

Original Article

A Review of Prevention and Control for Enterovirus Infections in Asia

Shu-Chun Chu, En-Tzu Wang, Ding-Ping Liu

Second Division, Centers for Disease Control, Taiwan

Abstract

Enterovirus has attracted the attention of health authorities in Asia since the occurrence of epidemic in Malaysia, 1997 and in Taiwan, 1998, and almost every country has established related surveillance systems, and prevention and control strategy in succession. During 2008 to 2011, Taiwan, Japan, China, Singapore and Vietnam again emerged serious outbreaks which show that enterovirus infections have become an important contagious disease of children in Asia. This article reviewed prevention and control strategy of enterovirus infections in different countries in Asia by collecting information from international conferences, related website of health departments, and literature review. In summary, monitoring of hand-foot-and-mouth disease (HFMD) is the main focus in surveillance aspect, and giving publicity to good personal hygiene is the main point in prevention and control strategy. Some countries implement class/school closures as control measure and enhance quality of medical care to reduce the rate of severity and death. A guideline for the clinical management and prevention control for HFMD issued by WHO Western Pacific Regional Office in 2011 October provides reference of surveillance, diagnosis, medical care, prevention and control, and expecting to reduce the harm of enteroviruses to children's health.

Keywords: Enterovirus, hand-foot-and-mouth disease, prevention and control strategy

Introduction

Enterovirus genus, belongs to family *Picornaviridae*, has more than 60 serotypes. The most common are poliovirus (3 serotypes), *Coxsackievirus* A(23 types) and B(6 types), *Echovirus*(30 types), and enterovirus 68-71. Enteroviruses classified by genetic sequences can be divided into four species, A, B, C and D. Enterovirus 71(EV71) is classified in species A, which could be further divided into eleven subgenotypes, A, B(B1~B5) and C(C1~C5). Enteroviruses can cause numerous kinds of diseases, most are asymptomatic or only mild

flu-like symptoms. Sometimes these viruses induce some specific clinical symptoms, including HFMD, herpangina, aseptic meningitis, viral meningitis, myocarditis, flaccid paralytic syndromes and acute hemorrhagic conjunctivitis. In all serotypes of *Enterovirus*, besides poliovirus, EV71 induces central neural system complications. Some cases develop non-life-threatening complications such as meningitis, mild encephalitis, acute flaccid paralysis, while serious complications have potentially lethal consequences. The epidemics caused by enteroviruses have given rise to great attention in Asia [1].

Each country programmed prevention and control measures against *Enterovirus* epidemics since these viruses induced great prevalence in Asia since 1997. Over the past decade, it again caused serious epidemics in Asia in 2008. Due to the severity of *Enterovirus* epidemics, Singapore convened an international forum [2] organized by the Regional Emerging Diseases Intervention (REDI) for experiences exchange between experts in Asia. China convened a HFMD symposium [3] and invited WHO and experts from Asia countries to share prevention and control experiences in Beijing in January 2009. Taiwan Centers of Disease Control convened the second APEC Enterovirus international conference [5] in May 2009 and the first APEC Enterovirus conference in 2000 [4]. In addition, WPRO has issued the "A guide to clinical management and public health response for hand, foot, and mouth disease (HFMD)" [6] in October 2011. This article refers to the content of forum and conferences mentioned previously, to review the epidemiology, surveillance, and prevention and control strategy of countries including Taiwan, China, Hong Kong, Singapore, Japan, Vietnam, Thailand and Malaysia.

Epidemiology

Because each country in Asia views differently on the importance of enterovirus infections, the surveillance strategy also differs. In a WPRO's publication - "A guide to clinical management and public health response for hand, foot, and mouth disease (HFMD)" [6], it has collated descriptive epidemiology of some countries. Table 1 illustrates epidemic trend, incidence rate and trend of virus, and Table 2 illustrates the case number of reported and death by country.

A. Epidemic trend

Generally, every country in Asia has at least one outbreak of HFMD every year, while the outbreak time happens mostly in spring and summer, and the outbreak peak is regular in every country except Thailand.

B. Incidence rate

HFMD incidence rate of children aged <5 years per 100,000 populations is 1,640 to 5,975 in Singapore in 2001-2007 [7]. China's HFMD incidence rate per 100,000 population is 37.01 and 59.56 in 2008-2009 [3,6,8], respectively. In Taiwan, enterovirus infection incidence rate of children aged <15 years per 100,000 population is 7,527 to 23,878, and HFMD incidence rate of children aged <15 years per 100,000 population is 552 to 8,313 in 2008-2011.

Table 1. The epidemic situation of Enterovirus/hand-foot-and-mouth disease in selected countries in Asia

Country/ region	Prevalence trend	Incidence rate	Hospitalization / severe disease rate	Case fatality rate	Severe disease cases complicated with EV71/ Death rate caused by EV71	Virus monitoring/ subtype of EV71
Taiwan	Every year, start increasing around end of March, reach to the peak at end of May to the beginning of June. Second prevalence sometimes appears in September.	Incidence rate, per 100,000, < 15 years old (Enterovirus/HFMD) : 2008 : 9,388/2,067 2009 : 7,257/552 2010 : 23,878/8,313 2011 : 11,668/1,469	Severe disease rate caused by Enterovirus (per 1,000) : 2008 : 0.983 2009 : 0.101 2010 : 0.017 2011 : 0.137	Death rate caused Enterovirus (per 1,000) : 2008 : 0.037 2009 : 0.007 2010 : 0 2011 : 0.009	Infection rate of severe cases caused by EV71 between 2000 and 2011 is 50%-98% 2. Death rate of severe disease cases caused by EV71 between 2000 and 2011 is 57%-100%	1. Mainly CA16 and EV71 during 2001-2008, among them, 2001(31%), 2002 (15%), 2005(18%), 2008(26%), has higher isolation rate of EV71. 2. EV71 subtypes are B4, C4, C5, B5 between 1998- 2011
Japan [9, 21]	Large outbreaks occurred in 1995, 2000, and 2003. The most extensive outbreak happened in 2001 since establishing monitoring system.	—	—	—	—	Mainly CA16 and EV71 over the years, and highest isolation rate of CA6 in 2011
Hong Kong [3]	HFMD peak is May to June every year	—	—	—	—	—
China [3, 6, 8]	HFMD started to increase in March, prevalence peak is April-July (2009)	HFMD incidence rate is 37.01, 59.56, per 100,000 in 2008 and 2009 (before July), respectively	Severe disease rate in 2008 and 2009 (before July) is 0.24%, 1.34% respectively	Death rate caused by HFMD is 0.026%, 0.032% in 2008 and 2009 (before July) respectively	In 2009(before July), severe disease caused by EV71 is 81%, death rate of severe cases caused by EV71 is 94%	1998-2008, EV71 subtype is C4
Singapore [2, 3, 7]	1. From 2005 to 2008, a bimodal trend was present. 2. The first wave started at March, reaches to the peak in April –May. Second wave happens in July-October.	From 2002 to 2007, the HFMD incidence rate for 0-4 years old; per100,000 is between 1640.5 (2002) and 5975.5(2007).	From 2002 to 2007, the hospitalization rate is 0.4%-2.6%	—	—	1. From 2001 to 2007, the main prevalent type is EV71 and CA16, in 2001, 2003, 2005, 2006, the isolation rate of EV71 was 45.6%, 68.0%, 52.7%, and 45.5%, respectively. 2. In 2000, EV71 subtype is B4, in 2006, B5.
Malaysia [2, 10]	1. Started to rise in January, and the prevalent peak is February to May. 2. In 2008, there were two prevalent trends.	—	—	—	—	EV71 subtypes 2000, B4. 2003, C1/B5. 2008, B5.
Vietnam [2, 5, 22]	1. From 2006 to 2007, epidemic trend is a single mode, and the peak is in October. 2. In 2008, epidemic trend is bimodal, separately at April to June and October to December.	—	—	The death rate is between 0.5% and 2.9% from 2005 to 2008.	—	1. In 2005, it is mainly CA16 and EV71 (C5) 2. In 2007 and 2008, the isolation rate of EV71 is 15.5% and 8.0%, respectively
Thailand [5]	1. The prevalent peak is different over the years. 2. The prevalent scale is increasing since 2005.	—	—	—	—	Among the EV71 isolation rates, 2001 (20.4%), 2002(14%), and 2007(12.9%) have higher rates.

Table 2. Case number of Enterovirus infections (reported) and deaths by country from 1997 to 2011

Explanation : () is the death number

country	Disease	year															
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	
Taiwan	EVSC		405	35	291	391	162	70	50	142	11	12	373	29	16	59	
	*EV71		(78)	(9)	(41)	(58)	(30)	(8)	(5)	(15)	(0)	(3)	(14)	(2)	(0)	(4)	
	confirmed		77	6	152	181	58	44	20	82	2	7	344	25	12	58	
			(34)	(1)	(25)	(27)	(8)	(4)	(5)	(8)	-	(2)	(14)	(2)	-	(3)	
Japan [9, 17, 21]	HFMD	75,090 (3)	126,019	50,814	205,365 (2)	127,754	91,024	172,659	88,727	88,408	99,936	93,699	145,185	68,578	151,021	346,164	
	Herpangina			154,802	147,275	140,215	111,441	148,674	105,486	144,260	115,151	126,105	113,709	75,666	139,209		
	Aseptic meningitis			1,126	1,873	1,254	2,985	1,625	1,028	773	1,140	797	744	644	811		
Hong Kong [23]	Infected by EV71	2	60	22 (1)	6 (1)	30	5	1	35	8	21	12	101 (1)	38	105	70	
	Infected by Coxsackievirus	30	170	214	269	230	459	46	226	415	428	286	638	315	1076	421	
China [3, 5, 6, 8]	HFMD				1,698 (3)							83,344 (17)	488,955 (126)	1,155,525 (353)	1,774,669 (905)	1,619,706 (509)	
Singapore [7, 24]	HFMD				3,790 (5)	5,187 (3)	16,228	5,603	6,411	15,256	15,282	20,003	29,686 (1)	17,278	30,878	20,687	
Malaysia [10, 25, 26]	HFMD	5,999 (31)										13,800 (1)	6,332 (13)	6,666	9,655	4,987	3,170
Vietnam [2, 5, 6, 17, 22]	HFMD									441 (13)	2,284 (13)	5,719 (23)	10,958 (25)	10,632 (23)		110,897 (166)	
Thailand [2, 3, 5]	HFMD					1,548	3,533 (2)	1,218 (1)	769 (2)	4,646	3,961 (7)	16,848	10,475 (5)				

C. Hospitalization/complication rate

Singapore's hospitalization rate of HFMD is 0.4 to 2.6% in 2001-2007[3,6,8]. China's complication rate of HFMD cases is 0.24% and 1.34% in 2008 and 2009, respectively [3,6,8]. In Taiwan, enterovirus infection complication rate per 1,000 populations is 0.017 to 0.983 in 2008-2011.

Additionally, among Taiwan's severe cases from 2000 to 2011, the attack rate by EV71 is 50-98%. Among China's severe disease cases in 2009, the EV71 attack rate is 81% [5].

D. Case fatality rate

The case fatality rate of HFMD per 1,000 population is 0.26 and 0.32 in China in 2008 and 2009, respectively [3,6,8]. In Taiwan, the case fatality rate of enterovirus infection per 1,000 populations is 0 to 0.037 in 2008-2011, while the case fatality rate of severe disease is 3.8 - 6.9%.

Besides, among Taiwan's death cases of severe disease from 2000 to 2011, the attack rate by EV71 is between 57% and 100%; while among China's severe disease cases, the attack rate by EV71 is 94% in 2009[5].

E. EV71 epidemic trend

After 1994, the epidemic cycle of EV71 is about three to four years in Japan. Malaysia's monitoring data of virus from 1998 to 2008 shows that EV71 induced a more extensive epidemic about every three years, while the epidemic situation of HFMD has a greater level of

spreading with EV71[2,10]. Singapore's main epidemic type is EV71 and CA16 from 2001 to 2007, and the isolation rate of EV71 is higher in 2001, 2003, 2005 and 2006, with the isolation rate between 45.5% and 68% and the epidemic cycle is about two years [7]. Taiwan's EV71 epidemic trend during 2001 to 2011 has a higher isolation rate in 2001, 2002, 2005 and 2008 with the rate between 15% and 31% and the epidemic cycle is about two to four years.

Surveillance strategy

Enterovirus is composed of more than sixty serotypes, besides poliovirus, EV71 gradually gives rise to each country's attention in recent years. Because each country in Asia places different importance on EV71, their surveillance strategy differs. Table 3 is the comparison of

Table 3. Enterovirus surveillance and disease classification

Country	Region	Disease monitoring	Notifiable/Reportable infectious disease discipline	Monitoring way/progressing
Taiwan	Whole country	HFMD Herpangina EVSC	EVSC is notifiable as of June 23, 1999	1.Active monitoring : (1)Enterovirus (including HFMD and herpangina) : A. Sentinel doctors (1998.03-2009.12) B. Real-time outbreak disease and surveillance system and (RODS, 2006.09~) C. National Health Insurance Claim Database (NHICD, 2008.12) . (2)Virus surveillance: Contract laboratory surveillance (1999.03) 2. EVSC (1999.06)
Japan	Whole country	HFMD herpangina aseptic meningitis	Enterovirus is not a notifiable disease	Active monitoring: Started to report HFMD, herpangina, aseptic meningitis and acute conjunctivitis by local doctors since April 1994.
Hong Kong	The administrative district	HFMD EV71 patients	Since 6 March 2009, EV71 infection is reportable	Active monitoring: Monitor by sentinel doctors (family doctor and clinics); Monitor in childcare center; Hospitalized HFMD case in public hospitals; HFMD cluster in organizations Passive monitoring : EV71 infection is a reportable infectious disease (2009.3) .
China	Whole country	HFMD	Since 2 May 2008, it is notifiable	Passive monitoring : HFMD is reportable (including severe disease and death)
Singapore	Whole country	HFMD	Since October 2010, it is notifiable	Active monitoring : Virus monitoring, sampling from hospitals and sentinel doctors, educational and childcare organizations. Passive monitoring : HFMD is reportable, all events of HFMD cluster should be reported by educational and childcare organizations, severe disease and death case should be notified by large scale hospital
Malaysia	State of Sarawak	HFMD	In May 2005, it is notifiable	Active monitoring: In March 1998, established HFMD surveillance by sentinel doctors and sampling system; monitor by private and public clinics; rumours surveillance and GIS monitoring. Passive monitoring : Since October 2005, HFMD is notifiable
Vietnam	South of Vietnam	HFMD	ND*	Active monitoring: Virus surveillance by sentinel stations Passive monitoring: HFMD is reportable.
Thailand	Whole country	HFMD	Since 2001, it is reportable	Passive monitoring: HFMD is reportable.

* : NO DATA , data not found

the surveillance strategy on enterovirus infection, and the following compare and explain the mandatory surveillance, surveillance method and surveillance focal points, respectively.

1. Mandatory surveillance

In this aspect, we use whether the enterovirus infection is one of the country's notifiable disease or reportable disease as a standard. Most countries include HFMD as notifiable or reportable infectious disease. With regard to enterovirus surveillance, Taiwan requests reporting from sentinel doctors before 2009 but the Enterovirus Infection with Severe Complications (EVSC) is a notifiable disease since 1998.

2. Surveillance methods

Surveillance methods on enterovirus infection in Asia are approximately divided to two ways, reporting case by case and sentinel surveillance. Countries adopting the way of reporting case by case on HFMD or enterovirus infection are China, Singapore and Thailand; countries adopting the surveillance by sentinel doctors are Japan, Taiwan, Hong Kong, Malaysia and Vietnam.

3. Surveillance focal points

As for the surveillance for EVSC, every case is notifiable in Taiwan, while in China and Hong Kong, the reported cases of HFMD is registered in order to understand the severe cases well.

As for the virus monitoring, each country steadily collect virus data for a long term by reported HFMD cases or collect specimens from sentinel doctors.

Strategy for prevention and control

Enteroviruses is characterized with biological property like long contagious time and multiple infection routes, and no effective drugs or vaccine available, the focal point for prevention and control is to block viral transmission and prevent the severe complications and death. WRPO's guideline on HFMD [6] summarizes the prevention and control measures into the following eight items: establishing and strengthening surveillance, conducting and education campaigns on good personal hygiene, providing assistance to childcare organizations during outbreaks, enhancing infection-control measures in both health care facilities and the community, upgrading the equipment of severe disease's medication and care, regional preparedness and response information exchange during outbreaks, establishing administrative framework beneficial to promoting prevention and control measures, evaluation and monitoring. Because *Enterovirus* has different impacts on each country, related strategy for prevention and control makes a difference. Countries like Singapore, Thailand and Hong Kong, monitoring and adopting prevention and control strategy earlier has fewer death cases; China started to monitor in 2008 and actively adopt the prevention and control measures, leading to the decrease of death cases in 2011. Taiwan has established complete prevention and control measures, and the case fatality rate of EVSC significantly decreased. Table 4 collates prevention and control strategy by country, according to three levels for prevention of disease, and the main points are summarized below:

Table 4. Prevention and control strategy for enterovirus infections

Country	Primary prevention	Secondary prevention	Tertiary prevention
Taiwan	<ol style="list-style-type: none"> 1. Monitor strictly, control the epidemic situation: <ol style="list-style-type: none"> (1) Set warning threshold and the epidemic threshold. (2) Set the standard of class closures 2. Health education campaign: <ol style="list-style-type: none"> (1) Target subjects: Child caretakers for children < 5 years old, educators, nurse in school and epidemic prevention staff (2) In the primary epidemic stage, cultivate correct concept and behavior of washing hands (3) Check hand washing equipments and sanitation education 3. Development of EV71 vaccine and rapid testing reagents. 	<ol style="list-style-type: none"> 1.Public health level: <ol style="list-style-type: none"> (1) The focal point of propaganda during epidemic stage, 「Early clinical manifestations of severe disease complicated by Enterovirus infection」及「Do not go to school when sick」. (2) Enhance communication of risk: <ol style="list-style-type: none"> A. General population communication: news announcement, usage of media. B. Minor communication: Using enterprise resources to enhance propaganda on target groups. C. Personal communication: To parents who have severe disease children (3) Measures of class closures and shut-down of play ground in hospitals 2.Medical level: <ol style="list-style-type: none"> (1) Set outlines of treatment management of severe disease (2) Conduct professional training along with medical societies, raising the professional capability of medical staff in clinical diagnosis (3) Assign responsible hospitals 	<ol style="list-style-type: none"> 1. Public health level: <ol style="list-style-type: none"> (1) Enhance campaigns on early clinical manifestations of severe disease complicated by Enterovirus infection, 「Related manifestations of EV71 infection and the transferring time of suspected severe cases」 (2) Assist parents to determine early manifestations before severe disease and receive medical treatment immediately 2. Medical level : <ol style="list-style-type: none"> (1) Maintain the operations of infectious disease consultants and provide professional consultation on prevention and control, and medication (2) Maintain the medical network of severe disease complicated by Enterovirus (3) Enhance hospital bed dispatch for severe cases to provide quality medical care for severe patients.
Japan	Monitor epidemic situation and control the trend	No special arrangement	No special arrangement
Hong Kong	<ol style="list-style-type: none"> 1.Monitor epidemic trend and propose criteria for school closing. 2.Ensure health suggestions : For example, Check the children's health status before going to school, don't go to school when being sick, enhance personal hygienic habits and washing hands frequently, wash the toys regularly 3. Avoid mixing different classes when exercising. 	<ol style="list-style-type: none"> 1.Public health level : <ol style="list-style-type: none"> (1) Monitor two times of incubation period (about 14 days) (2) Implement measures of closing classes 2.Medical level : Providing latest information of EV71 and clinical managing procedure for clinical doctors. 	Continue on medical level of secondary prevention: Providing latest information of EV71 and clinical managing procedure for clinical doctors.
China	<ol style="list-style-type: none"> 1.Enhancing monitoring : Active search for and report HFMD cases every day, conduct epidemiological survey on every severe disease case to achieve the monitoring of clinical cases, expecting to achieve the goal of early monitoring and preventing severe disease. 2.Enhancing national health activities, and strengthen the health campaign of HFMD. 3.Check if children got fever or rash every day, enhance environmental cleanness of school by sterilizing toys and table wares 4.Accelerate the development of rapid testing reagents and vaccine 	<ol style="list-style-type: none"> 1.Public health level: <ol style="list-style-type: none"> (1) Implement closing of class(es) (2) Enhance communication of risk, spontaneously announce outbreak status 2.Medical level: <ol style="list-style-type: none"> (1) Enhance the classifying system of patients, improve the classification of HFMD cases (2) Assign responsible hospital to offer treatment, increase the investment of prevention/control and medication to ensure that HFMD patients receive immediate medical care. (3) Gather experts to collect experience of curing severe disease and set treatment guide line and distributed to hospital. 	<ol style="list-style-type: none"> 1. Establish patients transferring standard procedure and the system for consulting experts. 2. Establish professional medical team and lead the training of technique, improving professional skills of medication; Implement medical care tiers system. 3. Upgrading equipments for severe disease caring and medical care quality of pediatrics. 4. Establish and expand pediatric intense cure units and upgrade PICU, ensuring available doctors and nurses standby in 24 hours.

Table 4. Prevention and control strategy for enterovirus infections (continue)

Country	Primary prevention	Secondary prevention	Tertiary prevention
Singapore	1. Set warning threshold and epidemic threshold. 2. Set Enterovirus outbreak levels in childcare organizations (three levels).	Divide the outbreak scale into three levels, enhancing the health education campaigns initially and gradually upgrading to forcing the class closing according to the rise of the level: (1) First level Issue alert and inspect the prevention/control measures of educational and childcare organizations when the HFMD incidence rate higher than previous epidemic threshold. (2) Second level If the outbreak is not weaken and severe cases appear, besides conducting the first level prevention and control measures, require related educational and childcare organizations reported severe case(s) to close classes. (3) Third level Besides continuing on the prevention/control measures of the second level, shut down all educational and childcare organizations and places crowded with children if death cases caused by HFMD appear and if the death case is related to those organizations.	No special arrangement.
Malaysia	1. Monitor outbreak status. Set warning threshold and epidemic threshold. 2. Health education: instruct target groups to wash hands by the media and face-to-face visit.	1. Public medical level: (1) Implement class closures. (2) Enhance reporting of Enterovirus and outbreak investigation. Enhance the cognition of educational and childcare organizations' on HFMD by closing classes, extend school holidays and strengthen campaign of hygienic habit. 2. Medical level: Set the criteria of hospitalization, clinical treatment guideline.	Continue on secondary prevention strategy to manage the cases on medical level, isolate patients and assign hospitals to implement at the right time.
Vietnam	Monitor the outbreak and control the trend	No special arrangement	No special arrangement
Thailand	Conduct health education. Announce and warn people when outbreak occurs. Adopt the measure of monitoring outbreak during the end stage and in normal times.	1. Public medical level: (1) Prevention measure like enhancing health education, isolating patients from healthy children, closing classes, investigating the outbreak, sterilizing the environment and articles, and cleaning. (2) Set the investigation standard of cases: Hospitalized cases, death cases and when cluster appears in childcare organizations. 2. Medical level: Set the HFMD clinical medication guide line.	No special arrangement

1. Primary prevention

The focal point in this stage is to lower the infection rate. Main strategy focuses on the alertness of epidemic, campaigns of sanitation and research and development of EV71 vaccine:

(1) Alertness of epidemic

Countries which designate alertness and epidemic threshold by surveillance data based on recent years are Taiwan, Singapore and Malaysia. According to designated epidemic threshold to decide the timing for announcing warning sign and arrange sanitation propaganda

(2) Sanitation propaganda

The main infection route of *Enterovirus* is oral-fecal infection, and as a result, all countries emphasize the importance of washing hands diligently. On the other hand, because *Enterovirus* is likely to infect children under 9 years old, every country put childcare organizations as the main target to disseminate on the propaganda of washing hands.

(3) Research and development of EV71 vaccine

The most effective and direct way to prevent contagious disease is vaccine. Except there is vaccine for poliovirus, other enteroviruses have no available vaccines. Countries known to research EV71 vaccine recently are Taiwan, Singapore and China, choosing the subgenotype B4/C4, B2 and C4.

2. Secondary prevention

(1) Public health

A. Class closures

Class closure is by far the most adopted measure when entering to the enterovirus epidemic stage. However, the closure time in each country differs, all at least seven days. In Taiwan, besides class closures, the children playgrounds in hospitals may be closed if the epidemic is severe.

In Singapore, the outbreak of HFMD divided into three levels, either the incidence rate reaches to the threshold, the appearance of severe disease or death cases. In addition, the prevention and control measures on educational and childcare organizations gradually upgraded from enhancing the propaganda to mandatory class closures, closing education and childcare organizations and places where children gathered.

B. Risk Communication

Enhancing the communication risk is a focal point not to be ignored during enterovirus epidemic stage. Epidemic situation is easily focused and exaggerated by the media, and to avoid misunderstanding and causing unnecessary panic, each country has meanings of communication of risk obviously or implied in the enterovirus prevention and control strategy. The content of the communication is to continuous alertness of outbreak situation and sanitation campaign of washing hands to avoid infection mainly. In Taiwan, besides the focal points mentioned previously, clarify epidemic situation is being placed more important, updating outbreak information every day through “Notifiable Infectious Diseases Statistics System” and convene press conference every week during epidemic period, and in addition, also enhance the propaganda to parents on “Prodromal symptoms of enterovirus infections with severe complication” and “Do not go to school when ill”. Risk communication divides into three levels more specifically in Taiwan:

- a) General population communication: News and media announcements.
- b) Minor group communication: Use enterprise resources and voice mail by phone to enhance propaganda to target groups.
- c) Individual communication: Individually communicate with parents of severe cases.

(2) Medical management

After entering the outbreaks, the demand of medical treatment for enterovirus infection patients is increasing. The main focus is early diagnosis and early treatment to avoid progressing into severe complications. Both in Taiwan and China, the main points are to raise the professional capability in clinical diagnosis and treatment, establish the guidelines for diagnosis and treatment of severe cases to the first line medical workers provide special training in conjunction with the medical organizations, designated responsible hospitals. Because the difference gap between rural and urban areas, in China, more emphasis on disease classification to improve the infection control is strengthened, increase the investment in the prevention/control and treatment to lift the feasibility for medical consultation, In Hong Kong, the newest EV71 information, and leaflets for clinical management procedures are provided to the physicians. In Malaysia, standard procedures of hospitalization and clinical management are established.

3. Tertiary prevention

Tertiary prevention is the extension of secondary prevention, essentially emphasize on avoiding severe complications and stopping the worsening and fatality. Taiwan and China have more specific arrangements.

On the medical care aspect, it is emphasized by providing prevention and control through professional medical consultation; establish the operation of Enterovirus severe disease medical network; also enhance hospital beds dispatch to ensure the healthcare quality of severe patients. On account of the wide range of land and the lacking of medical resources in remote regions, China has established and expanded pediatric intensive care units, upgrading the equipment for medical care of severe patients, establishing professional medical team and lead the training of technique and improve professional medical skills; implementing separate-tiers medical system and establishing standard procedure of patients transfer and mechanism, are the main points enhanced diligently in recent years.

Besides the medical care aspect, Taiwan also enhances the sanitation propaganda of “Prodromal symptoms of enterovirus infections with severe complication” and “EV71 related clinical manifestations and the transfer timing of suspected severe disease” for childcares and doctors through public media system, and also provide assistance for parents to determine the prodromal symptoms of severe disease and receive medical treatment immediately.

Discussion

1. Each country has own surveillance strategy, hard to evaluate the quality

Each country in Asia has different policy on monitoring enterovirus infection, besides including HFMD as a reportable disease; most countries also use the virus surveillance system to understand the virus epidemiology. Generally speaking, HFMD cases every year can reach to several thousand or even hundred times of that (Table 2), and virus epidemiologic data are mostly collected from sentinel doctors, while the proportion of laboratory confirmation of reported cases is not high, take China for example, the rate of pathogen confirmed by laboratory only 1.47% to 2.13% [5] during the extensive epidemics in China from 2008 to 2009. In Singapore, the reported HFMD are between 5,197 and 20,003 cases from 2001 to 2007, however, the numbers collected by virus monitoring is only 66 to 469 cases [6-7]. Though Taiwan has not included HFMD as a notifiable infectious disease, but has put HFMD, herpangina and influenza as sentinel surveillance disease to monitor the epidemic trend of mild disease. Specimen collected by sentinel doctors every year is almost over ten thousand cases [6, 11], which is more significant. Taiwan has listed EVSC as a notifiable disease, and any reported case will be sampled and tested. As a result, Taiwan's data of EVSC and death data is more accurate than other countries.

According to the statistics data of enterovirus infection or HFMD in Asia region, Taiwan, Japan and Singapore have more steady and complete monitoring system showing a two-to-four-year epidemic cycle. China, Vietnam and other countries showed a trend of increasing every year. Apart from the fact that the enterovirus epidemic has becoming more serious lately, it may also show the gradual maturation of surveillance system, improving the low reporting situation in the past. After including HFMD as notifiable contagious disease, China's epidemic becomes more serious. Besides the government's strict requirement to implement reporting, the expanding of outbreak area and lacking of medical resources in remote regions are reasons why the incidence rate and severe disease rate of HFMD both showed increasing [8]. Singapore's reporting sources include childcare organizations, while the number of childcare organizations has a trend of increasing. Additionally, the reported cases may increase owing to the expanded news reporting from the media in Singapore [7]. In general, it shows that the monitoring quality is gradually improving in China and Vietnam.

2. The research on pathogenicity of enterovirus and the development of vaccine should continue

Because EV71 prone to invade central nervous system, leading to more severe syndromes and even death. Hence all virologists work hard on EV71 genetic research, attempting to determine the relationship between subgenotype and outbreak. Before 1990, the main subgenotype prevalent in Europe and America is B type (B0-B2), and soon after, the C type (C1-C2). In Asia, only Japan started monitoring earlier, and it is B type which was prevalent before 1990. After that, the main prevalent subgenotypes were B3-B5 and C4-C5 after 1997 when outbreaks occurred in Malaysia, Taiwan and Vietnam; however, it was

always genotype C4 in China [12]. According to the long term subgenotype surveillance data from a prefecture in Japan, the virus subgenotype circulated within the region is similar to the type from other countries, it is speculated that the virus was directly or indirectly transmitted to the prefecture from other countries. Furthermore, since all subgenotypes induced severe neurologic complications, so the difference among subgenotypes probably is not the main factor causing severe complications [13]. The subgenotypes of EV71 in Taiwan from 1998 to 2009 are B4, C4, C5 and B5, while there was no higher death rate caused by a specific subgenotype [14]. At the present time, only the research in Malaysia found out that C1 subtype causes central nervous system complications more easily than B4 [2, 10].

Due to the higher neurological virulence of EV71, several Asian countries are vigorously conducting the research of vaccine. At the present time, the countries have obtained more concrete achievements on EV71 vaccine research are China's Hualan Biological Inc., Singapore's SingVax Inc., and Taiwan's National Health Research Institute, and all three are entering to the stage of clinical trials, estimating to be on the market in five to ten years [14]. Nevertheless, EV71 is not the only type that will cause severe diseases, CB3, Echo4 and Echo6 may also cause severe complications in newborns, furthermore, some enteroviruses which are untypeable by commercial fluorescein antibody reagent may also cause severe diseases or death. Because the focus is still on EV71 currently, the diagnostic development strategies are mainly on testing EV71, and after the EV71 vaccine hits the market, it is necessary to enhance the monitoring and the development of laboratory testing on other types of enteroviruses. Because enteroviruses are likely to generate intra- and inter-typic recombination, monitoring whether the genetic evolution of EV71 and the antigenicity change cause the increase of virus virulence or if it is still in the range of the vaccine protection are the issues that should proceed among the tasks of prevention and control.

3. The scientific evidence of prevention and control strategy needs improvement

The distribution and prevalence of enteroviruses are worldwide, and except Hungary and Bulgaria in Europe had severe epidemic in 1970, only Asia suffered greater threat after 1980. However, among risk factors which causing severe disease, except the age factor, other risk factors are still not understood so far. The prevalence rate of EV71 in Japan and Singapore are not low with a lot of HFMD cases every year, but the fatality is relatively lower. While in China and Vietnam, there are more death cases (Table 2). Nevertheless, both Singapore and Japan are developed countries, whose probability of dying aged < 5 years per 1000 live births (under-five mortality rate, U5MR) are three, and Thailand, Vietnam and China are between thirteen and twenty [15]. The 2002 estimation of U5MR in Taiwan is about 8 [16]. The U5MR in each country seems to be a little related to the severity level of enterovirus. In addition, the research in Singapore found out that the infected people between 0-4 years old in 2007 was 12% lower than in 2001. It is speculated that the implementation of prevention and control measures lead to the decrease of infected children and infants and also increased the age level of infected people [7]. Besides, many related researches also show that the infection at older

age yielded lower rate of severe diseases.

Each country's prevention and control strategies of enterovirus are mostly enhancing the hands sanitation and closure of class in epidemic stage, and no concrete result of class closure is evidenced so far. However, because it could lower or postpone the spread of outbreak to the community and reduce the impact of epidemic peak, though it may not lower the entire infected people, it is still adopted by several countries [1,6]. SARS and H1N1 novo influenza occurred separately in 2003 and 2009, at the same time, the prevalence of enterovirus infection was lower than a year before. Does this mean prevention and control strategies used to prevent respiratory diseases like wearing masks and washing hands guard against the enterovirus by droplet infection? Or the increase of people's awareness on personal hygiene and environmental health which lower the infection risk? These are deserved to be discussed.

4. Establish Asia *Enterovirus* comprehensive information platform

Responding to the extensive prevalence of EV71 in Asia-Pacific region in 1997, virologists from countries including Malaysia, Vietnam, Papua New Guinea, Singapore and Australia worked together and established Asia Pacific Enterovirus Surveillance Network (APNET, website <http://www.apnet.med.usyd.edu.au>). Network sponsored by England Welcome Trust Foundation, Australia National Health and Medical Research Council and AusAID for EV71 identification training and reporting, and supporting the regional surveillance of EV71 [2]. The network emphasizes on upgrading the laboratory diagnostic techniques and the communication of epidemiological information on virus strains, but less information on the surveillance of outbreaks and prevention/control strategy.

Besides monitoring and pathogen identification, medical care is also an important part of the prevention and control for enterovirus infection. Small number of cases infected by enterovirus may progress rapidly to severe or death if the timing of diagnosis and treatment are delayed. As a result, in 2011, WPRO's HFMD guideline collected published clinical medical documents, inviting medical experts including Taiwan to discuss and included the treatment principle in the guideline. Because Vietnam has more serious outbreaks in recent two years, Taiwan's Enterovirus medical team works with them and conducts related research project of treatment, expecting to see research achievement in the near future.

WPRO's official webpage has added HFMD subject into the project of Emerging Disease Surveillance and Response in 2012, updating Asian countries' epidemic situation about every two weeks. The integration of information on *Enterovirus* surveillance, treatment and prevention/control and inter-countries collaboration research in Asia region will be beneficial to the evaluation of *Enterovirus* disease burden and study of risk factors on severe cases, and also establish prevention/control strategy with evidence based research.

5. Taiwan's *Enterovirus* surveillance and prevention/control achievement can be shared with the international health societies

To control the enteroviruses outbreak, Taiwan implements the disease preventive concept, three-levels-five-tiers strategy, and obtaining a significant achievement in prevention and

control experience for over ten years. In the recent years, the case fatality rate caused by severe complications has been reduced to lower than 10% (except the higher death rate due to the fewer cases in 2007), showing that the accumulation of clinical management experiences over the years has greatly improved the medical care of severe cases. In addition, in order to comprehend the improving orientation in prevention and control strategy, "The opinion poll of *Enterovirus* prevention and control strategy" is conducted every year, to adjust the direction for education campaign. According to the poll result of May 2010, the cognition of people to the method of preventing *Enterovirus* generally reached to 90%, however, the cognition of prodromal symptoms of enterovirus infections with severe complication such as low activity, continuously vomiting, weak limbs and lethargy is only about 68-79%, and 45% still choose to receive medical treatment at clinics when Prodromal symptoms of enterovirus infections with severe complication on sick children. Hence, enhancing education on caregivers of children below five years old, recognizing Prodromal symptoms of enterovirus infections with severe complication and the action to seek medical assistance after appearance of severe primary clinical manifestation are the focal points that should be strengthened in the future.

As for the disease surveillance, in the prevention and control measures of enhancing surveillance system, in its HFMD guideline, WPRO has indicated that HFMD is a common disease of children in Western Pacific region, and most of them are mild and not necessary to report, but should put emphasis on monitoring events like clustering outbreaks, severe disease and death [6]. A complete picture of prevalent trend of enteroviruses is comprehended since Taiwan has been monitoring the medical management in clinics, outpatient departments and emergency rooms, and virus types circulating in community, meanwhile, including the EVSC on the list of notifiable disease, so the data of pathogens which cause severe disease becomes available, it has the same essence in surveillance as stated in the WPRO's guideline. Since the massive outbreak of EV71 occurred in 1998, Taiwan started to require reporting herpangina and HFMD every week monitored by sentinel doctors for twelve years from 1998 to 2009, monitoring mild disease's prevalent trend caused by *Enterovirus*. Nevertheless, due to the development and establishment of "Real-time Outbreak and Disease Surveillance System, RODS" and "National Health Insurance Claims Databas, NHICD" system or database, the role of sentinel doctors surveillance finished the stage mission at the end of 2009. The surveillance of *Enterovirus* is replaced with more sensitive, rapid and comprehensive systems, RODS and NHICD, and the precision level of it obtained on enterovirus epidemiology can be counted on top of the world. Using systematically claimed data is an effective tool to assist the monitoring of diseases, though health insurance data has lesser under-reported problems, but owing to the difference in claim timing at each hospital level, the timeliness of NHICD data, although considerable completeness, is not as the immediateness of RODS which monitors the emergency data.

About 80% of symptoms induced by EV71 are mainly HFMD [19]. As a result, most Asian countries rely mainly on monitoring of HFMD. Taiwan's *Enterovirus* surveillance

strategy not only aims at EV71, but includes other types of *Enterovirus*, so the collected epidemiologic information is more abundant, and it may provide important reference for WHO when formulating related rules. Consequently, the orientation in the future is to not only persisting monitoring strategies and the development of vaccine but conduct the scientific evidence-based research of prevention and control strategy as fast as we can in order to provide effective prevention and control strategy and to lower social costs.

Conclusion

As the economics develops, living standards rises and the medicine advances, children health is becoming an important issue now. Enteroviruses persist on causing severe epidemic situation in regions such as China, Hong Kong, Japan, Malaysia, Singapore and Vietnam. As each country's surveillance system gradually mature, the reported cases of enterovirus infections have rapidly increased over the past two years, leading to the attention of international health organizations. WHO Western Pacific Regional Office announced press release on 13 July 2009, pointing out that HFMD gradually becomes the contagious disease threatening on children's health in Asian area [20]. WPRO also accomplished the Guide for HFMD in October 2011, providing the guidance on monitoring, diagnosis, treatment and prevention, and at the same time, the Office announces the epidemic situation of Asian countries regularly, through the integration of information, hoping to reduce the harm of enterovirus to children and, achieving the targets of conspiring children's health and welfare.

Acknowledgements

We thank Kun-Bin Wu, Branch Chief, for providing the international forum and conference data, and to former Deputy Division Chief, Tzu-Mei Huang, for her guidance.

References

1. Solomon T, Lewthwaite P, Perera D, et al. Virology, epidemiology, pathogenesis, and control of enterovirus 71. *Lancet Infect Dis* 2010;10:778-90.
2. Forum on HFMD in Asia Pacific Region held by The Regional Emerging Diseases Intervention(REDI) and Ministry of Health, Singapore on Aug 21-22 2008.
3. Beijing International Symposium on Hand, Foot and Mouth (HFMD) cosponsored by Chinese CDC , WHO, and US CDC on Jan 13-14. 2009.
4. APEC Symposium Enteroviral Watch Program for Children Enterovirus 71 Epidemic in Asia Pacific Area in Chinese Taipei on Mar 26-27 2000.
5. APEC Conference for the Surveillance, Treatment, Laboratory Diagnosis and Vaccine Development of Enteroviruses in Chinese Taipei on Aug 13-14. 2009.
6. WPRO. A Guide to Clinical Management and Public Health Response for Hand, Foot and Mouth Disease (HFMD). Available at: http://www.wpro.who.int/emerging_diseases/documents/HFMDGuidance/en/index.html2011.

7. Ang LW, Koh BK, Chan KP, et al. Epidemiology and control of hand, foot and mouth disease in Singapore, 2001-2007. *Ann Acad Med Singapore* 2009;38:106-12.
8. Qian SY. Epidemiologic and Microbiologic Aspects of Enterovirus 71 Infection in Asia-Pacific Area. Presented at: 6th Congress of Asian Society for Pediatric Research, Taipei, Taiwan, on 15-18 April 2010.
9. Hand, foot and mouth disease in Japan, 2002-2011. *Infectious Agents Surveillance Report* 2012;3355-6.
10. Podin Y, Gias EL, Ong F, et al. Sentinel surveillance for human enterovirus 71 in Sarawak, Malaysia: lessons from the first 7 years. *BMC Public Health* 2006;6:180.
11. Tseng FC, Huang HC, Chi CY, et al. Epidemiological survey of enterovirus infections occurring in Taiwan between 2000 and 2005: analysis of sentinel physician surveillance data. *J Med Virol* 2007;79:1850-60.
12. Infection Disease Surveillance Center Japan. Annual Surveillance Data. available at :<http://idsc.nih.go.jp/idwr/ydata/report-Eb.html>.
13. Tu PV, Thao NT, Perera D, et al. Epidemiologic and virologic investigation of hand, foot, and mouth disease, southern Vietnam, 2005. *Emerg Infect Dis* 2007;13:1733-41.
14. WPRO. Hand, Foot and Mouth Disease (HFMD), Situation update. 2012. p. available at :http://www.wpro.who.int/topics/hand_foot_mouth/en/index.html.
15. Centre for Health Protection Hong Kong Yearly Enterovirus Infections 1994 - 2011, . available at :<http://www.chp.gov.hk/tc/data/4/26/44/292/53.html>.
16. Ministry Of Health Singapore. Weekly Infectious Diseases Bulletin. available at : http://www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/weekly_infectiousdiseasesbulletinhtml.
17. Hand, foot & mouth disease - Asia (27): Malaysia (SK) 20081112.3562 ProMED-mail 2008.
18. Hand, foot & mouth disease - Malaysia (Sarawak)(08) 20060821.2355. ProMED-mail 2006.
19. Sanden S, Koopmans M, Uslu G, et al. Epidemiology of enterovirus 71 in the Netherlands, 1963 to 2008. *J Clin Microbiol* 2009;47:2826-33.
20. Hosoya M, Kawasaki Y, Sato M, et al. Genetic diversity of enterovirus 71 associated with hand, foot and mouth disease epidemics in Japan from 1983 to 2003. *Pediatr Infect Dis J* 2006;25:691-4.
21. Lee MS, Chang LY. Development of enterovirus 71 vaccines. *Expert Rev Vaccines* 2010;9:149-56.
22. WHO. World Health Statistics. available at :http://www.who.int/gho/publications/world_health_statistics/en/index.html2012.
23. Wu JC, Chiang TL. Comparing child mortality in Taiwan and selected industrialized countries. *J Formos Med Assoc* 2007;106:177-80.
24. Chen YJ, Wu WC, Yan JJ. Review of Sentinel Surveillance System in Taiwan. Taiwan

Epidemiology Bulletin 2010;Vol.26; No.6.

25. Chang LY. Enterovirus 71 in Taiwan. *Pediatr Neonatol* 2008;49:103-12.

26. WPRO. Hand, foot and mouth disease a rising menace in Asia. Available at: http://www.prowhoint/media_centre/news/news_20090713htm 2009.

Outbreak Investigation Express

Shigellosis Outbreak at an Aboriginal Village, Hualien, 2012

Siao-Lien Huang¹, Mei-Chu Lee¹, Song-En Huang¹, Wan-Chin Chen², Jen-Hsin Wang¹

1. Sixth Branch, Taiwan Centers for Disease Control Taiwan

2. Office of Preventive Medicine, Centers for Disease Control, Taiwan

Abstract

On November 13, 2012, a hospital in Yuli, Hualien, reported a shigellosis case of a 17-year-old female who resides in a nearby aboriginal village. Because this village usually does not have shigellosis among adolescents, and they are usually not index cases of shigellosis outbreaks, it was suspected that there are additional cases in the village. The Sixth Branch of the Taiwan Centers for Disease Control, along with members of the local health station, began onsite investigation the next day. The investigation discovered that diarrhea cases among villagers began on October 27. By December 21, 2012, rectal swabs were taken from 67 residents, including 4 from hospital reported patients. Among the 32 symptomatic cases, *Shigella sonnei* were found in 14. Among the 35 asymptomatic residents, *S. sonnei* were found in 3. During this outbreak, 17 villagers in 5 families were confirmed to have shigellosis. Analysis of disease onset dates among patients indicated that the outbreak was caused by contact transmission. Through the implementation of symptom surveillance in the village, nearby school and work place, increased health education in the village, and environmental clean up, the outbreak was controlled and did not spread to nearby villages.

Keywords: shigellosis, aboriginal village, outbreaks

The Taiwan Epidemiology Bulletin series of publications is published by Centers for Disease Control, Department of Health, Taiwan (R.O.C.) since Dec 15, 1984.

Publisher : Feng-Yee Chang

Editor-in-Chief : Yi-Chun Wu

Telephone No : (02) 2395-9825

Executive Editor : Hsin-Yi Wang, Li-Gin Wu

Website : <http://teb.cdc.gov.tw/>

Address : No.6, Linshen S. Road, Taipei, Taiwan 100 (R.O.C.)

Suggested Citation :

[Author].[Article title].*Taiwan Epidemiol Bull* 2013;29:[inclusive page numbers].