陽性後 6 週と 11 週の血液検体は血清反応陰性であるが PCR は陽性であった。血清反応陽性の 5-21 か月前に採取された 11 検体は、全て血清反応陰性で、2 検体が PCR 陽性で、そのうち 1 検体は強陽性であった。対応するドナー3 人の検体は使用できなかった。

そのレシピエントはダニに暴露したことはなく、Bm が特有のコネチカット州のエリアに住んでいない。本研究に選ばれる前の 2 年間は 41 単位の赤血球を投与されていた。Bm に起因する臨床症状は現れていない。

血清反応陽性のドナーを特定できなかったが、輸血による Babesia microti 感染の可能性があるが、そのレシピエントがダニや以前の輸血から感染したかもしれない。

コネチカット州における Babesia microti 感染の危険性は 1920 回の赤血球輸血で 0 例または 1 例と計算できる。Gerber らの 1994 年の報告では、同州において 601 回の赤血球輸血で 1 例であり、結果が一致していた。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
バベシア症は赤血球内にバベシア原虫が寄生するため発症するが、本剤は血漿を原材料にしているため感染はないと考えられる。	今後とも新しい感染症に関する情報収集に努める所存である。

Abstract# 2900 Poster Board #-Session: 119-III

The Risk of Transfusion-Transmitted Babesiosis Due to *Babesia microti* in Connecticut. Ritchard G. Cable,[1] Yan-Yun Wu*,[3] Stephanie Johnson*,[1] Kerri Dorsey*,[2] Russell Melmed*,[1] Jonathan Trouern-Trend*,[2] Shimian Zou*,[2] Laura Tonnetti*,[2] David Leiby*.[2] [1]*Blood Services, American Red Cross, Farmington, CT, USA;* [2]*Jerome H. Holland Laboratory, American Red Cross, Rockville, MD, USA;* [3]*Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT, USA.*

Babesia microti (Bm) is a tick-borne intra-erythrocytic parasite endemic in NE and the upper Midwest. Although primarily a tick-borne disease, Bm has been transmitted by transfusion in at least 50 documented cases. Symptoms include fever, hemolytic anemia, and thrombocytopenia, typically arising 2-8 weeks following transfusion. In order to assess the risk of Bm transmission by blood transfusion in Connecticut (CT), we tested a repository of donor and recipient samples collected in 2004-2007. *METHODS:* The repository consisted of frozen whole blood and serum samples collected generally 1, 3, 6, and 12 months after blood transfusions in a chronically transfused population, along with associated donor serum samples, collected at blood drives in CT. All recipient follow-up samples were screened for antibodies to *Babesia microti* by IFA, as were the initial samples of any seropositive recipient, using a 1:64 cut-off titer. If recipients tested IFA positive after being seronegative (seroconversion), corresponding donor sera were screened for Bm antibody to identify transfusion-transmission. Stored DNA from serial seroconverting recipient samples were also assessed by real-time PCR for Bm. We defined an evaluable transfusion for Bm as a platelet or RBC transfusion with at least one follow-up sample 14-180 days later. 107 recipients received evaluable transfusions. Altogether these recipients received 1920 evaluable RBC transfusions and 1634 evaluable platelet transfusions. *RESULTS:* All follow-up samples were seronegative for Bm except for a single follow-up sample in a recipient with sickle cell anemia transfused with 45 RBC over 24 months. This sample was reproducibly seropositive in 2 labs with a titer of 1:64 and was PCR negative. Blood samples 6 weeks before and 11 weeks after the seropositive sample were seronegative, but PCR +. To investigate, 11 earlier recipient samples taken 5-21 months before the seroconversion were tested and all were seronegative, although 2/11 were PCR + (one strongly positive). Donor serum samples from 18/21 RBC transfused prior to the strongly PCR + recipient sample were negative for Bm. Three donor samples were not available. The recipient reported no exposure to ticks and lived in a non-endemic area of Connecticut. The patient had received 41 units of red cells in the two years before enrollment in the study. There were no clinical symptoms attributable to Bm. *CONCLUSION:* This may be a case of transfusion-transmitted *Babesia microti,* despite our inability to identify a seropositive blood donor. However, the recipient may have acquired Bm from a tick bite or from earlier transfusions. The risk of *Babesia microti* transmission by transfusion in CT has thus been measured either as zero cases in 1920 RBC transfusions (95% CI 0.0 - 0.0016 per RBC) or as 1 case per 1920 RBC transfusions (0.005, CI 0.000013 - 0.0029 per RBC). A previous report (Gerber, et al. JID 1994; 170:231-234) directly measured the risk of transfusion transmission of *Babesia microti* in CT as 1 in 601 RBC (.0017). A recent risk estimate based on the prevalence of PCR positive CT donor samples is 1/1800 RBC (0.0006) (Cable RG, et al. Transfusion 2001: 41(suppl):12S-13S.) This current study of chronically transfused recipients is consistent with these earlier estimates.

Disclosure: No relevant conflicts of interest to declare.