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Contents

OSIR, March 2014, Volume 7, Issue 1, p. 1-8

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Flood-related Outbreak of Peripheral Neuropathy among Prisoners in Bangkok, Thailand

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Abstract

During 9-20 Nov 2011, four prisoners in the national prison died with unknown cause and many prisoners developed diarrhea and neuropathy. The Bureau of Epidemiology launched an investigation to identify etiology and source of outbreak, and implement control measures. A case was defined as a prisoner or guard who developed gastrointestinal (GI) symptoms or neurological symptoms during 1 Sep to 31 Dec 2011. Foods, water, blood and urine samples were tested for heavy metals, vitamins B1 and B12. The prison had 33 guards, 3,668 male prisoners and 555 female prisoners. Among 475 prisoners who met the case definition, 307 (64.6%) GI cases, 49 (10.3%) neurological cases and 119 (25.1%) cases with both GI and neurological symptoms were identified. No case was found among the guards. Attack rates among male and female prisoners were 12.6% (462/3,668) and 2.3% (13/555) respectively. No female prisoners developed neuropathy. Eleven male prisoners had severe distal symmetrical peripheral neuropathy. Four men aged 26-47 years died after developing acute dyspnea. The cases rapidly increased after pipeline of the prison damaged on 2 Nov 2011. Blood and urine samples illustrated vitamin B1 deficiency and high arsenic concentration respectively. This outbreak of peripheral neuropathy possibly resulted from arsenic contaminated drinking water. After providing clean water on 24 Nov 2011, the outbreak subsided within 10 days.

Key words: peripheral neuropathy, arsenic, prisoners, outbreak, Thailand

Introduction

In Thailand on 22 Nov 2011, Department of Corrections under Ministry of Justice reported to Bureau of Epidemiology (BOE), Ministry of Public Health (MOPH) that four male prisoners from a prison died after developing acute dyspnea, diarrhea, edema of both legs and muscle weakness. Two prisoners died after hospital admission while other two died before they were sent to the hospital. They died 1-4 days after onset of symptoms which were developed following the worst flood in Thailand[1]. BOE, Department of Health from Bangkok Metropolitan Administration, Health Center 43 and Environment and Sanitation Section in Min Buri District joined together and launched an investigation to confirm the outbreak, identify nature and cause of the problem, and implement control measures.

Methods

A cross-sectional study was conducted from 23 Nov 2011 to 25 Jan 2012 in the prison and its surrounding community. For active case finding, we used a structured questionnaire to interview prisoners and villagers about common symptoms, and also performed neurological examination. We conducted door-to-door search to identify community cases.

A prison case was defined as a prisoner or a prison guard who developed at least one of following symptoms: abdominal pain, nausea and vomiting, diarrhea, muscle weakness or sensory loss during 1 Sep to 31 Dec 2011. A severe neurological case was defined as paralysis or loss in sensory function at upper or lower extremities. A community case was defined as a villager living within 500 meters of the prison and had onset of these clinical symptoms during 25 Nov to 10 Dec 2011.

Information of the prison cases was extracted from hospital records of Nopparat Rajathanee Hospital where severely ill prisoners were admitted for care. The extracted information included signs and symptoms, diagnosis, clinical progression and treatment.

For laboratory testing, urine samples were tested for total and inorganic arsenic using standard methods of inductively coupled plasma mass spectrometry (ICP-MS) with high-performance liquid chromatography (HPLC) technique.[2] In addition, blood samples were used to test for cadmium[3] and lead[4] by ICP-MS technique, cholinesterase by enzyme kinetic technique, vitamin B1 by HPLC, and B12 by electrochemiluminescence immunoassay (ECLIA). Vitamin B1 and B12 levels were also tested at the Bangkok Pathology Laboratory. We also requested neurological testing, including nerve conduction studies (NCS) and electromyography (EMG) for two prisoners with the most severe neurological symptoms. Stool and rectal swab samples were tested for enteropathogenic bacteria, including *Clostridium botulinum* and its toxin at the Thai National Institute of Health (NIH). We collected samples among prison cases with non-severe clinical manifestations using convenient sampling method.

Environmental investigation included mapping of prison facilities and interviewing prison guards and prisoners about their activities and exposures prior to illness in order to identify additional risk factors. Water samples were collected and tested for arsenic, cadmium and lead. *Clostridium botulinum* and its toxin were tested in food samples. Cutting boards and food handlers were also tested for enteropathogenic bacteria.

In the community, spot urine and water samples were tested for total arsenic at NIH and Bureau of Occupational and Environmental Diseases.

Results

Description of the Outbreak Site

The prison had a total of 4,223 prisoners (3,668 males and 555 females) and 33 guards. The prison was divided into four zones: 1, 2 and 3 for males, and 4 for females (Figure 1). Prisoners in Zone 1 were waiting for court judgment while wards for long term prisoners were in Zones 2 and 4. Zone 3 was the only zone for vegetables growing. Although male kitchen in Zone 2 served foods to both male and female prisoners, rice was cooked separately in each zone. In female kitchen of Zone 4, food was cooked for prison guards and for sale to prisoners. Due to flooding during 1-15 Nov 2011, the food was changed to preserved food, such as fermented lettuce, fermented bamboo shoots and canned fish.

Pipeline water supply in the prison was connected to the main pipeline of waterworks in Min Buri District outside the prison, with the feeder pipe ran near a police station. The pipeline was divided into two lines: the first line connected to female zone and another line to male zones. Tap water for washing hand, using in bathrooms and watering plants ran in pipes to each building.

For drinking water, tap water in storage tank from Zones 1, 2 and 4 (not shown in the figure) was supplied to water filters in the same zones. However, Zone 3 received drinking water from Zone 2. The filtered drinking water was not sufficient for consumption among male prisoners because the filtering machine in the male Zone 2 had been broken for a long time (Figure 1).

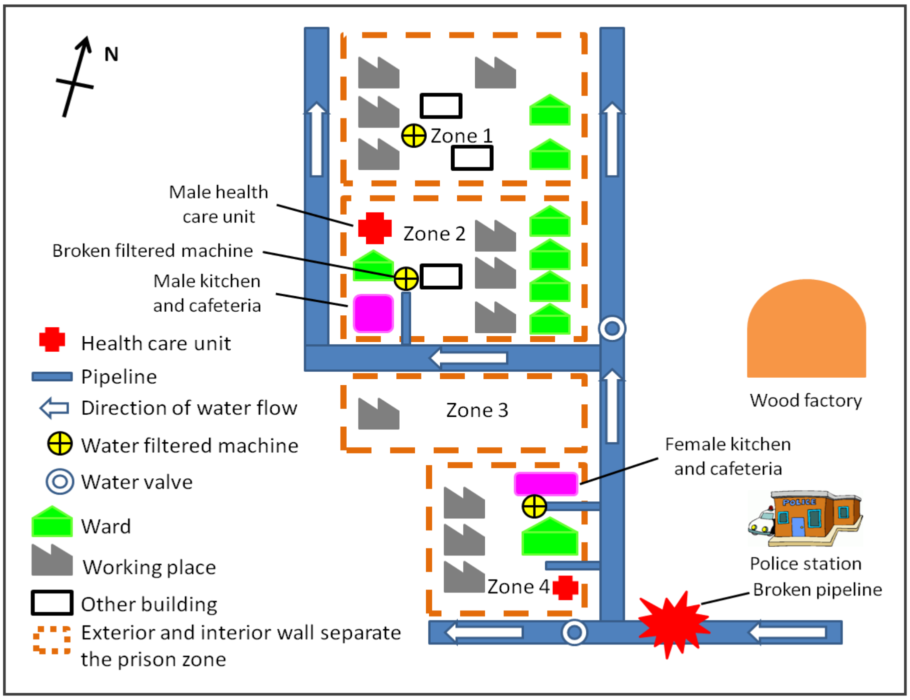

Figure 1. Schematic layout of the prison in Bangkok, Thailand, 2011

Therefore, some male prisoners drank tap water during the flooding. On 2 Nov 2011, the pipeline in front of the police station was broken. After that, some prisoners reported that tap water and drinking water were not clear and oddly smelled.

Outbreak Investigation

Total 464 non-severe cases and 11 severe cases were identified. No case was found among 33 prison guards. Attack rate in male prisoners (12.6%) was higher than that of female prisoners (2.3%). Majority of cases developed gastrointestinal symptoms (Table 1). No female prisoners developed neurological symptoms. Median age on non-severe cases was 30 years (range 17-80 years).

The most common symptoms among prisoners were watery diarrhea (68%), abdominal pain (42%), nausea or vomiting (38%), motor weakness (35%) and numbness (35%). Other symptoms included edema of legs (16%), dysphagia (13%), blurred vision (12%) and ptosis (6%).

There were 460 patients who remembered the first date of their illness which was started from 2 Sep to 3 Dec 2011 (Figure 2). Number of cases increased rapidly after tap water pipeline of the prison was broken on 2 Nov 2011, with the highest on 15 Nov 2011. Then, cases decreased gradually and no more case reported since 4 Dec 2011.

Table 1. Characteristics and symptoms of non-severe cases in the prison, Bangkok, Thailand, 1 Sep to 31 Dec 2011 (n=464)

Characteristic	Gastrointestinal symptom	Neurological symptom	Both symptoms
Total cases	307 (66.2%)	49 (10.6%)	108 (23.3%)
Male: female	294:13	49:0	108:0
Median age in year (range)	29 (17-72)	32 (19-53)	30 (19-80)
Prison ward			
Zone 1 (male, n=536)	0	0	0
Zone 2 (male, n=3,132)	294 (9.4%)	49 (1.6%)	108 (3.5%)
Zone 4 (female, n=555)	13 (2.3%)	0	0
Onset date of first case	28 Oct 2011	2 Sep 2011	15 Sep 2011
Onset date of last case	3 Dec 2011	28 Nov 2011	2 Dec 2011

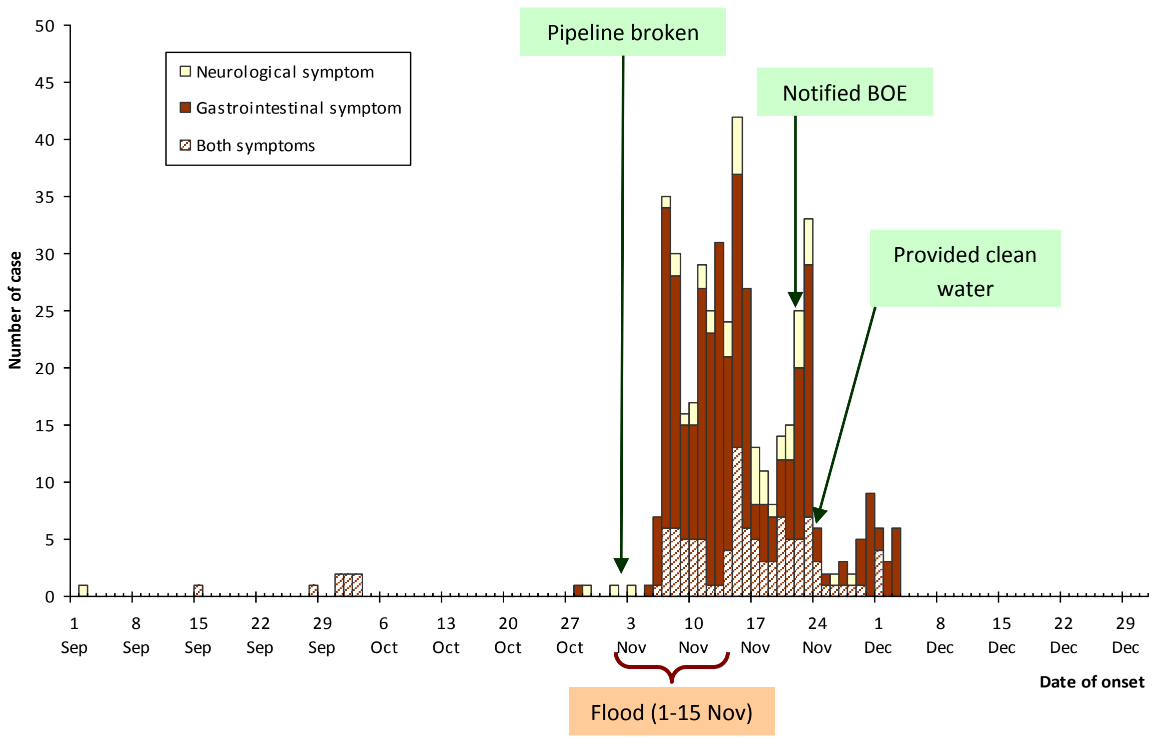

Figure 2. Cases in the prison by date of onset and type of symptoms, Bangkok, Thailand, 1 Sep to 31 Dec 2011 (n=460)

All 11 cases with severe neurological symptoms were males, with median age of 33 years (range 22-53 years). These severe cases were presented with symmetrical distal muscle weakness (Grade III)[5], followed by proximal muscle weakness involving lower extremities only without hemiparesis or eye movement limitation. Among severe neurological cases, 63% of them had sensorimotor deficit while 19% had motor involvement and 18% had sensory deficit. Although numbness was reported, there was no specific pattern of sensory loss. All severe cases had areflexia and also gastrointestinal symptoms. Ten (90.9%) of these severe cases had increased total arsenic concentration in urine (Table 2). Cadmium was also found in two cases (18.2%) and lead in one case (9.1%). All cases had normal concentrations of vitamins B1 and B12. Two cases tested with NCS and EMG presented sensorimotor axonopathy which was not specific for arsenic intoxification.

Information of the firstly notified cluster of four dead prisoners was investigated through other prisoners and guards. They were all males, aged 26-47 years and died after developing acute dyspnea. Their symptoms were ill-defined because of incomplete records. Therefore, we excluded them from the case group.

Laboratory results of ill prisoners and guards showed that 23 out of 54 prisoners (42.6%) and two out of eight guards (25.0%) had high arsenic concentration in their urine (Table 3). Of 24 samples testing for vitamin B1 function, 16 (66.7%) had low function. Among 24 rectal swab samples for enteropathogenic bacteria, *Shigella flexneri* was identified in five samples (25.0%), *Aeromonas spp.* in one sample (5.0%) and *Plesiomonas shigelloides* in one sample (25.0%). None of seven blood and stool samples contained *Clostridium botulinum* or toxin (Table 3).

Table 2. Laboratory results of severe neurological cases in the prison, Bangkok, Thailand, 1 Sep to 31 Dec 2011 (n=11)

Laboratory test	Total	Number positive	Percent
24-hour urine			
Total arsenic ≥ 120 mg	11	10	90.9
Inorganic arsenic ≥ 35 ug/L	11	0	0
Blood			
Cadmium ≥ 5 mg/L	11	2	18.2
Lead ≥ 40 mg/L	11	1	9.1
Cholinesterase > 5,320 unit/L	11	0	0
Vitamin B1 level, aETK* > 1.25	11	0	0
Vitamin B12 level < 211 pg/mL	11	0	0
Nerve conduction studies and electromyography			
Symmetrical peripheral sensorimotor axonopathy involved lower limbs more than upper limbs	2	2	100.0

* *aETK - erythrocyte transketolase activity coefficient*

Table 3. Laboratory results of non-severe cases in the prison, Bangkok, Thailand, 1 Sep to 31 Dec 2011

Laboratory test	Total	Number positive	Percent
Spot urine for total arsenic ≥ 50 ug/L			
Male prisoner	41	18	43.9
Female prisoner	13	5	38.5
Prison guard	8	2	25.0
Blood for vitamin B1 activity ≤ 49 ug/L			
Male prisoner	18	12	66.7
Female prisoner	6	4	66.7
Rectal swab for enteropathogenic bacteria			
Shigella flexneri (male)	20	5	25.0
Aeromonas spp. (male)	20	1	5.0
Plesiomonas shigelloides (female)	4	1	25.0
Blood for *Clostridium botulinum* and toxin (male)	4	0	0
Stool for *Clostridium botulinum* and toxin (male)	3	0	0

Table 4. Laboratory results of environmental samples in the prison, Bangkok, Thailand, 1 Sep to 31 Dec 2011

Laboratory test	Total	Number positive	Percent
Filtered water for arsenic, cadmium and lead*			
Zone 2	3	0	0
Zone 4	2	0	0
Tap water for arsenic, cadmium and lead			
Zone 2	2	0	0
Zone 4	1	0	0
Fermented lettuce for *Clostridium botulinum* and toxin	1	0	0
Cutting boards for enteropathogenic bacteria			
Zone 2			
Vibrio fluvialis	3	3	100.0
Aeromonas spp.	3	3	100.0
Escherichia coli	3	2	66.7
Zone 4			
Escherichia coli	2	2	100.0
Food handlers for enteropathogenic bacteria			
Rectal swab			
Plesiomonas shigelloides	12	2	16.7
Hand swab			
Escherichia coli	12	1	8.3

**Reference normal level: arsenic ≤ 0.05 mg/L, cadmium ≤ 0.005 mg/L, lead ≤ 0.05 mg/L*

Environmental Investigation

Environmental samples were collected one week after the flooding. At that time, drinking water and tap water were clear and no odd smell. We did not find heavy metals (arsenic, cadmium and lead) in water samples or *C. botulinum* and its toxin in food (Table 4). *Vibrio fluvialis* (100%), *Aeromonas spp.* (100%) and *Escherichia coli* (80%) were found on food cutting boards. *Plesiomonas shigelloides* (16.7%) and *E. coli* (8.3%) were identified from rectal and hand swabs of food handlers.

We surveyed 31 households in the community (Figure 3). Overall, we interviewed 193 people about history of diarrhea and neuropathy. Of those, we found nine (4.7%) persons with history of diarrhea, but no one with neurological symptoms. Onset of diarrhea was between 15 Oct and 25 Nov 2011. All 31 households drank tap water filtered by a machine or boiled water. The flood affected the community and a wood factory behind the police station.

Of 54 spot urine samples collected from the community, 15 (27.8%) had high total arsenic concentration. However, we did not find any arsenic contamination in seven water samples.

Risk Management

Since the tap water was suspected as the source

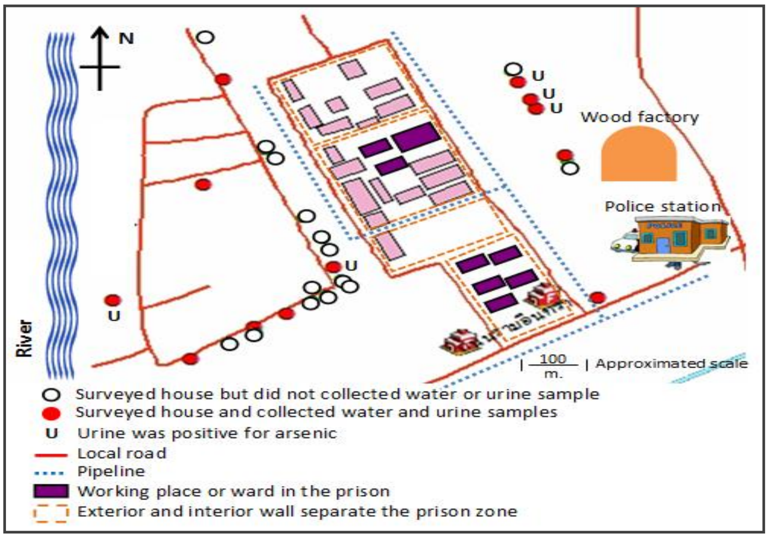

Figure 3. Map of the prison and surrounding community, Bangkok, Thailand, 2011

causing the outbreak, we informed all prisoners on 24 Nov 2011 to stop drinking the tap water and drink only water supply from the Metropolitan Waterworks Authority. Since then, number of new cases rapidly decreased and the outbreak stopped within 10 days. After male prisoners were treated with a combination pill of vitamins B1, B6 and B12 for 2-4 weeks[6], their neurological symptoms were improved.

Discussion

Clinical manifestations and laboratory findings suggested that this outbreak had possibly three etiologies.

One major etiology could be organic arsenic[7-9] due to several reasons. The first one was that arsenic poisoning is associated with nausea, vomiting, abdominal pain and watery diarrhea. Another important clinical sign is peripheral neuropathy which may occur rapidly and is similar to Guillain-Barré syndrome.

For the second reason, laboratory results among cases showed high total arsenic concentration without inorganic arsenic. In general, arsenic substance has two forms of organic and inorganic while the latter can cause more severe health effects. However, high level of organic arsenic can develop health effects as inorganic form. Most tests which measure total arsenic (both organic and inorganic) can give a high value reading when a person eats some fishes or seafood with high organic arsenic. Thus, in order to separate two forms, the ICP-MS technique which measures the level of inorganic form was used in this investigation.

The third reason for neurological cases was that arsenic can cause vitamin B1 (thiamine) deficiency[9-12] by inhibition of pyruvate oxidase that was used in vitamin B1 metabolism. Hence, neurological symptoms similar to dry beriberi were identified in some cases.

In this outbreak, vitamin B1 deficiency could be resulted from not only arsenic intoxication, but also thiamine antagonist[13] found in some fermented vegetables that were eaten during the flooding and malnutrition status because epidemic curve revealed some sporadic neurological cases before the pipeline was broken. These cases might be caused by malnutrition[14,15], or physical or mental stress[16] that can precipitate the neurological symptoms. Although some villagers had toxic level of arsenic in urine, they did not develop neurological signs possibly because they had enough vitamin B1.

For another etiology among gastrointestinal cases, cause of diarrhea could be shigella[17] which was found in rectal swab testing.

The investigation suggested the mechanism of water contamination and the outbreak was most likely to be caused by heavy metals and microbiological pathogens. The wood preservative solution used in the factory commonly composed of arsenic.[18] During the flooding, the wood factory was flooded and chemicals from wood preservatives might have contaminated the flood water. At that time, as the prison pipeline was also broken, tap water could also be contaminated with the flood water. By this way, heavy metals and microbiological pathogens could leak into the pipeline. Coincidently, the water filtering machine in Zone 2, which might have resin to capture chemical contaminants, was also broken and could not filter tap water effectively. Moreover, another precipitating cause could be fermented foods with thiamine antagonist that were eaten during the flood.

Previous arsenic poisoning outbreaks were caused by either intentional or unintentional contamination of food or beverage. A study by Gensheimer et al showed intentional arsenic contamination in coffee.[19] Of 16 people who drank the coffee, 13 (81.3%) vomited and had diarrhea, with one death (7.7%). Another epidemic of arsenic poisoning associated with ingestion of inadvertently contaminated milk powder in western Japan, which resulted more than ten thousand cases and 130 deaths.[20]

Acute arsenic poisoning is associated with gastrointestinal and neurological symptoms even if small amounts of arsenic (less than 5 mg) were consumed.[21] Other symptoms are hematological abnormalities, renal failure, respiratory failure, pulmonary edema, metabolic changes such as acidosis, skin rash, toxic cardiomyopathy and seizure. Lethal dose of arsenic ranges from 100 mg to 300 mg per person.[22]

In general population, prevalence of peripheral neuropathy ranged from 2.4 to 8.0 percent.[23,24] High prevalence may be associated with old age. Diagnosis and treatment of peripheral neuropathy require large amount of time and money as diagnosis often requires special clinical and laboratory tests such as nerve biopsy, EMG and NCS. These tests are helpful to identify pattern of nerve involvement and type of nerve fibers affected, and also narrow down the differential diagnosis.[25]

Epidemiological study for the disease profile in Texas prison[26] showed that major diseases in the prison were communicable diseases such as AIDS/HIV, TB and hepatitis while foodborne outbreaks were also common. Nevertheless, other prisons had reported outbreaks of beriberi due to inadequate food intake.[27-30] A study by Ahoua et al reported that of 5,038 cases recruited, 714 (14.2%) were beriberi cases.[31]

Samples from the four dead prisoners could not be collected for heavy metals testing. However, we hypothesized that the cause of death might be wet beriberi because these cases occurred during the outbreak period and their clinical manifestations were same as severe neurological cases.

Some prisoners could not remember details of illness or risk factors since the outbreak started long time before the investigation. Likewise, heavy metal might already have disappeared from the tap water before the sample collection. Thus, laboratory testing could not detect any heavy metal from the tap water samples.

We could not test the broken water filtering machine whether it was capable to filter microorganisms and heavy metals because the machine was removed from the prison before the investigation. In addition, we could not investigate or test chemicals used in the wood factory and soil around the factory. Finally, there were no more flood water samples available for testing.

Conclusion

This peripheral neuropathy outbreak could be resulted from total arsenic intoxication. Source of the outbreak was probably from drinking contaminated tap water which was carried into the broken water pipeline by the flood water. In addition, foods with thiamine antagonist provided during the flood could be another cause of neuropathy in some cases.

Recommendations

We recommended that maintenance of water supply system in the prison should be improved. The prison should provide adequate amount and types of food to prevent malnutrition and related diseases. A surveillance system should be established in the prison to monitor prisoners with severe illnesses for early detection of future outbreaks.

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Risk Factors of Lymphatic Filariasis in West Sumatera Province, Indonesia, 2010

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Abstract

Lymphatic filariasis (LF) has long been endemic in Indonesia. Agam District is an endemic area for LF in West Sumatera. We conducted a case-control study and performed spatial analysis to assess distribution and risk factors for filariasis in affected community. Data were collected by direct interview, household observation and geo-coordinate capture of their houses by global positioning system. Risk factors for filariasis were estimated by bivariate and multivariate analysis. Spatial analyses by GeoDa (spatial significant), SaTScan (clustering poisson model) and Excel Discalc (distance) were used as tools for mapping. Total 91 cases, including 51 elephantiasis, were identified. Most cases (56%) were from Tiku Sub-district, with median age 45 years (range 10-80 years). Living near a palm plantation (<100 meter) (p-value=0.002, OR (95%CI) = 11.5 (2.56-45.89)), and not using ventilation net (p-value = 0.023, OR (95%CI) = 9.0 (1.21-26.42)), or bed net (p-value = 0.002, OR (95%CI) = 2.1 (2.45-2.79)) were strongly associated with LF. Spatial analysis found significant clustering in one area with 15 cases (16.5%) at elevation between 400-700 meters above the sea level.

Key words: lymphatic filariasis, risk factors, GIS, clustering

Introduction

Lymphatic filariasis (LF) is a parasitic worm disease caused by *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori*. It is transmitted by mosquitoes, and causes disability and adversely impacts to economy of developing countries where it is endemic. Filariasis is the second most common vector-borne parasitic diseases after malaria and affects over 120 million people in 73 countries throughout the tropics and sub-tropics of Asia, Africa, the Western Pacific, part of the Caribbean and South America[1].

Most infected people are asymptomatic and never develop clinical symptoms, despite the fact that the parasite damages the lymph system. A small percentage will develop lymphedema.[1,2] Approximately 65% of those infected people live in Southeast Asia and 30% in Africa. About 40 million are disfigured and incapacitated by the disease, which comprised of 25 million men with genital disease and over 15 million with lymphedema. LF is a leading cause of disability and also creates social stigma for both individual and family from disfiguring limbs and genitalia.[3]

LF is a major health problem in many parts of Indonesia where all three species (*W. bancrofti*, *B. malayi* and *B. timori*) are prevalent and 22 competent vectors have been identified. Twenty six out of 32 provinces and 85 out of 444 districts, which comprised of approximately 150 million people, were found to be endemic for LF. During 2005-2009, 11,914 people were affected with elephantiasis and 6 million had LF, with microfilaria (Mf) rates of 1-39%.[3,4,5] LF was tested by microscopic thick blood smear stained with Giemsa, using venous blood collected between 9 pm and midnight. Mf prevalence rate was calculated as dividing number of person tested Mf positive by number of person tested.[6]

Agam District has an area of 2,232.3 km² and population of 439,611, with 16 sub-districts and 22 public health centers. It has been LF endemic region in West Sumatera Province since 2006, with 54 cases and 18.0% Mf rate in 2010 (Table 1).

These cases were reported from five sub-districts: Tanjung Raya, Lubuk Basung, IV Nagari, Palembayan and Tiku. Although filariasis could be identified by microscopy, laboratories in West

Sumatera did not routinely test for LF, which is very essential for understanding overall burden of LF disease and estimation of Mf rate.

Table 1. Number of lymphatic filariasis cases and microfilaria (Mf) rate in Agam District, West Sumatera, Indonesia, 2006-2010

Year	Number of prevalence case	Number of incidence case	Mf rate (%)
2006	37	Not available	12.3
2007	44	7	14.7
2008	48	4	16.0
2009	51	3	17.0
2010	54	3	18.0

In 2008, Agam District has initiated LF elimination program based on mass drug administration (MDA) with single dose of diethyl carbamazine (DEC) and albendazole according to World Health Organization (WHO) guidelines.[1] However, it was stopped in 2010 due to lack of funds.[6,7] Unfortunately, relatively little information was available to assess impact of the MDA on LF prevalence and incidence in Agam even though Mf rates have been increasing since 2004.[7]

Spatial analysis using geographic information system (GIS) has become an important tool for surveillance. Control of LF requires good monitoring and mapping of cases to guide decision making for LF treatment programs. The most important is that GIS can detect burden of LF early to improve LF control strategies in the region by identification of risk areas and provide early diagnosis and prevention by measuring risk factors.[8,9]

We also conducted a community study to measure risk factors for LF, actual prevalence, distribution and clustering by GIS. The goal was to generate useful data for the responsible persons to plan and implement national LF elimination program in Indonesia and other endemic countries as well.

Methods

The study was performed in five sub-districts (Tanjung Raya, Lubuk Basung, IV Nagari, Palembayan and Tiku) in Agam District of West Sumatera Province, Indonesia. These sub-districts are located approximately 90-110 km southwest of the provincial capital of Agam with 122,378 population. All five sub-districts were in endemic area and were selected with inclusion criteria of Mf rate more than 1%. We conducted active case finding with volunteer health practitioners from each sub-district to find suspect LF cases. Our field teams comprised of trained midwives, laboratory staff and nurses. We also met with community leaders and held outdoors activities to inform local people about significance of LF and importance of blood test for monitoring LF disease.

We conducted the study with three methodologies: case-control study to determine risk factors using odds ratio (OR), spatial analysis to analyze distribution and clustering of LF cases, and survey by standard diagnostic method of thick blood smear with 5% Giemsa stain[2] to identify villages with asymptomatic cases. Children under two years, pregnant women and people with severe chronic illness were excluded from the study.[10,11] Total 182 persons were included in the study, with 91 cases and 91 controls.

A confirmed LF case was defined as a person who lived in one of the five sub-districts and was confirmed to have LF positive by microscopic thick blood smear. Active case finding was conducted by survey of villagers in sub-districts. Total 185 villagers were surveyed and blood samples were collected from 182 villagers. Total 1-3 µl of finger spot blood was collected between 9 pm and midnight.[11] Laboratory confirmation was performed at provincial laboratories in West Sumatera. Clinical symptoms were assessed and households were spotted using global positioning system (GPS).

Controls were selected from people who lived in same villages with cases and had no LF by microscopic test. Cases and controls were matched for sex, age (range five years) and residency (less than 50 meter to the case's house).[13] We used simple random sampling to select 91 matched controls from five sub-districts.

Cases and controls were interviewed at their homes, and information on signs, symptoms and risk factors were collected by a standardized questionnaire. Home visit also allowed observation of participants' living environment and collecting of geo-coordinate spot using GPS.

To identify risk factors for LF, chi-square and logistic regression were used in bivariate and multivariate analyses. We conducted multivariate analysis (multiple logistic regression) to calculate the most association between risk factors and LF prevalence, and included all variables with p-value of less than 0.25 from the bivariate analysis. All the variables in the model had a normal distribution. The regression used an enter approach. Significant level was p-value less than 0.05.

For spatial analysis, we used GeoDa and SatScan to identify clustering of LF cases, and Excel Discalc to measure distance to health centers. SatScan approach (Bernoulli models) was used for analysis.[14] Ethical clearance of this study was reviewed and approved by institutional review boards in Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia.

Results

Through active case finding, we identified 91 cases and 91 matched controls in five sub-districts where 51 out of 91 cases had elephantiasis. Most cases were males (63.7%), with median age 45 years (range 10-80 years). Tiku Sub-district had 51 cases (56.0%), with prevalence of 2.0 per 1,000 population (total 26,037 population) and Lubuk Basung had 33 cases (36.3%), with prevalence of 0.6 per 1,000 population (total 59,470 population).

IV Nagari Sub-district had five cases (5.5%) while Palembayan and Tanjung Raya had only one case each (1.1%). The study revealed that 50.5% of cases and 42.9% of controls had no education background (Table 2). Although majority of them did not use bed net (97.8% of cases, 90.1% of controls) or ventilation net (86.8% of cases, 97.8% of controls), 79.1% of cases and 78.0% of controls used repellent (Table 3).

Table 2. Demographic characteristics of lymphatic filariasis cases and controls in 5 sub-districts of Agam District, West Sumatera, Indonesia, 2010 (n=182)

Characteristic	Case (n=91)		Control (n=91)	
	Number	Percent	Number	Percent
Gender				
Male	58	63.7	58	63.7
Female	33	36.3	33	36.3
Age (year)				
10-19	16	17.6	16	17.6
20-29	14	15.4	14	15.4
30-39	10	11.0	10	11.0
40-49	8	8.8	8	8.8
50-59	12	13.2	12	13.2
60-69	14	15.4	14	15.4
70-79	11	12.1	11	12.1
>80	6	6.6	6	6.6
Sub-district				
Tiku	51	56.0	51	56.0
Lubuk Basung	33	36.3	33	36.3
IV Nagari	5	5.5	5	5.5
Tanjung Raya	1	1.1	1	1.1
Palembayan	1	1.1	1	1.1
Education				
No education	46	50.5	39	42.9
Low	27	29.7	28	30.8
Middle	18	19.8	24	26.4
High	0	0	0	0

Table 3. Behavioral characteristics of lymphatic filariasis cases and controls in 5 sub-districts of Agam District, West Sumatera, Indonesia, 2010 (n=182)

Characteristic	Case (n=91)		Control (n=91)	
	Number	Percent	Number	Percent
Using bed net				
Yes	2	2.2	9	9.9
No	89	97.8	82	90.1
Using ventilation net				
Yes	12	13.2	2	2.2
No	79	86.8	89	97.8
Using repellent				
Yes	72	79.1	71	78.0
No	19	20.9	20	22.0
Had animal as reservoir				
Yes	64	70.3	48	52.7
No	27	29.7	43	47.3

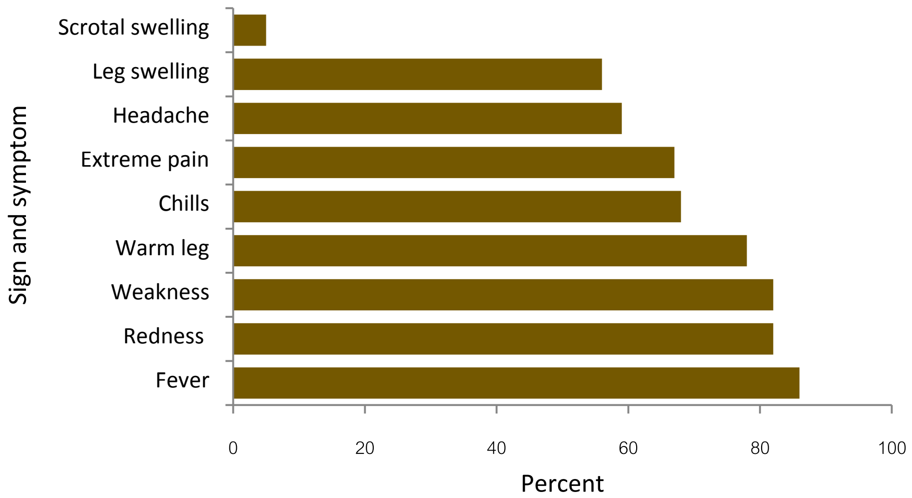

Figure 1. Signs and symptoms of lymphatic filariasis cases in5 sub-districts of Agam District, West Sumatera, Indonesia, 2010 (n=91)

The most common symptom of LF cases included fever (94.5%), followed by redness (90.0%), weakness (90.0%), warm leg (85.7%) and leg swelling (61.5%) (Figure 1).

Results of bivariate analysis showed that there were eight risk factors significantly associated with LF, including low level of knowledge, not using bed net, not using ventilation net, having a reservoir animal (cows, dog or monkey) based on observation, and living near swamp less than 100 meters, river, rice field and a palm plantation. Other factors were not significantly associated with LF (Table 4). Living near a palm plantation had the highest OR (Table 5) and thus, become the strongest risk factor for LF prevalence in Agam District.

Table 4. Bivariate analysis on risk factors of lymphatic filariasis cases in 5 sub-districts of Agam District, West Sumatera, Indonesia, 2010 (n=182)

Risk factor	P-value	Odds Ratio	95% CI
Low education level	0.312	0.7	0.24 - 2.24
Low income	0.441	0.9	0.49 - 1.67
Low level of knowledge	0.001	2.9	1.56 - 5.27
Not using bed net	0.002	1.7	1.24 - 2.35
Not using ventilation net	0.005	6.8	1.47 - 31.13
Not using repellent	0.500	1.7	0.53 - 2.17
Had an animal	0.010	2.1	1.15 - 3.91
Had activity at night	0.226	1.3	0.73 - 2.37
Living near swamp	0.001	6.2	1.75 - 22.30
Living near river	0.024	2.0	1.04 - 3.50
Living near rice field	0.018	2.0	1.08 - 3.53
Living near a palm plantation	<0.001	15.9	3.64 - 69.80

In addition, we found strong spatial correlation in one cluster of 15 cases (16.5%) at coordinate (00.185790S, 099.775720E). The farthest distance of case to public health centre was 840 meters, which was in Tiku Sub-district.

Table 5. Final multivariate analysis (logistic regression) on risk factors of lymphatic filariasis cases in 5 sub-districts of Agam District, West Sumatera, Indonesia, 2010 (n=182)

Risk factor	P-value	Odds Ratio	95% CI
Not using bed net	0.002	2.1	2.45 - 2.79
Not using ventilation net	0.023	9.0	1.21 - 26.42
Living near swamp	0.077	2.8	0.92 - 16.54
Living near a palm plantation	0.002	11.5	2.56 - 45.89

Discussion

This was the largest number of LF cases reported in West Sumatera Province from 2006 to 2010. Males were more exposed to LF than females. Level of knowledge, with median 45 out of 100, was associated with LF because people were lack of information about infection, drug administration and location of health facilities. Majority of cases did not know about drugs for LF and lived in rural areas which were far away from health facilities, thereby causing low compliance of drugs. Thus, giving health education to communities about benefits of LF drugs that kill the worms was necessary and global campaign to eliminate LF should be conducted.[15]

Our results showed that living near a palm plantation and not using bed net or ventilation net were significantly associated with LF. These could

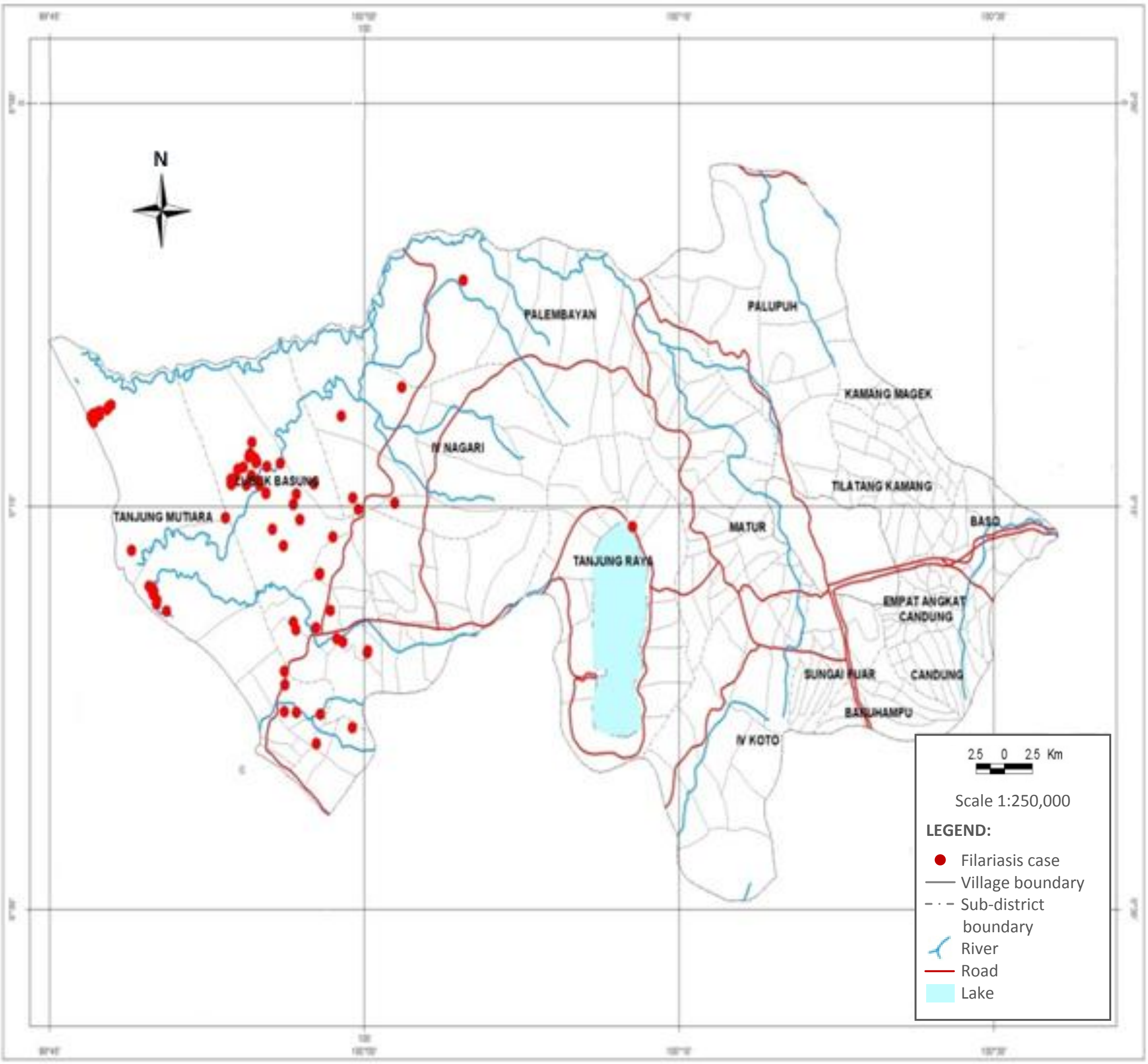

Figure 2. Spatial analysis on lymphatic filariasis cases in Agam District by mapping with GPS, West Sumatera, Indonesia, 2010

also relate to biological factors such as presence of mosquito breeding sites and frequent contact with mosquitoes during outdoor activities. Farmers and workers in palm plantation not only spend most of their time outside, but also work during night time which is the biting time of mosquitoes. The ways to prevent LF are to avoid bitten by mosquitoes especially at night, sleep under mosquito net such as long-lasting pretreated nets, wear long sleeves and trousers, and use mosquito repellent.[16] Another approach of prevention is implementing MDA by giving medicines that kill microscopic worms to all communities in order to reduce microfilariae in blood. Surprisingly, we also found five LF cases with scrotal swelling which indicated that more than one type of parasite causing LF were circulating in Agam District.[17]

Study on spatial analysis found that Tiku Sub-district had the highest number of cases (56.0%) and most of them lived in rural villages with environmental risk factors such as vector breeding sites. In addition, this study found significant clustering in one area with 15 cases (16.5%) at elevation between 400-700 meters above the sea level, which implied that the study area was highly endemic with LF. Spatial analysis is becoming important for epidemiology as control of LF requires good monitoring by good mapping. These mapping results provided tools to implement MDA which was going to conduct in 2012-2015 and provide basis information for future monitoring and evaluation of local LF elimination programs. In addition, the results could be helpful to early detect LF burden, and improve effectiveness and safety of LF control strategies in Agam Region.

Limitations

This study could not determine vector density, impact of vectors ecologies on local transmission and nature of parasite vector. Elimination of vector would be a cost effective measure to interrupt LF transmission in

Agam District. Since lymphedema may develop many years after infection and MDA had been implemented in Agam District, laboratory tests were most likely to be negative with the patients who had MDA before. Thus, more specific laboratory tests such as serologic antifilarial (IgG4) might be necessary.

Conclusions and Recommendations

Although the LF elimination program in Agam District has been ongoing for five years, it had not succeeded in reducing of LF prevalence. Living near a palm plantation which was the most significant factor was related to mosquitoes breeding places as vector also plays a role in LF transmission. More health education and awareness raising campaigns could improve drug compliance. More bed nets should be provided to stop the transmission. MDA should be implemented in the LF elimination program. The best ways to prevent LF are to avoid bitten by mosquitoes between dusk and dawn, and eliminate mosquitoes in the area.

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We thank local staff at health centers in Agam District, Tiku Sub-District, Palembayan Sub-District, Tanjung Raya Sub-District and Lubuk Basung Sub-District, and parasitological laboratory in West Sumatera Province for all kinds of support in LF investigation. We also appreciate Dr. Indra Rusli and Dr. Bakhrizal Koto for helpful review of the manuscript.

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Investigation of A Severe Enteroviral Encephalitis and Circulating Genotypes during Hand, Foot and Mouth Disease Surge in Nakhon Ratchasima Province, Thailand, August 2011

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Abstract

On 7 Aug 2011, a 1-month-old baby with encephalitis caused by unspecified enterovirus was reported during the period of widespread hand, foot and mouth disease (HFMD) outbreaks in Nakhon Ratchasima Province. An investigation was carried out to confirm the diagnosis, identify etiology of all severe enteroviral infection cases, determine magnitude of HFMD and enterovirus infection, including asymptomatic infections, and recommend prevention and control measures. A descriptive study was conducted by interviewing family members of the index case. Throat swab and stool specimens were collected to identify enterovirus. Survey on asymptomatic infection was done in schools attended by the index case's siblings. Stool culture and isolation for enterovirus were also performed. Coxsackie B5 virus was isolated from fresh stool specimens of the index case. Among total 244 students screened for HFMD symptoms in four schools, only seven (3%) met the suspect case definition. During HFMD outbreaks caused by EV-71 B5, coxsackie A16 and coxsackie B5, proportion of asymptomatic infection among students was 22%. Risk factors such as no soap in toilets and misuse of alcohol gel to clean hands in schools were observed during the environmental survey.

Key words: encephalitis, HFMD, enterovirus, EV-71, coxsackie B5, Nakhon Ratchasima, Thailand

Introduction

Hand, foot and mouth disease (HFMD) is a common viral illness that mainly affects children under five years old. However, sometimes it can also affect adults. The disease is transmitted through direct contact with respiratory droplets, feces, blister fluid from palms, soles and oral mucosa, or contaminated objects and surfaces such as utensils in school.[1,2] The disease is caused by a number of different genotypes of enterovirus, including enterovirus 71 (EV-71) and coxsackie A16. Spectrum of the disease ranges from asymptomatic or minor febrile illness and gastroenteritis to more severe syndromes, including aseptic meningitis, carditis and even fatal encephalomyocarditis in newborns.[3-6] In addition, case fatality ratio is high for HFMD with fulminant neurogenic pulmonary edema, especially in age group less than six months which is as high as 21%.[7-9] HFMD and herpangina are frequently caused by several distinct serotypes belonging to human enterovirus A species. Therefore, surveillance should be set up to determine clinical and epidemiological characteristics of HFMD and herpangina associated with enterovirus infections.[10]

Many countries in Asia, especially China, have encountered various HFMD clusters among children with high number of fatal cases.[11]During 2006, Thailand had detected many HFMD cases and four deaths caused by enterovirus in a northeastern province, Nakhon Ratchasima.[12] Between May and

August 2011, the province had experienced HFMD outbreaks again, especially among school children. On 7 Aug 2011, the provincial health office notified the Bureau of Epidemiology that a 1-month-old male was admitted to a hospital with seizure, suspecting encephalitis caused by enteroviral infection. His cerebrospinal fluid (CSF) showed positive for unspecified enterovirus by polymerase chain reaction (PCR). Local and central surveillance and rapid response teams (SRRT) conducted an outbreak investigation on 8-31 Aug 2011 to confirm the diagnosis, identify etiology of all severe enteroviral infection cases, determine magnitude of HFMD and enterovirus infection, including asymptomatic infections, and recommend prevention and control measures.

Methods

HFMD Situation

We reviewed national epidemiological surveillance information (506 report form) on HFMD reported from Nakhon Ratchasima Province during 2006 to 2011.

We also reviewed medical records of the index case, interviewed family members and collected stool and throat swab specimens. In addition, we searched for severe HFMD cases and encephalitis cases aged under five years and admitted to the provincial hospital between January and August 2011.

We conducted an active case finding among patients diagnosed with HFMD or herpangina, and visited hospitals in Wang Nam Khiao (X) and Pak Thong Chai (Y) Districts in the province during 1-31 Aug 2011. We interviewed patients and household members about demographic data, clinical manifestations, onset dates and risk factors using semi-structured questionnaire. Moreover, stool samples were collected and tested for viral culture and isolation.

A suspect case was a villager from District X or Y who had oral ulcer with or without skin rash on palms and soles during 1-31 Aug 2011. A confirmed case was a suspect case tested positive for enterovirus by isolation with or without seroconversion by microneutralization test in acute and convalescent phase of serology.

An enteroviral encephalitis case was a person, who lived in X and Y Districts, developed fever and alteration of consciousness or seizure during 1 May to 31 Aug 2011 and had been confirmed by positive enteroviral isolation and/or seroconversion by microneutralization test.

Severe HFMD case was a HFMD case with severe complication involving heart or nervous system.

Persons with asymptomatic infection included household members or school contacts without symptoms, but were tested positive for enterovirus by isolation with or without seroconversion by microneutralization test in acute and convalescent phases of serology.

School Survey for Asymptomatic Infection

A survey on enteroviral infection was conducted among students in four schools attended by the index case's siblings. School A was located in District X while Schools B, C and D were in District Y. All schools provided education for kindergarten and primary school (age ranged 3-15 years). All students were screened for HFMD clinical manifestations by the investigation team and teachers. Students screened positive were interviewed by the team using structured questionnaire. Their stool samples and throat swabs were collected for viral culture and isolation. Throat swabs were collected from the suspect cases who had oral ulcer during last two weeks whereas fresh stool samples were collected from all family members and school children.

Laboratory Testing

Fresh stool samples and throat swabs were placed in dry containers, stored in refrigerators at 4-8°C and sent to Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand for testing EV-71, coxsackie virus and *Enterovirus spp.* by viral culture, isolation and PCR.

In addition, 3-5 ml of serum was collected from severe HFMD and enteroviral encephalitis cases, and tested for serological titer of EV-71, coxsackie virus and *Enterovirus spp.* by microneutralization assay (Micro-NT) at the National Institution of Health (NIH), Department of Medical Science, Ministry of Public Health, Thailand.

Environmental Survey

Kitchen and toilet in the index case's house were inspected for sanitation. Other exposures were also assessed, including indirect contact transmission from public places such as public park or market.

In schools, we observed regular activities and inspected personal sanitation practices and environment that could be risk of transmission such as sharing of utensils, frequency of classroom cleaning, types of detergent, cleansing substances and soap in restrooms.

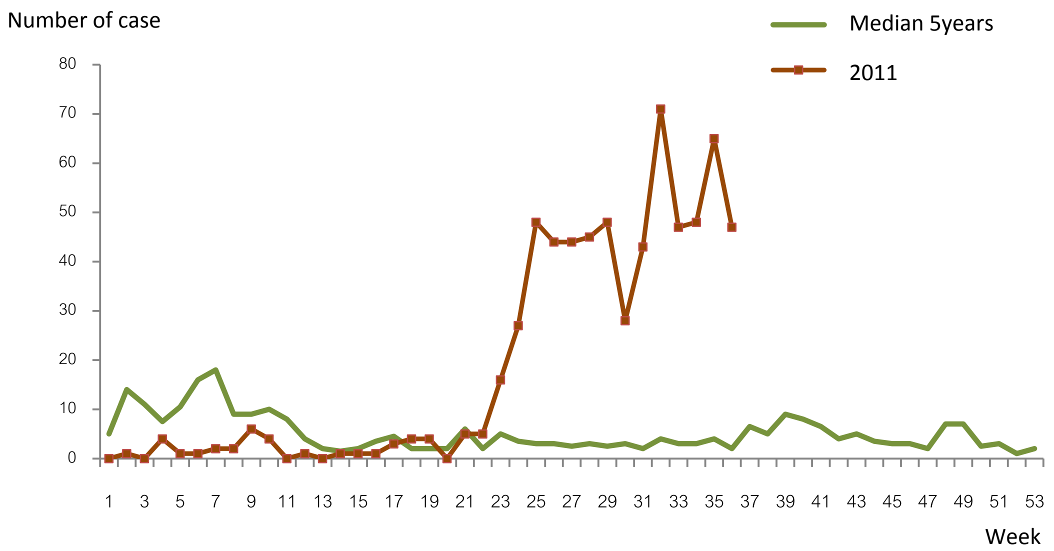

Figure 1. Number of reported HFMD cases by week and 5-year median in Nakhon Ratchasima Province, Thailand, 2011

Results

HFMD Situation

Number of HFMD cases reported to the Bureau of Epidemiology had increased since 20th week (May) of 2011 which was more than the median of the past five years (Figure 1). The period was correlated with semester opening of primary schools in Thailand.

Clinical Presentation and Exposures of the Index Case

On 31 Jul 2011, the index case, a 1-month-old Thai male, was brought to Wang Nam Khiao Hospital (Hospital X) with fever of 38°C and vomiting. At first, he was diagnosed with status epilepticus and acute viral infection. Few hours later, he developed generalized seizure and was transferred to the provincial hospital. After he was diagnosed of acute encephalitis, physician started antibiotics and provided ventilator support. He was treated with intravenous immunoglobulin (IVIG) the next day.

His CSF obtained on first day of admission was tested positive for *Enterovirus spp.* by viral culture and isolation at NIH. However, its genotype was not identified by PCR. Although the first stool sample collected four days after the onset was negative for enterovirus and coxsackie virus, the second stool sample collected one week later was positive for coxsackie B5 by stool viral isolation.

The index case lived with parents, elder twin brother and sister, and grandparents in District X. His mother was a teacher in School A and his father was a teacher in School D of District Y. His siblings were students in School B and C. Beside the index case, no other family members had symptoms of viral infection one week before his onset. Their stool culture and isolation for enterovirus and coxsackie virus were negative.

Active Case Finding in Hospitals

From January to July 2011, there was no report of severe encephalitis caused by enterovirus in the provincial hospital. In August 2011, three new cases of severe enteroviral infection without vesicles on hands, foot and mouth were notified in the province. They were reported as suspected cases of enteroviral encephalitis by nurses in pediatric intensive care unit during the investigation period. Two of them died suddenly after diagnosed as EV-71 encephalitis. All of them lived in the same district as the index case. Local and central SRRT joined together and conducted the investigation to contain the outbreak.

Among 43 HFMD cases diagnosed in August 2011, 20 confirmed cases and eight suspected cases were from Hospital X, and two confirmed cases and 13 suspected cases were from the hospital in District Y (Hospital Y). Nineteen cases (44%) were males, with median age two years old (range one month to six years old). All of them were out-patients with no clinical presentation of severe enteroviral infection.

Among total 22 confirmed cases, 55% were tested positive for EV-71 (B5) from stool culture and viral isolation, 27% for coxsackie A16, 9% for coxsackie B5 and 9% for unidentified type of *Enterovirus spp.*

Asymptomatic Infection in School Survey

Family members of the index case had contact with total 244 students from Schools A, B, C and D. All students were screened for HFMD symptoms. Of seven suspected HFMD cases identified (2.9%), four were from School B, with an overall attack rate of 5.9% (4/68), and three were from School C, with an attack rate of 3.8% (3/79). None of seven suspected cases were tested positive for enterovirus or coxsackie virus. Two (28.6%) out of seven cases were males and median age was 5.2, ranged 2-12.3 years old.

Students with asymptomatic infection were identified in all four schools, with EV-71 in School B and coxsackie B5 in Schools C and D. Average proportion of asymptomatic infection among students in these schools was 21.7% (53/244) (Table 1).

Circulating Genotypes of Enterovirus

A total of 287 fresh stool samples and 75 throat swabs were collected for viral isolation and PCR. Out of 287 samples, 82 were tested positive for enterovirus by PCR. EV-71 B5, coxsackie A16 and coxsackie B5 were identified in both districts, with 40.3% in District X and 25.3% in District Y. The circulating genotypes of enterovirus in hospitals, schools and communities were *Enterovirus spp.* (41/82, 50.0%), EV-71 B5 (25/82, 30.5%), coxsackie A16 (10/82, 12.2%) and coxsackie B5 (6/82, 7.3%).

All 50 cases with HFMD manifestations (28 suspected and 22 confirmed) from hospitals, communities and schools had oral ulcer (90%), rash on palm (79%), rash on sole (77%) and fever (67%) while other symptoms (<10%) were chest discomfort, seizure, gastrointestinal symptoms and rash on buttock. We found around 10% of clinical HFMD cases had only oral ulcer. Number of cases by onset date among patients in both hospitals and students of four schools was showed in figure 2.

Environmental Survey in Schools

School activities included learning in classrooms and playing or resting in the afternoon. Although they had lunch without sharing utensils, some shared milk bottles. Few soaps were provided for hand washing in toilets and children did not wash their hands properly. As teachers believed that enterovirus could be decontaminated by alcohol gel, all classrooms were

Table 1. Asymptomatic enterovirus infection in schools of Districts X and Y, Nakhon Ratchasima Province, Thailand, August 2011 (n=244)

School	Number of student			Enterovirus type			
	Total (n=244)	Symptomatic/ suspected (%)	Asymptomatic infection (%)	EV-71 B5	Coxsackie B5	Coxsackie A16	Unidentified genotype
A	34	0	5 (15)	0	0	0	5
B	68	4 (6)	12 (18)	11	0	0	5
C	79	3 (4)	21 (27)	2	1	4	17
D	63	0	15 (24)	0	3	0	12

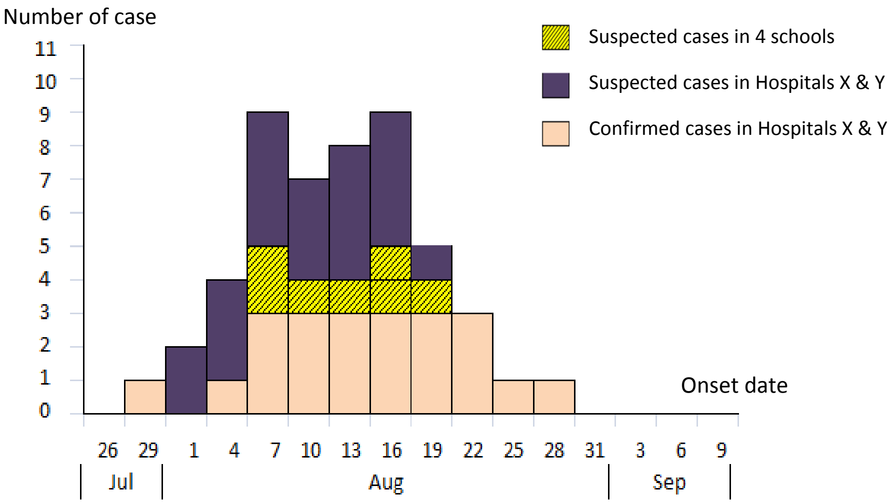

Figure 2. Suspected and confirmed HFMD cases in Districts X and Y, Nakhon Ratchasima Province, Thailand, August 2011 (n=50)

Figure 3. Environmental survey in 4 schools of Districts X and Y, Nakhon Ratchasima Province, Thailand, 2011

provided with alcohol gel instead of soap (Figure 3).

Follow up and Public Health Actions

After 35 days of hospitalization, the index case's clinical condition improved and was discharged from the hospital. One week later, he was in healthy condition with good neurological function.

Public education on mode of transmission of HFMD, case isolation and cleaning practice was provided to schools and affected communities. In addition, soaps were provided to schools and public toilets, and classroom cleaning was also promoted.

Discussion

In Thailand, number of severe HFMD deaths increased from zero in 2010 to six in following year.[13] However, reason for the surge was not clear. Severe and fatal cases of HFMD and encephalitis were probably associated with emerging EV-71 genotype B5 and coxsackie B5 due to numerous outbreaks in communities and schools.[14]

Increasing dynamics circulation of multiple enteroviruses among reported HFMD cases in Nakhon Ratchasima Province during 2011 might be associated with concurrent outbreaks of EV-71 B5, coxsackie A16 and coxsackie B5. Interestingly, the index case of the outbreak was an infant who developed severe encephalitis without HFMD lesions in early August 2011. He had coxsackie B5 viral infection detected by PCR. Coxsackie B5 and EV-71 infections are also frequently associated with irregular cases of neurological diseases and epidemics of encephalitis.[15,16]

There was no evidence of enterovirus circulating in the index case's family as stool culture and isolation of the family members for enterovirus and coxsackie virus revealed negative. Thus, with asymptomatic coxsackie B5 infection identified in Schools C and D, these schools were likely to be sources of the outbreak. From these sources, aerosol droplets might be route of transmission in this case and in the community outbreak which was similar to a previous study.[17]

Stool specimen isolated for *Enterovirus spp.* in human is highly specific for diagnosis of viral infection.[18] In this study, stool specimen testing of students showed high proportion of asymptomatic enterovirus infection from stool culture (17.6%, 26.6%). Asymptomatic persons can also shed virus and transmit the disease in lower rate than symptomatic individuals, thereby creating an invisible 'reservoir' for the virus.[19]

Implication is that containment measures alone may not stop outbreak progression since asymptomatic cases still could be shedding the viruses and creating reservoirs. A better understanding on transmission dynamics is essential in planning to control enterovirus outbreaks.

Although impact on course of epidemic by school-closing strategy was not clear, children and schools are believed to play an important role in spread of the disease. Therefore, closing schools might slow down the propagation of an epidemic. After this investigation, the Ministry of Public Health advised schools with HFMD outbreak to close for one week when two or more cases were detected in the same classroom.

Limitations

Some healthy family members of HFMD cases did not participate in the study or provide stool samples, which might result in overestimation of infection rate if non-participating individuals were healthy. As active case finding of HFMD could not be conducted for the entire two districts, true magnitude of symptomatic HFMD cases was likely to be underestimated, especially the mild cases.

Conclusion

This is an outbreak of HFMD due to EV-71, coxsackie A16 and coxsackie B5 in schools and communities. The index case was confirmed to have encephalitis by coxsackie B5 virus. Asymptomatic infection was found in all four schools associated with the family members of the index case.

Public Health Actions and Recommendations

Small children were at high risk of transmission since they did not understand about personal hygiene. Therefore, teachers should work hard to enhance personal hygiene for children and teachers, including limited sharing of materials and utensils, and hand washing with soap after using toilet, before eating, before preparing food and after changing diapers.

Schools were recommended to close for one week if two or more HFMD cases were found in the same classroom in order to reduce transmission. In addition, when the school reopened, screening of students for oral ulcer and rash on palms and soles, and isolating of suspected students at home should be emphasized.

A proportion of suspected and confirmed cases had only oral ulcer. These cases were not reported in current notifiable disease surveillance system of Thailand which only reported cases that fulfilled the definition of HFMD. Therefore, herpangina was subsequently added into the list of reported diseases in notifiable disease surveillance system of Thailand.

Health care workers should be aware of linkage between encephalitis and HFMD, and explore etiology and source of infection. Protocol for cases management of severe HFMD must be available in hospitals. Children with HFMD should be attended by a pediatrician and considered for IVIG treatment to reduce severity.[20,21]

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