Journal of

Volume 10, Issue 2
June 2017

Outbreak, Surveillance & Investigation Reports

OSIR

ACCESS ONLINE QR CODE

www.osirjournal.net

Outbreak, Surveillance and Investigation Reports

eISSN: 2286-8933

Outbreak, Surveillance and Investigation Reports (OSIR) Journal

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Outbreak, Surveillance and Investigation Reports

Volume 10, Issue 2, June 2017

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A Large Common Source Outbreak of *Salmonella typhimurium* Linked to Kuala Terengganu Night Markets, Malaysia, 2014

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Abstract

On 1 Mar 2014, the Terengganu District Health Office was notified of ten patients presented with acute gastroenteritis at Sultanah Nur Zahirah Hospital. Their illness was linked to consumption of foods from two night markets. An outbreak investigation was initiated to determine the source of the outbreak. Case finding was conducted in the hospital, and community. Patients were interviewed about demographics, symptoms and food consumption history. Stool samples from patients and food handlers as well as food and environmental samples were collected for laboratory analysis. Suspected food premises were inspected. A case-control study was conducted. Of 169 cases, 68.6% and 32.5% ate food from night markets A and B respectively while 1.2% ate food from both night markets. Major symptom was diarrhea (98.2%). There was one death from hypovolemic shock. *Salmonella typhimurium* was isolated from 13 patients and one food handler. All isolates showed genetic similarity by pulsed-field gel electrophoresis. The food handler tested to have the infection served the white fried rice sold in both night markets. Cases were 14 (95% CI = 4.05-46.61) and nine (95% CI = 3.36-24.3) times more likely to have consumed white fried rice from night markets A & B respectively. The source of infection was likely to be white fried rice that was prepared at the same place, contaminated by an infected food handler and sold at both night markets.

Keywords: Food poisoning, *Salmonella typhimurium*, night market, food handler

Introduction

Night markets have been around for decades in Malaysia. They are called 'Pasar Malam' and are popular places for social gatherings. Makeshift stalls selling local products and foods are the main attractions at these sites.

The Local Authority in Kuala Terengganu District, Terengganu State, designates and licenses the locations of night markets. There are 22 designated locations and three to five locations are opened from 6 to 10 pm every day. Each location consists of 100 to 200 food stalls. The designated stall is usually an empty space of about nine square meters without basic infrastructure and amenities such as water supply, electricity, washing, and drainage facilities.

Food stall operators move daily to different locations following a weekly schedule. In the makeshift stalls, the operators sell cooked or partially cooked foods prepared from home or at the shops. Most vendors prepare food items at home in the morning and bring it to the night market in the evening.

Major foodborne outbreaks were observed to be associated with markets.[1] Hazards related to markets are common due to biological cross-contamination, polluted water, inadequate preservation and storage, and poor environmental sanitation.[2]

At 19:00 on 1 Mar 2014, the Emergency Department in Sultanah Nur Zahirah (SNZ) Hospital notified the Kuala Terengganu District Health Office of 10 cases of suspected food poisoning. A rapid assessment team was assembled to verify and assess the extent of the

outbreak, identify the causative agent and source, make relevant recommendations, and institute appropriate control measures.

Methods

We interviewed the hospitalized and out-patient cases, and reviewed their medical records in SNZ Hospital. We searched for additional cases among out-patients attendance in health clinics and SNZ hospital, family members and friends of the acute gastroenteritis (AGE) cases who had history of consumed foods from Night Markets A (NMA) and B (NMB). Information was obtained on demographic details, date and time of onset of symptoms, and foods consumed, including the source of foods.

Case-control Study

We conducted a case-control study to identify the potential vehicle of the outbreak. We defined a case as a person who developed one or more of the following signs or symptoms: diarrhea, abdominal pain, vomiting, fever, nausea, or dizziness after consuming foods from NMA or NMB on 28 Feb to 1 Mar 2014. Controls were family members and friends of cases and other vendors who consumed foods bought from NMA or NMB, yet did not develop symptoms of AGE. Logistic regression was used to calculate crude odds ratios.

Stool samples were sent for enteropathogenic bacterial culture at the laboratory in SNZ Hospital, and serotyping and pulsed-field gel electrophoresis (PFGE) at Institute of Medical Research in Kuala Lumpur. No clinical samples were collected from controls.

Environmental Investigations

Food premises in NMA and NMB were inspected using a standard format for restaurants and food stalls issued by the Ministry of Health which covers food processing and storage, personal hygiene of food handlers, quality of cooking utensils, water supply and drainage system, solid waste disposal, and kitchen infrastructure. Food handlers were interviewed regarding food preparation and cooking methods of the suspected foods. Left-over raw food materials and ingredients from the kitchen and, environmental swabs from working surface and utensils were also taken.

We traced back the supply chain for chicken, eggs and vegetables. Food and environmental samples were taken from these premises and sent to the Terengganu State Health Department Food Laboratory for bacteriological testing.

Results

Descriptive Findings

Total 169 cases fulfilled the clinical case definition, including 116 (68.6%) had history of consuming food from NMA and 55 (32.5%) from NMB, with two (1.2%) cases consuming food from both night markets. No significant difference was observed in the demographic profiles of those who consumed foods at NMA and NMB (Table 1).

Table 1. Characteristics of acute gastroenteritis cases from two night markets in Kuala Terengganu District, Terengganu State, Malaysia, 28 Feb to 1 Mar 2014

	Night Market A (%) (n = 116)	Night Market B (%) (n = 55)
Mean age ± SD	22.80 ± 12.13	19.70±12.13
Age group		
Adult	92 (79.3)	39 (70.9)
Child	24 (20.7)	16 (29.1)
Gender		
Male	55 (47.4)	26 (47.3)
Female	61 (52.6)	29 (52.7)
District		
Kuala Terengganu	97 (83.6)	49 (89.1)
Marang	13 (11.2)	4 (7.3)
Hulu Terengganu	4 (3.4)	0
Setiu	2 (1.7)	1 (1.8)
Treatment Status		(n=53)
In-patient	65 (56.0)	43 (81.1)
Out-patient	34 (29.3)	7 (13.2)
No treatment	17 (14.7)	3 (5.7)
Outcome		
Alive	116 (100.0)	54 (98.2)
Died	0	1 (1.8)

Major presenting symptoms were diarrhea (98.2%), followed by abdominal pain (91.8%), vomiting (78.4%), fever (63.7%), dizziness (49.7%), and nausea (46.2%).

The epidemic curve contained two peaks: the first peak consisted of cases with a history of eating food from NMA and the second peak with cases in NMB. Median incubation period of cases consumed food from NMA and NMB was 9.5 hours and 11 hours respectively (Figure 1).

About 63% of 169 cases were hospitalized (60% from NMA, 40% from NMB). One death was reported, the cause of death was hypovolemic shock secondary to severe dehydration (0.6% case fatality rate).

Laboratory Results

Total 118 stool samples collected were from 107 cases

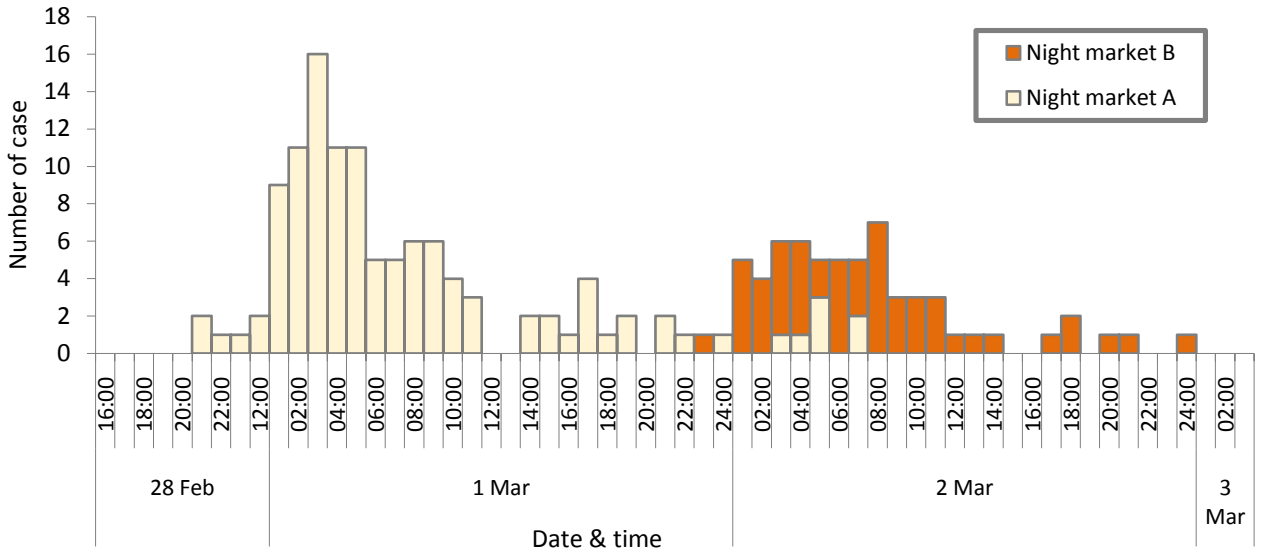

Figure 1. Date and time of onset of acute gastroenteritis cases from two night markets in Kuala Terengganu District, Terengganu State, Malaysia, 28 Feb to 1 Mar 2014

and 11 asymptomatic food handlers, and 100% were cultured. Among them, 53 (49.5%) out of 107 cases and two (18%) out of 11 food handlers were cultured positive for *Salmonella*. Of 55 isolates tested positive, 24 were sent for subtyping and PFGE, and *S. typhimurium* was detected in 15 (63%), including 13 cases and two food handlers. Fourteen isolates showed fingerprint similarity: 13 from cases (including the fatal case) and a food handler who prepared white fried rice at both night markets (Figure 2).

Case-control Study

The data were stratified by night markets where the case bought the food items. Total 168 subjects (116 cases and 52 controls) consumed food from NMA,

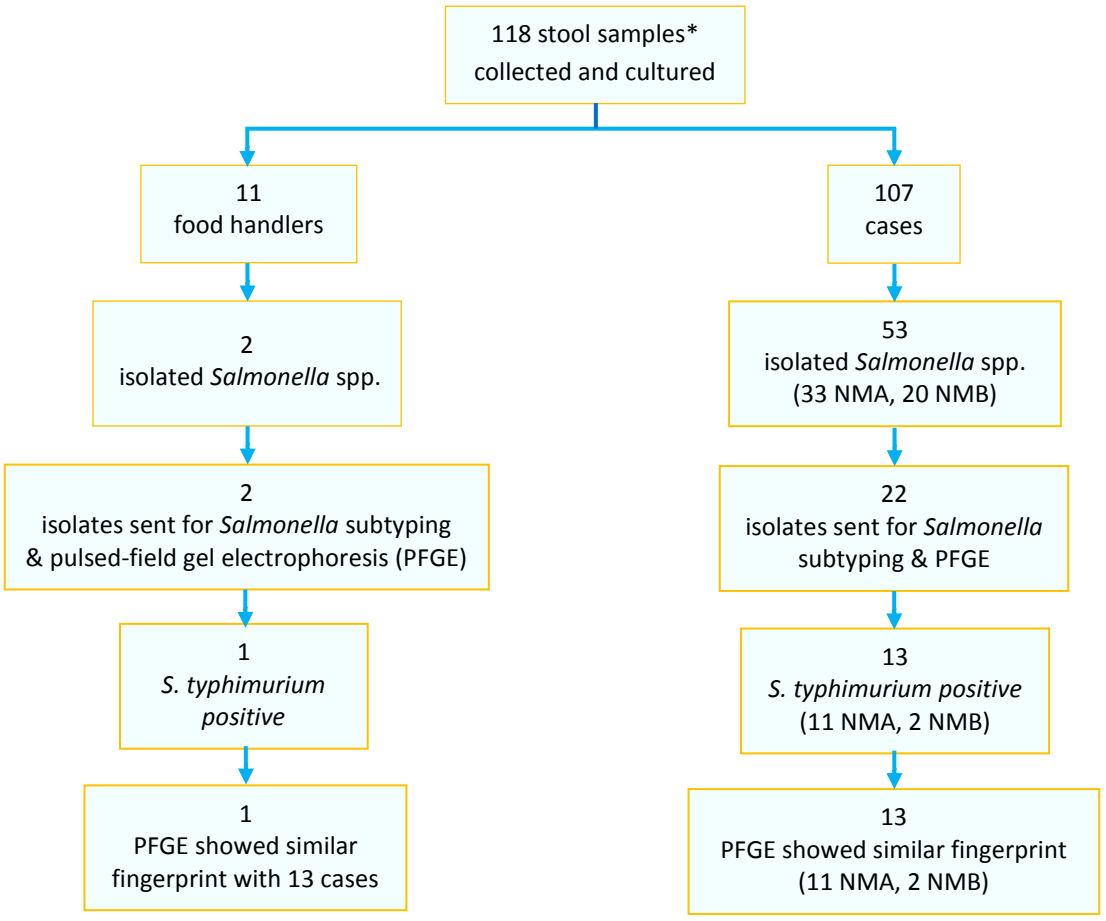

Figure 2. Laboratory investigation and results of acute gastroenteritis cases from two night markets in Kuala Terengganu District, Terengganu State, Malaysia, 28 Feb to 1 Mar 2014

while 131 subjects (55 cases, 76 controls) consumed food from NMB. As there were two cases consumed food from both night markets, the number of cases were accounted based on each night market.

Cases were 14 (95% CI = 4.05-46.61) and nine (95% CI = 3.36-24.3) times more likely to have consumed white fried rice from NMA and NMB respectively (Tables 2 and 3).

Environmental Investigation

The foods were prepared at a shop, and cooked and readily sold at a food stall named FS1 Kitchen in both night markets. Food premise inspection at the preparation shop scored 44.8% which was lower than acceptable score of more than 70%. Violation of food hygiene standard was identified at processing of raw materials, and storage of mixed raw materials and cooked food items (Figure 3). Temperature of the chiller was 16˚C while the standard should be less than 8˚C. No enteropathogenic bacterial isolated from 26 food and environmental samples taken from the kitchen. However, high count of coliform was detected.

The main ingredients of white fried rice sold at the FS1 kitchen were rice and chicken. Hazard analysis and critical control point (HACCP)[3] showed two main violation points. Chicken was prepared unhygienically. The half-cooked chicken were cut into small pieces, kept in a plastic container, mixed with gravy consisting of sugar, monosodium glutamate and salt, and left in the ambient temperature for two hours. The chicken was fried with rice at the night markets. The ready-to-eat white fried rice was displayed in an opened big casserole for at least 4-8 hours at room temperature (Figure 4).

Out of 24 food samples taken from chicken, eggs and mixed vegetables, *Salmonella corvalli* were detected in fresh and semi-frozen chickens from the cool box.

Discussion

The epidemic curve showed the outbreak occurred first at NMA and subsequently followed by another outbreak at NMB. Both showed similar point source pattern, with an interval of 1-day lag suggesting a common exposure. Those who consumed white fried rice sold at the FS1 kitchen in both NMA and NMB were found to have higher risk of getting ill.

The infecting agent was *S. typhimurium* and the cases had symptoms compatible to infection by *S. typhimurium*[4]. The source of the outbreak was the food handler from the FS1 kitchen who could have contaminated the white fried rice during food preparation. Isolation of *S. typhimurium* and the similar fingerprint pattern from cases and food handlers showed an epidemiological link between the cases and the food handler.

S. typhimurium is reported as one of the most common serotypes infecting humans.[5] Our findings were consistent with a large outbreak reported in Sydney in year 2011 which involved 154 cases positive for *S. typhimurium*, and was linked to consuming chicken salad roll at a restaurant.[6]

Table 2. Results of a case-control study from people who consumed food at Night Market A in Kuala Terengganu District, Terengganu State, Malaysia, 28 Feb to 1 Mar 2014 (n=116)

	Ate		Did not ate		Odds Ratio	95% CI
	Case	Control	Case	Control		
White Fried Rice	53	3	63	49	13.74	4.05-46.61
Red Fried Rice	30	8	86	44	1.92	0.81-4.54
Fried Mee	15	24	101	28	0.17	0.08-0.37
Fried Keow Teow	23	15	93	37	0.61	0.29-1.30

Nagelkerke R^2 = 0.405, Hosmer and Lemeshow Test = 0.967

Table 3. Results of a case-control study from people who consumed food at Night Market B in Kuala Terengganu District, Terengganu State, Malaysia, 28 Feb to 1 Mar 2014 (n=55)

	Ate		Did not ate		Odds Ratio	95% CI
	Case	Control	Case	Control		
White Fried Rice	24	6	31	70	9.03	3.36-24.3
Red Fried Rice	22	8	33	68	5.67	2.28-14.07
Fried Mee	9	30	46	46	0.30	0.13-0.70
Fried Keow Teow	4	17	51	59	0.27	0.09-0.86

Nagelkerke R^2 = 0.471, Hosmer and Lemeshow Test = 0.994

(a) Improper storage of the utensils

(b, c) Improper storage of raw foods in the refrigerator and temperature tested to be higher than the acceptable standard

(d) Chili paste container not sealed materials and utensils

(e) Dirty kitchen floor

(f) Water in the buckets for washing of raw and kept at room temperature

Figure 3. Photos of food preparation shop for selling food at two night markets in Kuala Terengganu District, Terengganu State, Malaysia, March 2014

Figure 4. Ready-to-eat fried noodle and rice (left) from the FS1 Kitchen at two night markets (middle and right) in Kuala Terengganu District, Terengganu State, Malaysia, March 2014

Salmonellosis outcomes differ substantially by serotypes. A study on invasive disease, *S. typhimurium* was significantly less invasive, compared to *S. enteritidis*, Heidelberg, Choleraesuis, and Dublin.[7] Case fatality rate in this outbreak was 0.6% which was consistent for non-typhoidal *Salmonella* infection reported elsewhere as less than 1%.[7] Although we detected *S. corvalli* from environmental samples, the serotype had been less frequently reported in humans, compared to the environment. In addition, this serotype was not discovered from human cases in this outbreak.

Ready-to-eat foods are commonly sold in the food markets of the developing countries as it is accessible and affordable for people in the community as well as tourists discovering the local food culture.[2] Raw vegetables and ready-to-eat foods pose higher risk for bacterial contamination such as *Staphylococcus*[8], *Salmonella*[8,9], *Campylobacter*[9], norovirus, and hepatitis A and E[10]. Hence, according to the World Health Organization, multidisciplinary approach in microbiology, food science, health promotion and sanitation management are essential to provide safe and nutritious foods in the markets.[2]

Multi-drug resistant *S. typhimurium* (phage type DT104) isolates had been reported from several countries.[11] However, in this outbreak, information on antibiotic treatment was not available, and phage typing and antibiotic sensitivity test specifically for these strains were not performed.

Although the interviews were conducted within one week of event, the information obtained from

personal interviews could not be verified and the food handlers' food handling practices were not observed. However, the environmental investigation supported the epidemiological findings. There was poor food handling practices in the kitchen as well as in the night market that might have allowed cross contamination. The stool samples from asymptomatic food handlers on duty during the event were positive for *S. typhimurium*, suggesting that contamination could have happened during the preparation of white fried rice.

Another limitation was no samples taken from controls. If there were asymptomatic cases among controls, the odds ratio would be underestimated.

Action Taken and Recommendations

The FS1 kitchen was immediately closed for two weeks under the Ministry of Health Communicable Disease Act of 1988[12]. The two food handlers with *Salmonella* were barred from handling the foods until all three consecutive stool cultures were tested negative for *Salmonella* spp. The food premise operator was recommended to improve the cooking facilities, including fixing tile flooring for easy maintenance and storage of dried raw materials and utensils. Top loading refrigerator for raw materials and chiller for cooked foods were suggested. Food handlers were advised and educated in the hygienic preparation and serving of foods.

Reassessment of the kitchen was done after two weeks, and showed an improvement and its score increase to 83% (Figure 5). In total 18 night markets visited, 776 food premises were inspected of which 477 (61.5%) were scored grade A and 77 (19.9%) grade B. Grade A was given to food premise with the scoring of 80% and more, and grade B was 60 to 79% score. There was no proper documents on health examination and immunization card in 222 food premises (28.2%), and were compounded by the Local Authority.

Health education pamphlets on food safety, prevention of poisoning and how to choose safer food from night market were distributed to food handlers and public at night markets. A radio talk session was given via local radio station aimed to increase consumers' awareness on the food safety issues particularly ready to eat foods from night markets.

Health clinics in neighboring districts: Marang, Setiu and Hulu Terengganu were alerted on the second day of the outbreak. They were required to notify any acute gastroenteritis case related to consumption of foods from NMA and NMB.

Figure 5. Improved situation after 2 weeks of closure of the food preparation shop for selling food at two night markets in Kuala Terengganu District, Terengganu State, Malaysia, March 2014

The findings of this outbreak were presented to the Food Safety and Quality Unit Terengganu State Health Department and the following recommendations were suggested: strengthen the monitoring of night market food premises including home kitchens where the foods are prepared, institute effective health promotion and education strategies for night market food handlers and consumers, strengthen the enforcement of food safety law related to night markets, advocate local authority to enforce food premise licensing, and improve night markets infrastructures such as provision of safe water supply, and standard mobile stalls.

Conclusions

This is a common source outbreak caused by *S. typhimurium* with case fatality rate of 0.6%. The most probable source of infection was the asymptomatic food handler who may have contaminated the white fried rice during food preparation. Possible contributing factors were unhygienic food handlers and food handling practices,

and poor sanitation and substandard kitchen infrastructure. The outbreak was controlled first by removing the source (infected food handler), educating to food vendors and consumers, and prompt outbreak management with multi-departments' involvement.

Suggested Citation

Ab Karim B, Latip AL, Abd Shukor AS, A Rashid N, Wan Mohd WM, Kamaludin F. A large common source outbreak of *Salmonella typhimurium* linked to Kuala Terengganu night markets, Malaysia, 2014. OSIR. 2017 Jun;10(2):1-7.

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Clinical Profile and Circulating Dengue Virus Serotype among Adults Admitted to Yangon General Hospital during the 2015 Dengue Outbreak

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Abstract

During the 2015 dengue season in Myanmar, there was an unusual increase in occurrence of adult dengue cases. To identify circulating serotypes and clinical profiles of adult dengue during the outbreak, blood samples were collected from clinically suspected dengue patients admitted to Yangon General Hospital during July to September 2015. Among 75 samples tested for NS1Ag and immunoglobulins IgG/IgM, 33 (44.0%) were serologically confirmed, including 11 (33.3%) primary and 22 (66.7%) secondary infection. The mean age was 20.8 years (range 13-49 years). There were 77.3% (17/22) of secondary infection and 45.5% (5/11) of primary infection developed into severe types of dengue infection. Bleeding manifestations occurred in 13 (39.4%) patients, with gastrointestinal bleeding as the most common form. Out of the 33 samples serologically confirmed, dengue virus was detected in six (18.2%) and all were serotype 1 which has been the predominant serotype in Myanmar since 2009. These findings contributed information on the recent adult dengue outbreak and aided to bridge the knowledge gap concerning adult dengue in Myanmar. Further molecular research should be conducted on serotype negative samples.

Keywords: dengue outbreak, adult dengue, dengue virus serotypes, Myanmar

Introduction

Dengue is the most important arthropod-borne viral disease of public health significance.[1] In 2012, approximately 390 million dengue infections occurred annually worldwide and about four billion people which was 55% of the world's population were living in 128 dengue endemic countries.[2] Among dengue infections around the world, nearly two million cases developed into severe dengue hemorrhagic fever (DHF), resulting in 21,000 deaths.[3]

Although dengue is typically acknowledged to be a childhood disease, there is evidence of a changing epidemiology of the disease among older age groups.[4] An increasing occurrence of adult dengue infections have been reported from Latin America since the early 1980s and also from Asian countries such as Singapore, Indonesia, Bangladesh and Sri Lanka.[5-8]

Myanmar is a dengue endemic country as well and epidemic peaks occur every 2-3 years. During 2009-2015, the number of reported dengue cases increased from 24,285 to 42,913, an increase of 77% over six years. The most common affected age group was 5-9 years (50-60%), and serotypes 2 and 3 were found to be more associated with severe dengue.[8-9] As most studies on dengue in Myanmar have focused on children, epidemiological and serotype data concerning adult dengue is relatively rare.[10] A few studies reported an increase in the number of adult dengue infections in 1994, 2007 and 2009, most presenting with bleeding manifestations.[11-12]

In July 2015, the admission number of adult dengue cases in Yangon General Hospital was increased when compared to the data from previous months. Identification of the dengue serotypes that caused this outbreak is important and would help to fill the knowledge gap on adult dengue epidemiology. This study was, therefore, conducted, aiming to describe the clinical profile of adults diagnosed with dengue during the 2015 outbreak and identify the circulating dengue serotypes.

Methods

Study Setting

A cross-sectional descriptive study was carried out at Yangon General Hospital.

Selection Criteria

We recruited all patients aged more than 12 years and admitted with any of clinical diagnoses of dengue, namely dengue fever (DF), DHF and dengue shock syndrome (DSS). Patients who were admitted to intensive care unit with severe shock or had fever lasting for more than five days were excluded.

Case Definition

In hospital settings, the dengue case definition of World Health Organization in 1997 was applied for clinical diagnosis and for grading the severity of dengue[13].

Probable dengue was defined as an acute febrile illness with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations and leucopenia. A DF case was a probable case confirmed with supportive serology. A DHF case was defined if the following signs or symptoms were clinically observed: high fever of acute onset, and hemorrhagic manifestations with at least positive tourniquet test and hepatomegaly; plus one of the following laboratory findings: thrombocytopenia (≤100,000 cells per mm^3) or hemoconcentration (hematocrit >45%).

In addition, DHF was classified into four grades, depending on clinical presentation and severity. DHF Grade I included those with fever accompanied by non-specific constitutional symptoms, positive tourniquet test and/or easy bruising. In Grade II, there was spontaneous bleeding usually in the forms of skin or other hemorrhages. Grade III patients were those exhibited circulatory failure (rapid and weak pulse, and narrowing of pulse pressure <20mmHg), or hypotension (presence of cold and clammy skin, and restlessness). Grade IV was deemed when profound shock occurred with undetectable blood pressure or pulse. Grade III and IV were considered to be DSS.[13]

Sample Collection and Serological Confirmation

Approximately 3 ml of blood was collected from each patient under aseptic conditions on the first day of admission after proper history taking and clinical examination. Blood collection was carried out between Monday and Friday. The blood samples were labeled and transported to the Virology Research Division, Department of Medical Research, Ministry of Health and Sports, Myanmar. The sera were tested by standard diagnostics BIOLINE Dengue Duo NS1 Ag and IgG/IgM test kit (SD, Korea) on the same day of blood collection. The presence of immunoglobulin M (IgM) line was regarded as primary dengue infection while observation of either immunoglobulin G (IgG) line alone or both IgM and IgG lines were regarded as secondary infection. The positive samples were stored at -20°C until serotype identification was done.

Serotyping

RNA was extracted from the seropositive samples using QIAamp viral RNA extraction columns (Qiagen) as per manufacturer's instruction. The extracted RNA was transcribed to cDNA which was used for reverse transcription polymerase chain reaction (RT-PCR) with sense primer Seah DV1 and anti-sense primer (DSP1, DSP2, DSP3 and DSP4). PCR products were then checked for specific target by gel electrophoresis.[14]

Ethical Issue

Written informed consent was obtained from each study participant. The study was approved by the Ethics Review Committee, Department of Medical Research.

Data Analysis

For descriptive analyses, frequencies and percentages were used for categorical variables, and means and standard deviations for continuous variables. Chi-square tests were used to determine statistically significant differences between groups and p-value of less than 0.05 was considered as significant.

Results

The clinically suspected dengue cases admitted to Yangon General Hospital mostly in July and August 2015 (Figure 1). A total of 75 suspected dengue patients (30 in July, 30 in August and 15 in September) were enrolled in the study. Among the participants, 33 (44.0%) were serologically confirmed to have dengue infection, including one (3.0%) DF case and 32 (97.0%) DHF cases.

Of 33 confirmed cases, there were 11 (33.3%) primary and 22 (66.7%) secondary dengue infections. The mean age was 20.8 years (standard deviation 7.6 years, range 13-49 years). Majority (85.0%) of the cases are 15-24 years old (Figure 2). There were 23 males and 10 females, with a male to female ratio of 2.3:1.

All cases presented with fever; 11 (33%) and 22 (67%) cases were admitted on onset days 1-3 and days 4-5 of fever respectively. Most common presentations were tourniquet test positive (84.8%) and headache (60.6%).

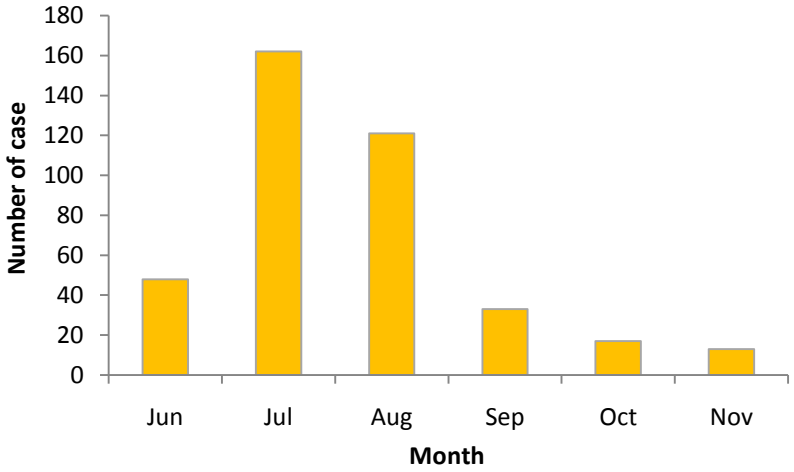


Figure 1. Clinically diagnosed dengue cases admitted to Yangon General Hospital, Myanmar, June to November 2015

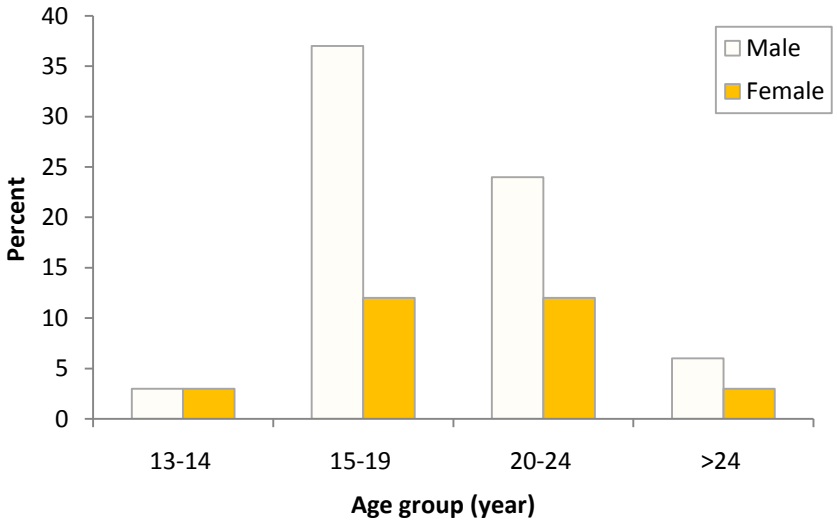


Figure 2. Age and gender distribution of adult dengue cases admitted to Yangon General Hospital, Myanmar, July to September 2015 (n=33)

Bleeding manifestations in one or more forms occurred in 13 (39.4%) patients. Thrombocytopenia (platelet count <100,000/mm3) was found in 24 (72.7%) and mean platelet count was $61x10^9$/l. Regarding to platelet counts, 13 (54%) were 50-$100x10^9$/l, 10 (42%) were 20-$50x10^9$/l, and one (4%) was less than $20x10^9$/l. Hemoconcentration was present in 15 (45.5%) patients. Among 13 DHF cases that presented with bleeding manifestations, there were thrombocytopenia in nine (69.2%) and hemoconcentration in seven (53.8%) patients.

Out of 11 primary dengue infections, 1 (9.1%) developed into DF 5 (45.5%) while five (45.5%) each were progressed to DHF I and DHF II (Figure 3). About 77.3% (17/22) of secondary infection and 45.5% (5/11) of primary infection developed into severe dengue. There was no significant association between severity of dengue infection and type of infection (primary or secondary).

Table 1. Clinical manifestation and laboratory results of serologically confirmed adult dengue cases in Yangon General Hospital, Myanmar, July to September 2015 (n=33)

Clinical manifestation	Number (%)
Fever	33 (100)
Tourniquet test positive	28 (84.8)
Headache	20 (60.6)
Vomiting	12 (36.4)
Skin rash	11 (33.3)
Drowsiness	10 (30.3)
Muscle and joint pain	9 (27.3)
Abdominal pain	8 (24.2)
Hematamesis	8 (24.2)
Melena	6 (18.2)
Epistaxis	4 (12.1)
Bleeding gum	2 (6.1)
Hemoptysis	1 (3.0)
Hepatomegaly	12 (36.4)
Platelet count <100,000/mm^3	24 (72.7)
Hematocrit >45%	15 (45.5)

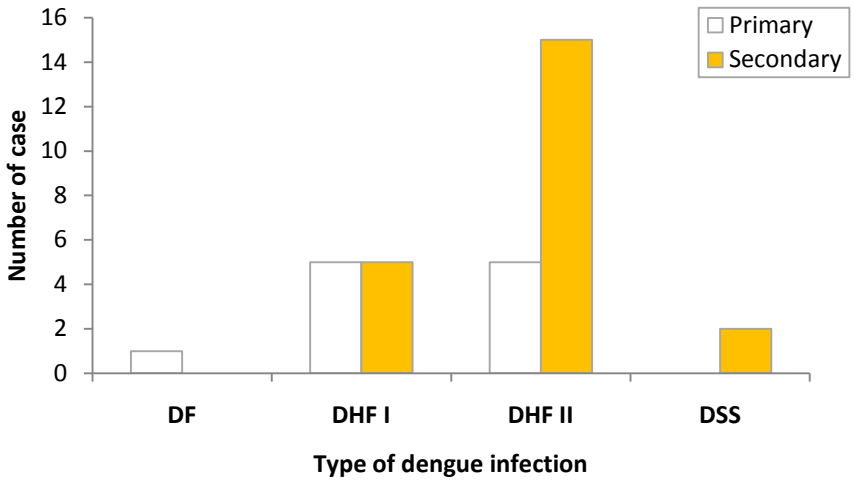
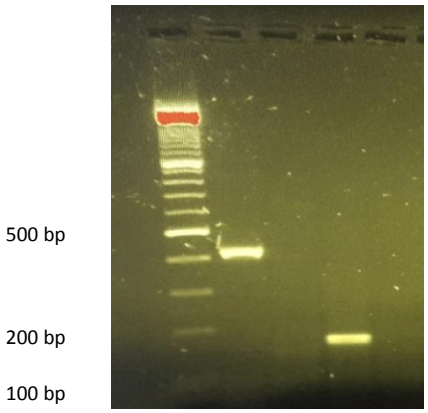


Figure 3. Distribution of primary and secondary dengue infections among dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) cases in Yangon General Hospital, Myanmar, July to September 2015 (n=33)

Among 33 samples analyzed for dengue serotype by RT-PCR, dengue antigen was detected in six (18.2%) samples and all were of serotype 1 (DENV 1) (Figure 4). The characteristics of PCR positive cases are shown in Table (2).

Discussion

The year 2015 was characterized by large dengue outbreaks worldwide with 3.2 million reported cases globally.[15] According to reports from the Vector Borne Disease Control Programme, Ministry of Health and Sports, Myanmar, the number of reported dengue cases more than doubled from 20,255 cases in 2013 to 42,913 cases in 2015 while the affected rate among those aged more than 15 years increased from 2.5% to 5.0%. In Yangon General Hospital, total 392 suspected dengue cases were admitted during June to November 2015, with peaks in July and August, the period of the rainy season and the months when dengue is known to be in highest transmission.[11]



Lane 1 100 bp DNA ladder
Lane 2 Positive control (DENV4 - 426 bp)
Lane 3 Sample (Serotype not detected)
Lane 4 Sample (DENV1 - 169 bp)
Lane 5 Negative control

Figure 4. Gel image of polymerase chain reaction products, showing DENV 1 among adult dengue cases admitted to Yangon General Hospital, Myanmar, July to September 2015

Table 2. Information of adult dengue cases admitted to Yangon General Hospital, Myanmar, July to September 2015

ID	Age (year)	Gender	Diagnosis	Type of infection	Serotype	Hemorrhagic manifestation		Platelet count (per mm^3)	Hematocrit (%)/ Evidence of plasma leakage
						Tourniquet test	Symptom		
AD 1	18	M	DHF I	Primary	DENV 1	Positive	-	78,000	53.3%
AD 2	16	M	DHF I	Primary	DENV 1	Positive	-	87,000	41.7% Hepatomegaly
AD 4	18	F	DHF II	Secondary	DENV 1	Positive	Hematamesis	98,000	44% Hepatomegaly
AD 5	14	F	DHF II	Primary	DENV 1	Positive	Epistaxis, melena	64,000	39.2%
AD 6	15	F	DHF II	Primary	DENV 1	Positive	Hematamesis	100,000	43%
AD 20	24	M	DF	Primary	DENV 1	Negative	-	171,000	43.2%

Based on serology, secondary infections accounted for nearly two-thirds of all cases. In dengue endemic countries like Myanmar where all four dengue serotypes are co-circulating and the vector *Aedes aegypti* are abundant year round, most of the population might have been infected at least once by a dengue virus in their childhood. A higher proportion of secondary dengue infection in adults had also been reported from other dengue endemic countries such as Thailand and Sri Lanka.[8,16]

In this study, the age of confirmed dengue cases ranged from 13-49 years and the majority (85%) was in 15-24 year age group. However, another study from Yangon General Hospital between 2000 and 2008[12] and one from Pyin Oo Lwin in 2009[17] revealed lower attack rates in 15-24 year age group. Therefore, this study indicated that an increasing number of dengue infection occurred in economically productive young adults, a fact that might have significant adverse financial effects on the community. A previous study from 12 countries in Southeast Asia, using available data from 2001-2010, showed an aggregate annual economic burden of dengue reaching USD 950 million among the studied nations, with approximately 52% of these costs coming from productivity loss.[18]

Fever, headache, vomiting and skin rash were the most common presentations found in this study with hematamesis (24.2%) and melena (18.2%). Similarly, the study from Pyin Oo Lwin revealed that fever and vomiting were the most common clinical presentations in adults while hematamesis and melena was found in 33% and 41% of patients respectively.[12] Therefore, physicians should be aware that gastrointestinal bleeding may be a common hemorrhagic manifestation in adults diagnosed with dengue. Thrombocytopenia is not an uncommon presentation among adults hospitalized with dengue infection. Our thrombocytopenia of 72.7% was comparable to a study in Sri Lanka which reported a rate of 79%.[8]

Evidence of an association between sequential dengue infection and increased risk of more serious disease has long been reported.[19] In this study, 77.3% of secondary infection developed severe dengue types of infection, DHF II and DSS, while only 45.5% of severe dengue was observed among primary infection. Moreover, 97.0% of cases in this study were DHF and all DSS cases were also secondary infection.

DENV-1 has been the predominant serotype in Myanmar since 2009 although the other serotypes have been identified,[20] which was also predominant during recent years in other countries such as Thailand, Nepal and Singapore.[21-23] Intensive virological surveillance should be continued to detect changes of serotypes.

Limitations

The findings of this study might not be fully representative of the current adult dengue outbreak due to small number of cases enrolled. Analysis of the association between severity and serotype was not possible as only six samples were identified as being DENV-1. Additional molecular analysis of PCR negative samples was recommended to ensure that these were truly negative as different primer sequences and thermal cycling conditions or further nucleotide sequencing methods could detect similar nucleotide sequence of the target virus.

Acknowledgements

We would like to thank Director General and Board of Directors from the Department of Medical Research for their permission to conduct this study. We also appreciate the Medical Superintendent and staff of Yangon General Hospital for their kind permission to review the data and recruit the patients, and Dr. John Aaskov from the Queensland University of Technology for providing dengue PCR primers.

Suggested Citation

Myat TW, Thu HM, Win HM, Than KS, Tun ZT, Aye KM, et al. Clinical profile and circulating dengue virus serotype among adults admitted to Yangon General Hospital during the 2015 dengue outbreak. OSIR. 2017 Jun;10(2):8-13.

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Identification of a Tuberculosis Cluster through Epidemiological and Geographical Tracing of a Patient with Multidrug-resistant Tuberculosis in Lopburi Province, Thailand, 2014

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Abstract

In May 2014, a suspected multidrug-resistant tuberculosis (MDR-TB) outbreak in Lopburi Province was investigated following the national guidelines for tuberculosis (TB) outbreak investigation and assessed the quality of patient care based on the International Standards for TB Care. The case finding focused on TB cases diagnosed during December 2012 to August 2014. Medical charts were reviewed at Khok Samrong Hospital and contacts of a MDR-TB case who was lost to follow up were traced back. Study findings found an epidemiologically linked cluster of TB cases with five geographically related cases and four cases were from the same family. Factors that might have contributed to this TB outbreak were identified as well, including delay in diagnosis and sub-standard care, low socioeconomic status, delay in conducting contact tracing, and an ineffective TB database system. Diagnosis, treatment and prevention activities should be improved to prevent further TB outbreaks in the communities.

Keywords: tuberculosis, multidrug-resistant, contact tracing, quality of care, Thailand

Introduction

Tuberculosis (TB) is an airborne infectious disease that can be transmitted by the bacterium *Mycobacterium tuberculosis*.[1] In 2015, Thailand was ranked in the top 22 high TB burden countries.[2] Multidrug-resistant TB (MDR-TB) is caused by a TB bacterium that is resistant to at least isoniazid and rifampicin, the two most potent first-line drugs for TB infection.[3] According to the information from Supranational Reference Laboratory in Thailand, MDR-TB was found among 2.0% of new cases and 18.8% of previously treated cases in 2012.[4]

During 2005, among immigrants in the United States, four MDR-TB cases who were Hmong refugees migrated from a refugee camp in Lopburi Province of Thailand were identified. Tracing back and screening of 15,455 refugees in the camp resulted in 272 TB cases; of which, 24 (42.1%) out of 57 samples were MDR-TB.[5] Following another MDR-TB outbreak in 2010 which affected 15 cases in a community from the western part of Thailand[6], the first national guideline for investigation of TB outbreaks was developed. The guideline recommends performing an investigation when there are at least two TB patients who share the same place or activity during a 3-month period; or at least one new or relapse MDR-TB case; or at least one extensively drug-resistant TB (XDR-TB) case in the community.[7] The guideline also suggests five steps for completing an investigation of a TB outbreak: first, perform a case review for diagnosis and outbreak verification; second, identify source and/or contact cases, and collect laboratory and environmental samples; third, conduct a descriptive

study of the outbreak; fourth, test the hypothesis for mode of transmission, source of infection and determine risk factors; and fifth, recommend specific control and prevention measures. At the national level, the Bureau of Tuberculosis and the Field Epidemiology Training Program in the Bureau of Epidemiology follow the guideline in respond to TB outbreaks. However, at the provincial and district levels, this guideline was not widely used or followed in a systematic way.

In May 2014, a MDR-TB patient from Khok Samrong Hospital in Lopburi Province had been lost to follow up for a year and currently, one of his family members and a neighbor were found to have TB. Hence, a joint investigation team from Bureau of Tuberculosis, Bureau of Epidemiology, Thailand MOPH - US CDC Collaboration, Office of Disease Prevention and Control for Region 4, Lopburi Provincial Health Office, Khok Samrong Hospital, and Dong Marum Health Promoting Hospital initiated an investigation to verify a possible MDR-TB outbreak following the national guideline on TB outbreak investigation and assess the quality of patient care based on the International Standards for TB Care (ISTC)[8].

Methods

After notification of the MDR-TB patient in May 2014, information was reviewed and consulted between the local health personnel and the central teams. A descriptive epidemiological study was conducted on 28-29 Aug 2014. Diagnosis of the notified patient (Patient B) was confirmed to be MDR-TB by drug susceptibility result at the TB clinic in Phuket Province. An investigation was carried out to identify the source and contacts of Patient B using case and contact record forms following the national guideline[7].

Case Finding

The case finding focused on the TB cases that were diagnosed during December 2012 to August 2014 in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province. In addition, medical charts in Khok Samrong Hospital were reviewed according to the standard forms described in the national guideline[7].

A suspected TB case was defined as a person living in the same village with an index/source case and had a cough lasting two weeks or more, or hemoptysis, or at least two of the following symptoms: cough less than two weeks, fever, weight loss and abnormal night sweats during 2012 to 2014. A probable TB case was a suspected case who had an abnormal finding in chest X-ray compatible with TB and did not improve after treatment with antibiotics for two weeks. A confirmed TB case was a person who was diagnosed as TB by sputum smear, culture, or molecular testing such as Xpert MTB/RIF and line probe assay.

Latent TB infection (LTBI) is a state of persistent immune response to stimulation by *M. tuberculosis* antigens without clinical manifestation of active TB disease. The diagnosis is based on a positive result of either a skin (tuberculin skin test) or blood (interferon-gamma release assay) test, indicating an immune response to *M. tuberculosis* with negative mycobacteriological test of *M. tuberculosis*[8]. An MDR-TB case was a patient who had laboratory-confirmed *M. tuberculosis* resistance at least to isoniazid and rifampicin. Probable and confirmed (TB and MDR-TB) cases were regarded as cases in this study.

An index case was defined as a confirmed or suspected case of new or recurrent TB infection first identified in a specific household or workplace. A source case was defined as a case or a person who might be the source of TB infection for index cases and secondary cases. In this investigation, Patient B could not be traced back; therefore, contact tracing was initiated from Patient A (father of Patient B).

Contact Tracing

A contact list of Patient A, containing information such as place and duration of contact, was created. Types of contact included household members and close contacts. Household contacts were those who shared the same enclosed living space with Patient A for one or more nights. Close contacts were people who were not in the household, yet shared an enclosed space with a TB patient for extended periods (>8 hours/day or >120 hours/month)[1]. The team then interviewed all the names on this list. To assess the possibility of TB transmission in the community, patients were asked about their social links to other persons and genograms were generated.

Data were analyzed and collated, including demographic information, date of onset and treatment, clinical characteristics, laboratory results, treatment outcome, and clinical and laboratory information of contacts. Attack rates among household and close contacts were calculated using number of probable and confirmed TB cases as the numerator and number of all household contacts and close contacts as the denominator.

Laboratory Testing

Sputum specimens were collected from four household contacts and submitted for molecular testing using Xpert MTB/RIF assay at the National

TB reference laboratory in Bangkok. The Xpert MTB/RIF assay was approved by the World Health Organization in 2013 to diagnose pulmonary and extra pulmonary specimens in adults and children[9]. This assay is a rapid and polymerase chain reaction (PCR)-based TB diagnostic test that was being incorporated into the recommendations for diagnosing MDR-TB in programmatic settings of Thailand.

The Xpert MTB/RIF can be used to identify both the presence of *M. tuberculosis* and rifampicin resistance in less than two hours. It has high sensitivity and specificity for both smear-positive and smear-negative diseases.[10,11] Any specimen diagnosed as rifampicin-resistant TB by Xpert MTB/RIF would additionally be confirmed as MDR-TB by line probe assay at the national TB reference laboratory.

Line probe assay is a deoxyribonucleic acid strip assay that uses PCR and hybridization to detect genetic mutations in specific genes that confer rifampicin-resistance and isoniazid-resistance from *M. tuberculosis* cultured isolates and acid-fast bacilli (AFB) smear positive specimens. A published case series of TB patients in Thailand confirmed that mutations in the rpoB gene were specific to rifampicin-resistance.[12] Resistance to isoniazid has been demonstrated to be significantly associated with mutations in the katG, inhA and ahpC genes.[13] It has been proven to diagnose MDR-TB within 24 hours in several controlled laboratory studies.

Assessing Quality of Care

Informal interviews were carried out with Patient B's family members and neighbors about their treatment experiences, how they took medication and cared for themselves, and basic knowledge of TB. Information obtained from interview and records review were used to assess the quality of care by four dimensions (diagnosis, treatment, TB co-infection with human immunodeficiency virus (HIV) and other co-morbid conditions, and public health and prevention) as stated in the ISTC guidelines[14] as well as explore the impact of TB on socioeconomic status.

At the end of the investigation, preliminary results were disseminated and practical recommendations were provided to the local health care staff and all stakeholders. A report was also submitted to the Provincial Health Office and the Department of Disease Control, Ministry of Public Health.

Results

The case investigation revealed five TB cases from a cluster with epidemiological and geographical linkage, including three confirmed cases (Patients A, B and C) identified by reviewing medical records in the TB clinic of Khok Samrong Hospital during February 2013 and June 2014, and two more probable cases discovered in Patient A's family through contact tracing. Evidence from the investigation implied that Patient A was likely to be the source and spread the disease to the other four cases as he was the first one who developed the symptoms one year earlier than others (Figure 1).

Case Description

Patient A was the first TB case in this outbreak. He started to have TB symptoms while staying with his son (Patient B) in Phuket during August 2012. Patient A returned to Lopburi in February 2013, and was diagnosed with TB and received treatment there. In January 2014, Patient B was diagnosed with TB and started treatment in Phuket. After receiving treatment for two months, results of his sputum AFB still revealed 3+. Patient B went to Lopburi during the second month of TB treatment to visit his mother who developed acute respiratory failure with suspected TB and eventually died. After his mother's funeral, Patient B returned to Phuket, yet did not visit the hospital again for TB treatment.

Contact Tracing

As Patient B's sputum was tested to have *M. tuberculosis* resistant to isoniazid and rifampicin, TB clinic staff in Phuket tried to contact him. However, he could not be traced back for further investigation since the TB database systems across the country

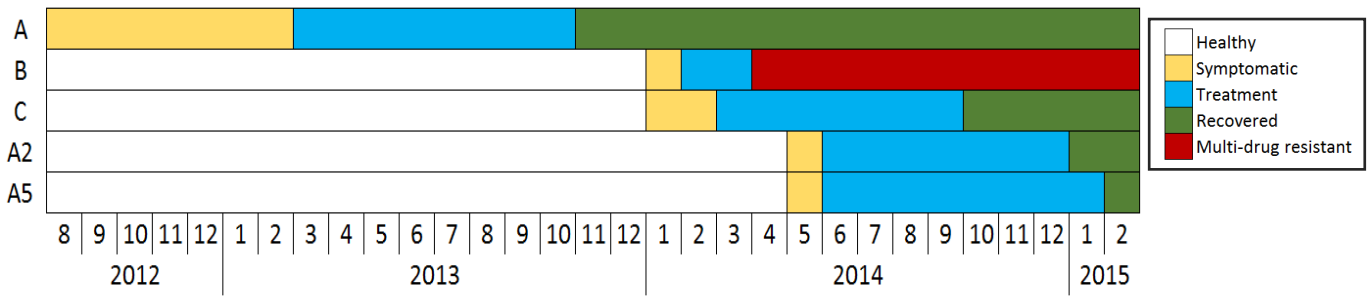

Figure 1. Timeline of confirmed (Patients A, B and C) and probable (Patients A2 and A5) TB cases in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2012-2014

were not properly linked. Nonetheless, his deceased mother was suspected of having TB and his father was diagnosed as having TB. Hence, his father (Patient A) was regarded as the source case and the contact tracing was initiated from Patient A.

The investigation team found eight household contacts (Patients B and A1-7) and three close contacts (A8, A9 and C) of Patient A. Expanding the investigation through a genogram revealed that one of the household contacts (A5) was related to two more household contacts (A5-x and A5-y) who were the parents of A5. Thus, total ten household contacts and three close contacts were identified from Patient A.

Patient C was a confirmed TB case with human immunodeficiency virus (HIV) co-infection. Tracing of Patient C from a separate genogram observed two more household contacts (C1 and C2), however, only one of them (C2) who was staying at home was included in the study (Table 1).

Among all contacts, Patient B was diagnosed with MDR-TB and Patient C was recently confirmed to have pulmonary TB in March 2014. The investigation team found two more probable TB cases: Patient B's son who developed pleural effusion with HIV co-infection (A2), and Patient B's great grandson who had perihilar infiltration based on a chest X-ray (A5).

Assuming that Patient A was the source case, the attack rate of contacts from Patient A was 30.0% (3/10) for household contacts and 33.3% (1/3) for close contacts.

Social Determinants

The family genograms highlighted the geographical and relationship linkages of a TB cluster. In Patient A's family, early marriages and history of divorce with remarriage were observed. Patient A's house had limited ventilation and lighting, and there were no windows. The house was crowded with eight family members. Patients A5 (aged 3 years) and A6 (aged 1 year with LTBI) stayed in Patient A's house during the day-time while their parents (A5-x and A5-y) who lived in another house went to work. Patient C's house, a noodle shop frequently visited by Patient A, was across the road (Figure 2).

Patient A sought medical care seven months after onset of symptoms. When interviewed, he and his family members had a low education level and lacked of knowledge on TB infection, symptoms and preventive measures such as the wearing of a protective face mask. Patient A perceived that TB could be cured by taking one tablet of a drug per day, could not be transmitted to others, and did not relapse. He was a heavy tobacco smoker and consumed alcohol every day.

Table 1. List of contacts of Patient A and contact tracing results in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2013-2014

ID	Status	Age (year)	Result of Acid-fast bacilli	Xpert MTB/RIF Result*
A	Source case, Confirmed TB	65	3+/3+/3+	Not detected
Household				
B	Notified case, Confirmed MDR-TB	35	3+/3+/1+	N/A
A1	Dead (respiratory failure), Suspected TB	59	Not found	N/A
A2	HIV Probable TB	39	Not found	Not detected
A3	TB Negative	33	Not found	Not detected
A4	TB Negative	16	Not found	Not detected
A5	Probable TB	3	Not collected	N/A
A5-x	TB Negative	20	N/A	N/A
A5-y	TB Negative	22	Not found	N/A
A6	Latent TB	1	Not collected	N/A
A7	TB Negative	43	Not found	Not detected
A8	TB Negative	67	Not found	N/A
A9	TB Negative	72	Not found	N/A
Community				
C	Confirmed TB	37	1+/1+/1+	N/A
C1	N/A	18	N/A	N/A
C2	TB Negative	8	N/A	N/A

*Tested in September 2014 N/A = not available

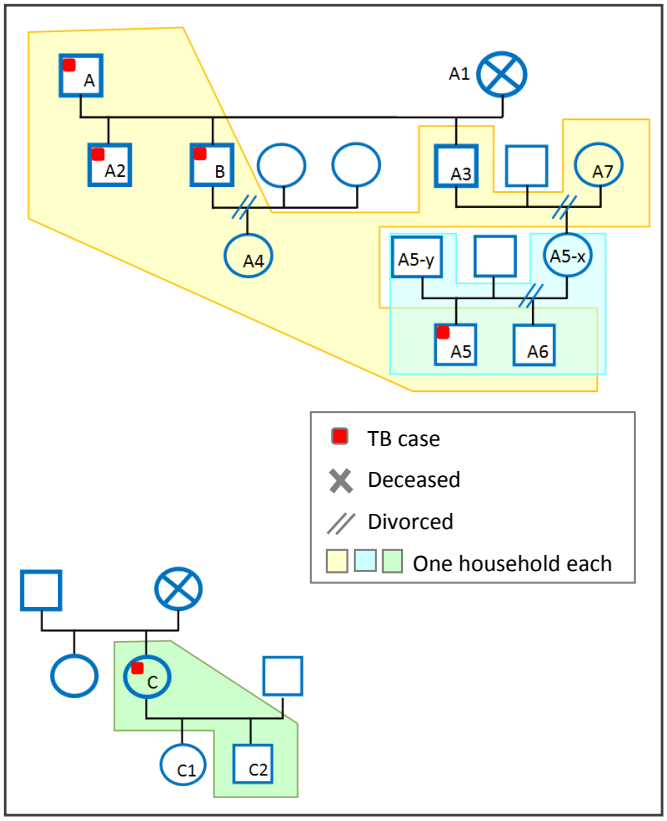

Figure 2. Genograms of tuberculosis cases and their contacts in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2014

Quality of Care

Quality of patient care was assessed for five TB cases (A, B, C, A2 and A5) in this outbreak. Strengths and weaknesses in the quality of care linked to the ISTC guidelines were observed and compared (Table 2). A delay in diagnosis of TB was found for Patient A and diagnostic testing such as gastric aspirate was not performed to confirm TB in children under five (A5). Taking a sub-optimal dosage of anti-TB drugs by Patient A and misconceptions about TB care were identified as well.

At the end of second and third months of treatment, Patient B had a positive result for *M. tuberculosis* by culture, and resistance to isoniazid and rifampicin by drug susceptibility testing while Patient A had no growth in culture. Patient A was treated for eight months before being cured; however, Patient B traveled to Phuket and Chumphon Provinces, and refused to receive any treatment. In February 2015, Patient B was admitted to Chumphon Hospital with pneumonia and started treatment as an MDR-TB patient in March 2015.

From public health and prevention perspectives, although the staff in the TB clinic conducted the second step of the investigation by interviewing Patient A about household contacts in his family, they did not complete the clinical evaluation process at the very beginning. However, they performed all steps of contact investigation by June 2014. For TB infection control in Khok Samrong Hospital, the TB clinic was separated from the general out-patient department. There was also a 'fast track' infection control system in the TB clinic for suspected patients. Moreover, all TB cases in this hospital were recorded in an electronic database system and reported in a timely manner.

Discussion

This outbreak investigation revealed an epidemiologically linked cluster of TB cases. Out of five geographically related cases identified, four cases were from the same family. We found the practices that did not follow the ISTC guidelines which negatively impacted on the quality of patient care. Potential factors contributing to this community TB outbreak were delay in diagnosis of the source case, sub-standard care, low socioeconomic status, delay in conducting contact tracing, and an ineffective national TB database system. Elimination of these contributing factors could help TB-related health personnel achieving their ultimate goal to eliminate TB in the community.

The source case spent six months in a private clinic before being diagnosed with TB. This delay in diagnosis and sub-standard care led to a prolonged period of possible TB transmission. Furthermore, no specimens were collected from the source's two grandchildren, who were diagnosed with probable TB and latent TB infection, and no pediatric anti-TB drug was given to them. Sputum specimens of the source's contacts were sent to Bangkok for Xpert MTB/RIF testing. As Thailand is a middle income country, case finding and diagnosis remain major challenges to TB control. In 2013, the Global Fund and National Health Security Office supported the use of Xpert MTB/RIF and line probe assay for early detection of *M. tuberculosis* and diagnosis of drug resistance in high risk MDR-TB groups, people living with HIV/AIDS and MDR-TB suspected cases[1]. The Xpert MTB/RIF is a rapid test and should be installed at or near the point of care.

However, many challenges existed in district hospitals with limited staff and infrastructure. We recommended the Ministry of Public Health to ensure a good logistics for accurate diagnoses and proper management of TB in district hospitals by allocating up-to-date equipment in TB laboratories.

Therapeutically, there is no evidence to support the efficacy of taking rifampicin for three times a week as recommended by WHO. In addition, a sub-optimal

Table 2. Comparison between the guideline and actual practices during a tuberculosis outbreak in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2013-2014

Guideline from the International Standards for Tuberculosis Care[14]	Actual practice in a tuberculosis outbreak
Diagnosis (standard 1-3 and 6)	
To ensure early diagnosis, all clinically suspect patients, including children, should be evaluated for tuberculosis (TB).	Patient A did not seek appropriate health care and the provider at a private clinic did not suspect the disease for six months, leading to ongoing transmission.
All patients should have at least two specimens for smear microscopy or one specimen for Xpert MTB/RIF, and all children should have bacteriological confirmation.	All adult patients had at least two specimens. However, no specimen was tested for a pediatric case (Patient A5) since health staff were not familiar with collecting specimens from children.
Treatment (standard 7-11 and 13)	
Prescribe an appropriate regimen. The dose and regimen of anti-TB drugs should conform to the recommendation from World Health Organization.	All adult patients received an appropriate regimen from health care staff (fixed does combination of HRZE three tablets/day). Patient A5 took rifampicin 25 mg/kg/day three times weekly.
A patient-centered approach to treatment should be developed in order to promote adherence, improve quality of life and relief suffering.	Patients lived with poverty and lack of basic knowledge on TB disease. Though Patient A took medicine every day, he took only one tablet which was considered as sub-optimal.
Response to treatment should be monitored by sputum smear microscopy at the time of completion of the initial phase. Smear-positive cases should be assessed for drug resistance.	Regular follow up with smear microscopy was performed. At the end of third month, if acid-fast bacilli (AFB) was still positive, sputum was sent for culture.
Records of all medication given, bacteriological response, outcomes and adverse reactions should be accessible and systematically maintained.	There were individual folders for each patient and each contained complete information.
Addressing human immunodeficiency virus (HIV) infection and co-morbid conditions (standard 14-15 and 17)	
All providers should conduct a thorough assessment for co-morbid conditions and other factors that could affect TB treatment response or outcome.	Patient A had alcohol dependence and was a heavy tobacco smoker.
HIV testing and counseling should be conducted for all patients. For all patients with HIV and TB, antiretroviral therapy should be initiated within two months.	Patient C received anti-retroviral therapy within two weeks after confirmation for HIV infection by laboratory result.
Public health and prevention (standard 18-21)	
Persons in close contact with patients who have infectious TB should be evaluated and managed in line with the recommendation.	There was no evaluation for contact cases after Patient A was diagnosed with TB.
Children less than five years of age who are close contacts of a person with infectious TB, and who do not have active TB should be treated as presumed latent TB infection.	Children under five were evaluated and treated for TB and latent TB infection, but no pediatric formula was provided.
Each health care facility should develop and implement an appropriate TB infection control plan to minimize possible transmission.	The TB clinic was isolated from the general out-patient department for minimizing possible transmission.
Providers must report about new and relapse cases, and their treatment outcomes to local public health authorities.	Neat and systematic recording and reporting was observed.

HRZE = Isoniazid, rifampicin, pyrazinamide and ethambutol

dosage of anti-TB drugs can lead to drug-resistant strains of *M. tuberculosis*. These problems suggest that both public and private health care systems need more supervision in TB diagnosis, especially in obtaining gastric aspirate in children who have close contact with MDR-TB cases for identifying their drug resistant status. Members of a family with a low socioeconomic status, living in congested and crowded conditions with poor ventilation, and having personal behaviors of smoking may increase susceptibility to TB as well as more negative treatment outcomes[15].

In 2012, WHO stated that a person with TB could infect up to 10-15 people through close contact over the course of a year.[16] For MDR-TB transmission, a study on household contacts suggested that circulating MDR-TB strains in Peru were less likely to result in the disease among household contacts compared to drug-sensitive strains.[17] A mathematical model demonstrated that even when the most fit MDR-TB strain was assumed to be less fit than the drug-sensitive strain. However, the MDR strain would eventually outcompete the drug-susceptible strain.[18] In our study, the delay in conducting contact tracing increased the likelihood of disease transmission from Patient A. He had only been asked about the number of members in his family and none had been contacted for a clinical evaluation until his son (Patient B) was diagnosed with MDR-TB merely 16 months later. Due to this time lapse, the investigation team could not find additional TB cases and this might have potentially promoted further transmission. Treatment of contacts with latent TB infection is recommended for individuals at increased risk of developing TB such as those with HIV.[19] Therefore, actions should be taken to limit the transmission of not only drug-sensitive strains, but also drug-resistant strains by conducting contact tracing as early as possible and giving treatment to TB cases as a prevention measures.

Lastly, from public health and prevention perspectives, ineffectiveness in the national TB database system allowed Patient B to avoid receiving treatment. At the time of his initial diagnosis, he was not required by law to receive treatment. The stand-alone database system, which was not linked with other surveillance databases, was a major reason behind the fact that other hospitals were not informed about MDR-TB. Implementation of a national-linked database system would enable health care providers to aware of the patient's status and trace the history of all suspected TB cases. Policies and laws should be advocated for regulation of persons with serious communicable diseases such as MDR-TB.

Limitations

Two TB cases (Patients B and A2) could not be traced or interviewed. Thus, identification of their contacts was not possible. This probably resulted in under-reporting of actual TB cases in this outbreak. In addition, we used clinical criteria to diagnose TB in two patients (A2 and A5) since the sputum result was cultured negative for one and could not be collected from the other. However, based on the guidelines of Thai National TB Control Programme in 2013[1], pulmonary TB could be diagnosed with a negative or unknown smear result. In the process of contact tracing, sputum samples from four contacts were sent for molecular testing using Xpert MTB/RIF in order to increase the sensitivity of TB diagnosis and early detection of resistant to rifampicin if TB developed.

Public Health Recommendations

Our study suggested that there was an opportunity to prevent future TB outbreaks by addressing the short and long-term public health responses to TB. This included improving access to care, upgrading TB laboratory equipment in clinics and hospitals, improving adherence to TB follow up, and advocating an inclusive and shared national database system for tracing TB patients in Thailand. To reduce the transmission of *M. tuberculosis*, the following specific interventions should be implemented. First, community awareness could be raised by promoting social campaigns on important occasions such as the World TB Day. Moreover, regular trainings for all health personnel from both public and private sectors should be provided to improve the quality of care. Conducting a contact investigation for every TB case, especially for MDR-TB, should be the first priority for TB clinics in order to receive accreditation. Lastly, a national database for TB, based on the current system for the National AIDS Programming which facilitates health personnel to track patients for early treatment and follow-up, should be established.

Acknowledgements

The authors would like to thank the staff from Field Epidemiology Training Program, Thailand. We also appreciate Patama Monkongdee, Michael Martin and TB program staff from the Thailand MOPH – US CDC Collaboration (TUC) for editing the laboratory information. Additionally, we acknowledge the support of the staff from Office of Disease Prevention and Control for Region 4, Lopburi Province, Khok

Samrong Hospital and Dong Marum Health Promoting Hospital. We are also grateful to Dorothy L. Southern (US CDC) for reviewing and editing this manuscript.

Suggested Citation

Soontornmon K, Aye YM, Phankhor N, Watanatorn S, Modmoltin W, Jiraphongsa C. Identification of a tuberculosis cluster through epidemiological and geographical tracing of a patient with multidrug resistant tuberculosis in Lopburi Province, Thailand, 2014. OSIR. 2017 Jun;10(2):14-22.

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Outbreak, Surveillance and Investigation Reports
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The Grammar of Science: Let's 'Log' (Part 1)

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No. I am not asking you to go "Rock'n Roll' with me at the "Let's Rock: The Retro Festival" in UK. And I am not asking you to go cut down trees in the forest. But I would like you to reflect back to the "logarithm" function in mathematics and statistics that you learned in your high school days. Many people get blocked out and start to not like statistics or mathematics when they see numbers get converted into "logarithm". Why do we have to do it in "log-scale"? Why not just use or analyze data in simple numbering scale? There are reasons behind this. And it is as fun as going rock and roll at the concert!

Back to basic - "Logarithm" is rockin!

You may think mathematics is fixed and full of unchanging rules and truths. But it may not be so. As an example of the "logarithm" you will be surprised that modern mathematicians will give very different definitions from the mathematicians several centuries ago[1]. If we go back through the history of "logarithm", we will see that the concept and methods had been evolved over time. Historically, the concept of logarithm was independently invented in the 17th century by at least two mathematicians, the Scottish John Napier (1550-1617) and the Swiss Joost Bürgi (1552-1632). In summary, logarithm was developed to speed up calculations, mainly to reduce the time required for multiplying numbers with many digits[2]. Napier was the first mathematician who named the term "logarithm" from the Greek roots - "logos" meaning proportion + "arithmus" meaning number; this is because he used it to relate numbers to another value when he wanted to calculate complex formula for multiplication of very large numbers in astronomy. Almost at the same time period, Burgi came up with the concept of logarithm similar to Napier when he tried to make mathematical operations simpler by combining multiplication, division, square roots, and cube roots together in one table. Burgi did not get much credit as a founder of the logarithm because he did not share his work at that time while Napier published his findings[3].

By mathematical definition, "logarithm" is the exponent or power to which a base must be raised to yield a given number[2]. That is, x is the logarithm of n to the base b if $b^x = n$; in which we can write: $x = \log_b n$. To make it clear, look at these two examples:

$2^3 = 8$, so we can say that 3 is the logarithm of 8 to base 2; or $3 = \log_2 8$

$10^2 = 100$, so we can say that 2 is the logarithm of 100 to base 10; or $2 = \log_{10} 100$

Perhaps many of us are more familiar with the second example, "logarithm base 10" which is called "common" or "Briggsian" logarithm. Historically, Napier's ideas were taken up and revised by the English mathematician Henry Briggs (1561-1630) who had invented the common logarithm table and made it accepted throughout Europe. Again, his innovation was used to solve the burden of mathematicians, astronomers, and other scientists in performing the long and tedious calculations[2]. The common table of logarithm base 10 concept is shown in figure 1.

Number	Logarithm		Antilogarithm	
1	$\log_{10}(1)$	= 0	10^0 =	1
10	$\log_{10}(10)$	= 1	10^1 =	10
100	$\log_{10}(100)$	= 2	10^2 =	100
1000	$\log_{10}(1000)$	= 3	10^3 =	1000
10000	$\log_{10}(10000)$	= 4	10^4 =	10000
100000	$\log_{10}(100000)$	= 5	10^5 =	100000
1000000	$\log_{10}(10000000)$	= 6	10^6 =	1000000
10000000	$\log_{10}(100000000)$	= 7	10^7 =	10000000

Figure 1. Common Logarithm, Log base 10

The basic idea behind "logarithm" is that "addition and subtraction" are easier to perform than "multiplication and division" which Napier had said that the latter operation require a "tedious expenditure of time" and are subject to "slippery errors"[2]. As an example of the law of exponent, the

multiplication of numbers could be presented as the exponents additively: i.e., $b^x b^y = b^{x+y}$. Thus by correlating the geometric sequence of numbers b, b^2, b^3,… (b = base) and the arithmetic sequence 1, 2, 3,…, we don't have to do series of "multiplication and division" but simply do "addition and subtraction". For the sake of simple example, we will express in terms using common logarithm base 10 (we can do similar operations with logarithms of other bases); the calculation of long and tedious numbers like 100000 x 1000000000 could be done by:

- Exponent or power base 10: $b^x b^y = b^{x+y}$

  100000 x 1000000000 = 10^5 x 10^9 = 10^{5+9} = 10^{14} = 100000000000000

- Logarithm base 10: $\log_b mn = \log_b m + \log_b n$

  $\log_{10}(100000 \text{ x } 1000000000) = \log_{10}(100000) + \log_{10}(1000000000) = 5+9 = 14$,

  then convert back (so-called antilogarithm) = 10^{14} = 100000000000000

What is so natural about the "natural log"?

Besides "common" logarithm or "log base 10", when you look at different statistical procedures, you will see a lot of "natural" logarithm or "log base e". Let's go back a bit in time. Natural log was developed by Leonhard Euler (1707-1783) (pronounced "oiler") who was a mathematician of 18th century and is considered one of the greatest mathematicians of all time[2]. In fact, Euler studied with Johann Bernoulli ("Bernoulli" is another statistical term that you see a lot in statistics textbook – we may have another article on this later). Despite his blindness later in life, Euler had written nearly 900 books or produced on average one mathematical paper every week, covering almost all aspects of mathematics, from geometry to calculus to trigonometry to algebra to number theory, as well as optics, astronomy, cartography, mechanics, weights and measures and even the theory of music[4]. A lot of mathematical notation created or popularized by Euler included, for examples, e the base of the natural logarithm, f(x) the function f as applied to the variable or argument x, Σ sigma, the sum of total of a set of numbers, etc.

So what is "natural logarithm"?

The "natural log" is usually written as $\log_e x$ or ln(x). Why do they use "ln" not "nl" for "natural log"? One of the explanations is given that it comes from the Latin name is "logarithmusnaturali". And the natural log is the inverse of "e". The "e" is sometimes called "Euler's number" which Euler said that "e" is not his name but rather means "exponential". As one of the easy way to define "natural log", we can say that the natural log gives you the time needed to reach a certain level of growth[5].

ln(x) = amount of time needed to reach a certain level of continuous growth
= time needed to grow to x (with 100% continuous compounding)

e^x = amount of continuous growth after a certain amount of time
= amount of growth after time x (with 100% continuous compounding)

Again what is "e"? ("ln" is the inverse of "e")

One way to explain the "e" or the amount of growth is to think about the scenario of calculating interest growth of your deposited money (Figure 2). Suppose you open a bank account with $1 deposited and the interest rate of 100% per year growing continuously.

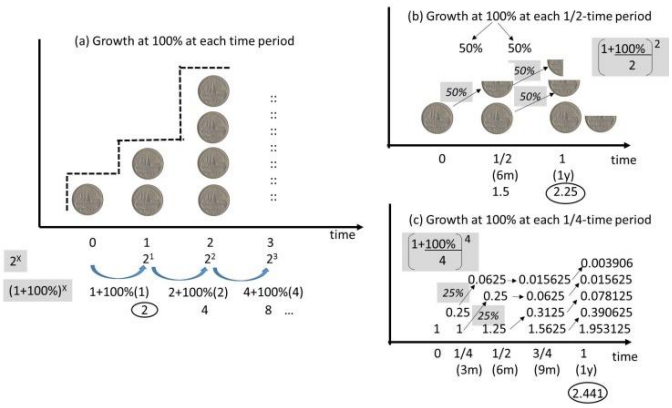

Figure 2. Growth and time of interest

As shown in figure 2(a), at the end of year 1, you will have $2; at year 2, you will have $4; at year 3, the money will increase to $8, and so on. The formula for increase could be written as $[1+100\%]^x$ where x = 1 time (1 year) to reach 100%.

But if the interest rate of 100% is given at two times-period over the year (thus 50% increase every half year), the money that you will get at the end of each year will be different. As shown in figure 2(b), you started at $1, but at the end of year 1, you will have $2.25, not $2. The formula for this increase is $[1+100\%/x]^x$ where x = 2 times (in 1 year) to reach 100%.

Again, if the interest rate of 100% is given at four times-period over the year (thus 25% increase quarterly), you money that you will get at the end of each year will also be different. As shown in figure 2(c), you started at $1, but at the end of year 1, you will have $2.441, not $2 or $2.25. The formula for this increase is $[1+100\%/x]^x$ where x = 4 times (in 1 year) to reach 100%.

If this is the case - how much growth will you get after many x units of time per year to reach 100% continuous growth? It seems that – "the larger number of x, the larger number of gain." (When x=1, 2, 4, …, from initial $1 with 100% growth per year, you get $2, $2.25, $2.441.. at the end of the year, respectively!). If so, you should ask for x = 100 times per year to reach 100% growth rate so that at the end of the year you will get much higher than $2. The bank will not accept that for sure! But wait – the bank has no such worry. It has been proved that when x is getting higher to a certain limit, the gain will be somewhat stable as shown in figure 3.

Time (x)	$\left(1+\frac{100\%}{x}\right)^x$
1	2
2	2.25
4	2.44140625
100	2.704813829
1000	2.716923932
10000	2.718145927
100000	2.718268237
1000000	2.718280469
10000000	2.718281694

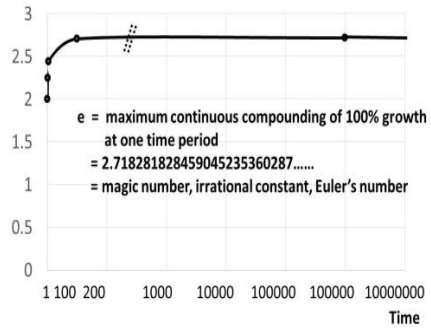

Figure 3. Natural logarithm, Log base e

As you can see, when x keeps getting larger and larger, the growth is slowing down. Or mathematically said - as the number of compounding increases, the computed value appears to be approaching some fixed value - "2.71828182845904523536028……". This number we're approaching is called "e". So "e" is defined as "the maximum continuous compounding of 100% growth at one time period"[6]. It is also called magic number, Euler's number, or irrational constant. Irrational number means its value can't be given precisely in decimal notation. Like π in geometry, the ratio of the circumference of a circle to its diameter, its value is 22/7 or "3.141592653589……" which is another irrational number. So in any mathematical formula, we usually write this number as a letter-name (e or π) because that was easier[2].

The number "e" is the "natural" exponential, because it arises naturally in math and physical sciences. We may think the numbering system of base 10 (0..10..20..) that we are familiar is "natural" to us because almost all of us have 10 fingers. But we should say that the numbering base 10 is "common" to us; that is why logarithm base 10 is sometimes called "common log" as mentioned before. But in mathematical and scientific sense, there are several other bases that we also actually use but hardly realize it, for examples, base-60 in hours-minutes-seconds, base-12 in feet-inches, or based-2 (0-1 or on-off) or base-16 in computer science. Base 10 is good for counting in simple way, but it becomes more complicate when we monitor continuous growth like calculating interest rate in the banking example. The exponential functions are thus useful for modeling many systems that occur in our "natural" world[6,7]. It represents continuous growth in "real life" situations[6]. We will see that "e" is the "natural" base rate of growth of any systems or processes that grow continually and exponentially; for example, population, radioactive decay, interest, bacteria, and more. Even jagged systems that don't grow smoothly can be approximated by "e"[8].

In brief, we can simply say that "e" and "ln" can tell us the relationship of growth and time[5] such that:

e^x where x is "time", we will get growth at that time

ln(x) where x is "growth", we will get time it would take to get that growth

For example:

$e^4 = 54.59815$

= After 4 units of time with 100% growth rate, we get the amount of growth increasing to 54.59815 times of the original amount that we start with.

(i.e., if we start with 1, it will increase to 54.59815 at the end of 4 units of time)

$\ln(54.59815)$ or $l_e(54.59815) = 4$

= If we want growth of 54.59615 times from what we started with, at the growth rate of 100%, we have to wait for 4 units of time.

However, the growth rate does not have to always be continually at 100%. It could be at any rate. The generic formula for exponential growth is e^{rt}; as an example of growth rate at 150% and timing is 4 units of time, we will get:

e^{rt} *where*
r = rate
t = time period

If growth rate = 150% and time = 4 unit
then $e^{1.5x4} = e^6 = 403.42879$
or $\log_e(403.42879) = \text{Ln}(403.42879) = 6$

How "taking log" helps solve complex calculation

Based on its development, the logarithm has become a magic tool for mathematicians, physicists, and engineers used for simplifying complex calculations as it would make the multiplication and division of large numbers into an easier form of looking up values in a table and then adding them for addition and subtracting them for division[3]. This notation can generally apply to different kinds of log – "common log", "natural log" or log of other bases. The following explanation will use "natural log" or "ln" as examples.

Let's start with basic properties of "log".

- ln(x) where x is "growth", we will get time it would take to get that growth[5].

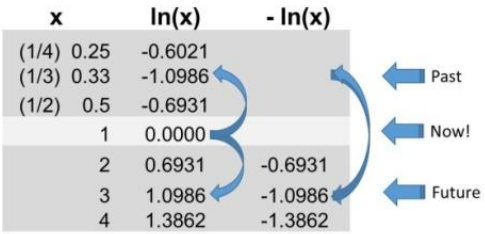

Figure 4. Basic properties of logarithm

What is ln(1)?

- ln(1) = 0
- As we want to have growth of 1 but 1 is our starting point (we put in $1 the bank and wait to get $1 in the bank!) – we don't have to wait, so time = 0.

What is ln(3)?

- ln(3) = 1.0986
- As we want to have growth of 3 when 1 is our starting point (we put in $1 the bank and wait to get $3 in the bank) – we have to wait 1.0986 units of time.

What is ln(1/3) or ln(0.33)?

- ln(0.33) = -1.0986
- Now we want to look at a fraction growth of 1/3 when 1 is our current point or reference and our continuously growth is still 100%. As ln(3) means we will get the amount three times from the current amount. So ln(1/3) means we have to inverse it; and it is equal to -1.0986. That means - if we have time machine going backwards to the past1.0986 units of time we would have 1/3 ($0.33) of our current amount of 1 ($1) today.
- As shown in figure 4, the value we get from ln(1/3) is equivalent to –ln(3).Thus, ln(1/x) = – ln(x)

What is ln(-x)?

- ln(-3) = impossible!
- It is impossible that money or others (say, bacteria) will grow from 1 to -3 or any other negative amount. (Note that in real life we may have negative money printed in red in bank account because we overspent from what we have and the bank allows us to do so before claiming that we are bankrupt! But the truth is we cannot have "negative" amount of money! Thus, ln(negative number) = undefined. "Undefined" means that there is no amount of time we can wait to get a negative amount.
- Using the same logic, the real logarithmic function ln(x) is defined only for x>0. We can't find a number x that would get $e^x = 0$. As that x does not exist, then ln(0) is also undefined.

Now, how logarithm turns "multiplication into addition" and "division into subtraction" (Figure 5).

- ln(x) – where x is "growth", we will get time it would take to get that growth[5]

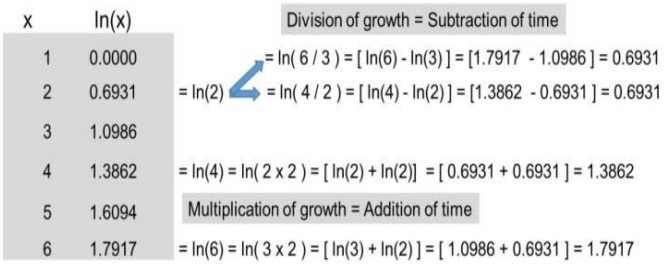

Figure 5. Operations of logarithms

How long does it take to grow money from the current amount of $1 to $4?

- ln(4) = 1.3862; so we have to wait 1.3862 unit of time.
- But the growth from $1 to $4 can happen in a complex situation such that the growth was doubling the amount at 2 time points, from $1 double to $2 and then from $2 double to $4. Thus, ln(4) = Time to double and double again;

  ln(4) = ln(2x2) = [ln(2)+ln(2)] = [0.6931+0.6931] = 1.3862

  Same answer as simple ln(4)!

How long does it take to grow money from the current amount of $1 to $6?

- ln(6) = 1.7917; so we have to wait 1.7917 unit of time.
- But, the growth from $1 to $6 can happen in a complex situation such that the growth was triple first and then double, from $1 triple to $3 and then from $3 double to $6. Thus, ln(6) = Time to triple and then double;

  ln(6)= ln(3 x 2) = [ln(3) + ln(2)] = [1.0986 + 0.6931] = 1.7917.

How long does it take to grow money from the current amount of $1 to $2?

- ln(2) = 0.6931
- But the growth from $1 to $2 can happen in a situation that the growth increase four times first

and then get decrease 2 times downwards, from $1 triple to $4 and from $4 doubling downwards to $2. Thus, ln(2) = Time to 4-times increase and then 2-times decrease;

ln(2) = ln (4/2) = [ln(4)-ln(2)] = [1.3862-0.6931] = 0.6931

- Or, the growth from $1 to $2 may occur in another different situation that the growth increase six times first and then get decrease 3 times downwards, from $1 increase 6-times to $6 and from $6 reduced down 3-times to $2. Thus, ln(2) = Time to 6-times increase and then 3-times decrease;

ln(2) = ln(6/3) = [ln(6)-ln(3)] = [1.7917-1.0986] = 0.6931

The basic rules of logarithm turning "multiplication into addition" and "division into subtraction" are as follow:

ln(a x b) = ln(a)+ln(b)

ln (a/b) = ln(a)-ln(b)

In the next issue, we will discuss how statisticians use 'Log' in managing and analyzing data. (To be continued)

Suggested Citation

Kaewkungwal J. The grammar of science: let's 'log' (Part 1). OSIR. 2017 Jun;10(4):23-27.

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