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Enterovirus 71 infection: a new threat to global public health?

The Asia-Pacific region has seen more frequent and widespread outbreaks of enterovirus 71 infections in the past decade. Clinicians and researchers are calling for a better understanding of the evolution of such epidemics and for more proactive international public health polices. Jane Qiu reports.

For more on **EV71 and HFMD** see *N Engl J Med* 1999; **341:** 936–42

Enterovirus 71 (EV71), a single-stranded RNA virus that belongs to the same category as poliovirus, has made another comeback in many parts of Asia. The reported frequency of EV71 infections are rising on a weekly basis: in Hong Kong, the number of cases reached 79 by late August, the highest in a decade. In some cases, EV71 infections cause hand–foot–mouth disease (HFMD), a common, contagious disease that usually affects children and that is characterised by flu-like symptoms; rash on hands, feet, and buttocks; mouth ulcers; poor appetite; and vomiting and diarrhoea. However, HFMD can be life threatening, particularly if the virus causes inflammation of the brain stem, which can progress to heart failure and pulmonary oedema.

The first sign of an outbreak of EV71 was from Fuyang, a city in the Anhui province, central China, with a population of 10 million people. At the end of March, three infants with severe pneumonia were admitted to the Fuyang First People's Hospital and died soon afterwards. Alerted by the unusual coincidence of these three infants, the hospital staff reported these cases to the provincial health bureau and started to investigate the aetiology.

After two unsuccessful weeks, during which more children were dying of a similar disease, the local officials began to realise the seriousness of the situation—another epidemic of severe acute respiratory syndrome was the worst possible scenario—and asked for assistance from the health ministry. The ministry and the Chinese Center for Disease Control and Prevention tested for virus infection in samples from fatal and mild cases, and organised a group of clinicans and researchers to review clinical reports and evidence from autopsies.

On April 23, the group of experts concluded that it was an outbreak of HFMD and that EV71 was the main pathogen—a conclusion that the health ministry disseminated immediately. Since then, the number of cases of HFMD has continued to rise, affecting most of the 34 districts of China, including Beijing, Hong Kong, and Macau. By mid-May, there had been 27 500 reported cases of HFMD and 42 deaths. In a report jointly released by the Chinese Center for Disease Control and Prevention and WHO China, by May 9, there had been 353 severe cases of HFMD and 22 fatalities out of over 6000 reported cases in Fuyang, where the situation was being closely monitored.

> **"...public health policies are not yet in place to deal with a potential global epidemic in the future."**

According to Deng Guo-hua, director of the infectious disease department of the Peking Union Medical Hospital, this year's epidemic of EV71 in China is unlikely to be an isolated incidence. Indeed, the virus is no stranger to Asia. After the first report of an EV71 infection with neurological manifestation in California in 1969, there were sporadic outbreaks in Australia, Sweden, the USA, Bulgaria, and Hungary. In 1997, the virus was reported in Sarawak, on the island of Borneo, Malaysia, causing a major outbreak of HFMD. Since 1997, EV71 infections have been a recurrent feature in the Asia-Pacific region, affecting Malaysia, Singapore, Australia, Taiwan, Hong Kong, Vietnam, mainland China, Korea, Japan, and Mongolia. As recent as last year, there was an outbreak of HFMD in the Shandong province, with about 40 000 HFMD cases and 14 subsequent deaths reported.

It is a mystery to many clinicians why the virus has reached such a stage of evolution that it is causing frequent, widespread outbreaks in the Asia-Pacific region. Tom Solomon, an expert on neurological infections at the University of Liverpool, UK, has worked on EV71 since 1998. "Why Asia?" he asks. "What is it about Asia that makes it more susceptible to EV71 infection? And where will the virus go next?"

Unfortunately, little is known about the biology of EV71 or the evolution of EV71 epidemics, and there are no effective antiviral treatments as yet. "Therefore, early diagnosis and early intervention are particularly important," remarks Mong How Ooi, a paediatrician at the Sibu Hospital in Sarawak. He adds that clinicians have found that treating children at the early stage of brain-stem encephalitis with intravenous infusion of immunoglobulin may help to reduce the fatality rate. Some clinicians suspect that the beneficial effect might be due to a boost in immune function of the patient and inhibition of viral replication.

Since the first EV71 outbreak in 1997, the Sarawak heath department of the Malaysian Ministry of Health has initiated a sentinel surveillance programme to build an epidemiological understanding of the viral infection and to predict future outbreaks. Under the scheme, three clinics are required to report every case of HFMD—regardless of severity—and to collect specimens to determine the aetiology for each case.

According to Jane Cardosa, a virologist at the University of Malaysia, Sarawak, who is leading the programme, these efforts are not enough to monitor EV71 infections because not all cases have HFMD manifestations. In addition, other enteroviruses, such as coxsackievirus A16 can also cause HFMD but do not generally result in severe or fatal disease.

In collaboration with the Sibu Hospital in Sarawak, Cardosa and her co-workers also screen for viruses in children who are admitted for suspected infection of the nervous system. "We don't just focus on EV71, but look for whatever aetiology that could be responsible for the condition," she says. "When you do the two surveillance programmes simultaneously, you get a good picture of the situation." It is clear from both of these research efforts that outbreaks of EV71 infection take place in Sarawak every 3 years, with the next outbreak expected to peak in 2009.

The researchers suspect that the interval between outbreaks of EV71 infection might be related to maternal immunity: children who are born within 1 year after an epidemic are still protected from the mother's immunity. Therefore, these children might only become susceptible from the second year onwards. In addition, large enough susceptible cohorts might be necessary for a major outbreak, which could be affected by the population density of a particular region.

The study by Cardosa, Solomon, and their co-workers also shows that distinct genotypes of EV71 have different abilities to form family clusters and cause neurological manifestations. For example, children infected with the B4 genotype, the cause of the epidemic in Sarawak in 2000, had fewer complications of the CNS than those children with the newly emerged B5 genotype, which was responsible for the outbreak in 2003.

The rapid mutation rate of EV71 is a major challenge for understanding the pattern of transmission and the associated risk factors of this virus, says Ih-Jen Su, director of the clinical research division of the National Health Research Institute in Taipei, Taiwan. Since the first major outbreak on the island in 1998, when more than 400 children were critically ill and 78 of these children died, the predominant genotype of subsequent epidemics has been shifting. "Different genotypes are also found in different parts of Asia," says Su. "So we know very little about whether—or how—it can be spread over a long distance."

WHO China maintains that EV71-associated HFMD is not an emerging infectious disease, and that the public health effect is no more serious than for other common childhood diseases. Since the outbreak in 1997, the EV71 virus has been estimated to have infected millions of children and to have caused hundreds of deaths of infants. "For reasons I don't understand, EV71 does not seem to have attracted quite the same attention as other pathogens like avian flu, which has caused much fewer deaths," says Solomon. "With increasing travel, there is a wide threat from EV71. But public health policies are not yet in place to deal with a potential global epidemic in the future."

Some researchers think that an improved surveillance capacity for a spectrum of pathogens is extremely important. "The training and funding options need to be more generic rather than focusing on a particular pathogen," says Cardosa. It is unclear whether EV71 is the only cause of the severe cases of an HFMD outbreak or whether other viruses that are co-circulating might exacerbate the situation. "We should consider all possible causes of an epidemic before concluding that the first virus identified is the causal agent," she says. "And we should not assume that all severe cases during an outbreak are caused by the same agent."

Indeed, of the 12 fatal cases from Fuyang that were tested for EV71 infection in April, only five were positive, suggesting that there might be other fatal pathogens. The Chinese health ministry has not revealed the progress of the investigation into the epidemiology or which other pathogens have been tested. Details of the latest affected cases and the fatality rate of HFMD and EV71 infections in China are also not available. Although Mao Anqun, a spokesman of the ministry, said in a press conference in May that there would be monthly updates of the epidemiology on the website of the ministry, no such information can be found. After repeated requests, an information officer told *The Lancet Neurology* that the ministry does not have the data.

Many researchers feel strongly that there is a greater need for a better understanding of infectious diseases of the nervous system—a neglected area of research in past decades. Cardosa emphasises that this should be done using a combination of approaches that involve systematic testing of all likely pathogens over a long period of time, as well as focusing on particular causes. "Otherwise, we would get total disruptions all the time," she says.

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AP Photo/EyePress

Hospital ward treating enterovirus 71 infection in Fuyang

For more on the **EV71 outbreak in Taiwan** see *N Engl J Med* 1999; **341:** 929–35

For more on the **EV71 outbreak in Sarawak** see *Clin Infect Dis* 2007; **44:** 646–56