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Editorial

It is a Time to Catch the Real Killers

Wiwat Rojanapithayakorn, Chief Editor

Nowadays, most epidemiologists are staying in their comfort zones, and let the real killers go away. As epidemiological experts, it is hard to believe they are not aware that non-communicable diseases (NCDs) are the main causes of population mortality, up to 70% of the deaths in most countries. Yet, very few of them are paying attention to the NCDs. This can be witnessed by the nature of the articles published in this OSIR Journal. Last year, all OSIR articles were on communicable diseases and none was on NCDs. Perhaps, it is now the time for epidemiologists to put their brains and hands on the prevention and control of NCDs although it is already very late.

Contribution of epidemiologists is very crucial, and they will not work alone. At the global level, the United Nations (UN) has put a lot of efforts for NCD control. The high level meetings in 2011 and 2018 are a clear sign of the global concern. The World Health Organization (WHO) has also been working synergistically with the UN movement. The set of nine-global-NCD-targets developed by WHO has been adopted worldwide, and much resource has been allocated for its country offices to support operation at country level.

In Thailand, the prevention and control of NCDs has been a main component of the Thailand-WHO Country Cooperation Strategy (CCS) over the last 10 years. For the current CCS (2017-2021), the main focus is on NCD control systems improvement using existing formal and informal networks through the engagement of multiple stakeholders from the government sectors and the civil society. The CCS program will provide strategic support, and catalyze the implementation of the national NCD strategic plan and other existing strategies for NCD risk factors. Building upon the previous CCS, the new program aims to (i) facilitate multi-stakeholder co-ordination; (ii) support knowledge generation and dissemination networks; (iii) improve policies on tobacco and alcohol control and the policies to reduce obesity, including unhealthy diet and physical inactivity; (iv) strengthen the quality of hypertension and diabetes services and capacity building of stakeholders; (v) strengthen surveillance, monitoring and accountability system; and (vi) facilitate international collaboration to drive the global NCD movement. A perusal over the objectives, the role of epidemiologists will be specific toward the surveillance of NCDs and the risk factors. However, epidemiological data are required to achieve all of the five objectives.

One outstanding effort of the CCS was the arrangement of a 3-day Joint Mission of the United Nations Interagency Task Force (UNIATF) on the Prevention and Control to visit Thailand in August 2018. The Mission was led by Dr. Soumya Swaminathan, Deputy Director-General of WHO from Geneva. Eleven UN agencies participated the Mission, together with four Thai experts. They had a chance to meet General Prayut Chan-o-Cha, the Prime Minister of Thailand and many leaders of main stakeholders, including Ministry of Public Health, Ministry of Education, Ministry of Finance, etc., and some key agencies such as the National Health Security Office, National Health Commission Office and Thai Health Promotion Foundation. At the end of the mission, 17 recommendations were proposed for the Thai side and two for the UN. Some significant recommendations include the followings:

- The Prime Minister to establish and chair a new inter-ministerial steering committee on NCD prevention and control in order to squarely place accountability of NCDs on relevant government ministries and fully translate policies and plans into action, and increase domestic investment on NCDs and mental health in line with national development priorities

- The Prime Minister's Office to track progress on national NCD and NCD-related SDG targets (e.g. through a simple progress scorecard) reported to cabinet and parliament annually
- Accelerate enforcement of NCD-related regulations at local levels, particularly actions by provincial tobacco and alcohol control committees
- Sustain innovative financing mechanisms from tobacco, alcohol and sugar sweetened beverages (SSBs) for NCD prevention and control, including the Thai Health Promotion Foundation, health promotion fund of National Health Security Office (NHSO) and local government health budgets
- Designate high level focal persons for NCDs in ministries with accountability to the new inter-ministerial group

This set of UNIATF recommendations is taken seriously by the National Committee on NCD. It is expected that all concern sectors will work together to make the recommendations come true. It is very clear that epidemiologists are a main component in the fight against the NCD threat; and their support by providing relevant data and taking part in the program development will be very helpful for the policy and strategy development as well as for the implementation of NCD control in Thailand. It is the time to act now!

The Prime Minister of Thailand with delegates of the United Nations Interagency Task Force on the Prevention and Control of Non-communicable Diseases, Thailand

(Source: World Health Organization. Joint Mission of the United Nations Interagency Task Force on the Prevention and Control of Noncommunicable Diseases, Thailand, 28-30 August 2018. Nonthaburi: [publisher unknown]; 2018.
Photo credit: Department of Disease Control, Ministry of Public Health, Thailand)

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Risk Factors Associated with Post-operative Wound Complications in the Animal Birth Control Program, Chiang Mai Municipality, Thailand, 2017

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Abstract

While surgical sterilization is applied in the animal birth control program, Chiang Mai Municipality, with limited resources under field condition, there was concern about complications in post-operative wound healing. This study aimed to describe the incidence of wound complication after surgical sterilization and evaluate the associated risk factors. The investigators conducted a cross-sectional study on the owners and animals participated in the program from March to June 2017. The investigators recorded wound complications and possible risk factors for seven days after the operation, and assessed those factors using risk ratios (RR) with 95% level of confidence. Out of total 141 owners of 252 animals included in this study, 15 (6.0%) animals had post-operative wound complications. Animal receiving cefazolin injection prior to the operation was 0.36 times (95% CI = 0.14–0.97) likely to have wound healing complication than those received penicillin with dihydrostreptomycin. Complete course of either antibiotic or anti-inflammatory drug after the operation could protect animals from wound complications (RR = 0.15; 95% CI = 0.05–0.43). Among female animals, midline incision had lower incidence of complication than flank incision (RR = 0.23, 95% CI = 0.07-0.77). In conclusion, there were 6% of post-operative wound complications in this program. Monitoring of wound complications should be included in every surgical sterilization campaign.

Keywords: Sterilization, wound, complication, Chiang Mai Municipality, Thailand

Introduction

Approximately, 60,000 people die from rabies each year worldwide.[1] Control of dog and cat population is an effective strategy for reducing susceptible population to rabies, and creating a sustainable rabies control program.[2] Although the best method of animal population control is surgical sterilization, the surgical operation requires experienced veterinary surgeons, clean instruments and effective post-operative management.

Post-operative management should aim to prevent and control of wound swelling, inflammation and infection. Improper wound management can lead to complications such as scrotal swelling in male dogs, pyometra in female animals and post-operative infection.[3] While standard guideline protocols for surgical sterilization are available,[4] the Wide Veterinary Service (WVS) developed a surgical protocol, aiming to improve animal welfare and reduce complications after operation[5].

Sterilization is also the main method for dog and cat population control in Chiang Mai Province of Thailand. The WVS surgical protocol was adopted by the Chiang Mai Municipality as a basis to achieve good rabies control measures. The procedure includes hand scrubbing, scrubbing of incision site, sterilization of instruments and administering antibiotic or anti-inflammatory drugs post-operatively.

However, due to limitation of surgical instruments, time and personnel resources in field conditions, all sterilization procedures may not fully meet the standard protocol, and the veterinary officers need to follow up all animal owners to assess post-operative wound healing and complications.

Hence, the aims of this study were to describe the incidence of wound complication in dogs and cats after the surgical sterilization that were performed under the animal birth control program in Chiang Mai Municipality, and evaluate risk factors of post-operative wound complications.

Methods

A cross-sectional observational study was performed by collecting data of the animals sterilized under the animal birth control program in Chiang Mai Municipality from March to June 2017.

In brief, the protocol for surgical sterilization under the animal birth control program included:

1. Physical examination, including measuring weight, rectal temperature and dehydration status
2. Antibiotic prophylaxis before operation (Either intramuscular procaine penicillin 12,000 IU/kg with dihydrostreptomycin 20 mg/kg (PSLA) or cefazolin injection 20mg/kg at least 15 minutes before the operation was used in this study.)
3. Anesthesia by propofol 4mg/kg or tiletamine-zolazepam 5mg/kg
4. Scrubbing of surgeon's hands by chlorhexidine scrub solution and cleaning with alcohol
5. Autoclaving instrument or disinfection by alkyl dimethyl ammonium chloride due to limited number of autoclave machine
6. Midline or flank incision sites for female animals, and scrotal incision in cats and pre-scrotal incision in dogs for male animals
7. Giving antibiotic (Cephalaxin 10mg/kg) or anti-inflammatory drug (Carprofen 4mg/kg) for post-operative treatment

Prior to the operation, health status of animals and other risk factors were assessed, and condition during the sterilization was recorded using the anesthesia monitoring form and a questionnaire. Risk factors were categorized into before, during and after the operation (Table 1).

Wound healing status and complications were assessed using telephone interview on the seventh day after the operation. Broken wounds, wound swelling, having pus or exudate were considered as a post-operative wound complication. Animals that died, those received antimicrobial or anti-inflammation drugs by another source, or the animal owners who could not be contacted were excluded from the analysis.

Descriptive statistics were used to quantify the wound complications. Risk ratio (RR) were calculated to measure associations between wound complications and factors with 95% confidence interval (CI). Statistical analyses was performed using Epi Info version 7.2.1.0[6].

Results

Information was collected from 149 owners for total 260 animals. Eight animals from eight owners were excluded due to loss of contact, receiving antimicrobial drugs by private animal clinics and death. Thus, total 252 animals (122 dogs and 130 cats) and 141 owners were included in the analysis (Table 2).

Table 1. Risk factors assessed before, during and after the surgical sterilization in the animal birth control program, Chiang Mai Municipality, Chiang Mai Province, Thailand, 2017

Condition	Risk item	Risk factor
Pre-operation	Animal signalment	Species, weight, gender and age
	Animal husbandry	Free-roaming or restricted
	Physical examination	Temperature, dehydration status and color of mucous membrane
During operation	Surgeon's hand scrubbing	
	Sterilization of instruments	Autoclave or disinfection
	Prophylaxis	Procaine penicillin with dihydrostreptomycin or cefazolin
	Type of operation	Castration or ovariohysterectomy
	Surgeon	Thai or foreign veterinarian
	Surgical site	Frank or midline incision, only for female animals
	Duration of operation	
	Frequency of anesthetic drug given to maintain animals in surgical anesthetic stage	Unconsciousness, amnesia, immobility and unresponsive to surgical stimulation
Post-operation	Type of drug given by the owner	
	Completing of oral drug administration by the owner	Antibiotic or anti-inflammation drug

Table 2. Baseline characteristics of animals undergone the surgical sterilization in the animal birth control program, Chiang Mai Municipality, Chiang Mai Province, Thailand, March-June 2017

Characteristic	Number (Percent)	Mean (Range)
Owner (n=141)		
Gender		
Male	46 (32.6)	
Female	95 (67.4)	
Age (year)		45.6 (18-73)
Animal (n=252)		
Type		
Dog	122 (48.4)	
Cat	130 (51.6)	
Gender		
Male	63 (25.0)	
Female	189 (75.0)	
Age (month)		24.8 (2-120)
Body weight (kg)		7.1 (1.1-24.3)
Dog		11.1 (2.4-24.3)
Cat		3.4 (1.1-5.9)

Out of 252 animals, 48.4% (122/252) were dogs and the rests were cat. About 75.0% (189/252) were female animals. The overall incidence of wound complications on the post-operative day seven was 15 (6.0%). Wound complications were found in 5.3% (10/189) of female and 7.9% (5/63) of male animals. The common wound complications included serous exudate (33.3%), followed by broken wound (26.7%) and broken wound with pus exudate (20.0%) (Table 3).

Table 3. Post-operative wound complications in the animal birth control program, Chiang Mai Municipality, Chiang Mai Province, Thailand, March-June 2017

Description	Number	Percent
Wound complication	15	6.0
Broken wound	4	26.7
Having pus	1	6.67
Broken wound with pus	3	20.0
Serous exudate	5	33.3
Swollen wound	1	6.7
Swollen wound with serous discharge	1	6.7
Animal type		
Dog	8	53.3
Cat	7	46.7
Animal gender		
Female	10	66.7
Male	5	35.3

Two factors were significantly associated with wound complications. Animals that were given with cefazolin before the surgical operation were 0.36 times (95% CI=0.14-0.97) likely to have wound complications than animals that received penicillin/streptomycin. Wound complications in animals that were provided with full dose of drug after the operation were 85% less than animals that received the drug partially (RR=0.15, 95% CI=0.05-0.43) (Table 4). For female animals, having a midline incision had a significantly lower incidence of wound complications than a flank incision (RR=0.23, 95% CI=0.07-0.77). Other risk factors including disinfection methods, operation/anesthesia duration and body weight of animals showed some association with the wound complications but non-statistically significant.

Discussion

Our study found that post-operative complications occurred in 6% of animals after the surgical sterilization while wound complications occurred equally in dogs and cats. Two primary protective factors identified for wound complications were type of prophylactic antibiotic and continuous administration of the drug until seven days after the surgical operation.

The incidence of wound complications after sterilization operation among animals in Thailand had never been published. The incidence in this study was similar to a study in Philadelphia, Pennsylvania[7]. Flank incision is practiced by some veterinary surgeons in Thailand as they believed that it is easier to remove ovaries and reduce wound complications. However, this study revealed that flank incision in female animals was associated with increased incidence of wound complications five times higher than the midline incision. This result was also similar to a report in the United Kingdom[8]. Thus, the finding of this study can be used to support the use of midline incisions to reduce wound complications in the future.

In addition, the use of appropriate antibiotic prophylaxis treatment is crucial to protect animal from any wound complication. We found higher prophylaxis effect by cefazolin injection to post-operative wound complications, compared with penicillin/streptomycin injection. The results of this study also supported the conclusion from the report of the Companion Animal Control Project of Chiang Mai Municipality in 2015, stating that penicillin and streptomycin susceptibility to *Staphylococcus* spp. and *Bacillus* spp., which were commonly found around the incisional site, was reducing and cefazolin had a better prophylaxis effect than penicillin and streptomycin[9].

Table 4. Post-operative wound complications and associated factors of animals undergone the surgical sterilization in the animal birth control program, Chiang Mai Municipality, Chiang Mai Province, Thailand, March-June 2017

Factor	Number/total	Percent	Risk ratio	95% CI
Pre-operation				
Animal husbandry (n=249)				
Restrict housing	2/49	4.1	0.63	0.15-2.69
Free roaming	13/200	6.5	Reference	
Animal type (n=252)				
Dog	8/122	6.6	1.22	0.46-3.26
Cat	7/130	5.4	Reference	
Age in year (n=207)				
0-1	5/93	5.4	0.88	0.29-2.67
>1	7/114	6.1	Reference	
Physical examination				
Body weight in kg (n=252)				
0-10	10/183	5.5	0.75	0.27-2.13
>10	5/69	7.2	Reference	
Temperature in °C (n=137)				
0-38	1/27	3.7	0.81	0.10-6.69
>38	5/110	4.5	Reference	
Dehydration (n=142)				
Normal hydration	6/126	4.8	NA	NA
Dehydration	0/16	0		
Mucous membrane (n=219)				
Pale	2/30	6.7	0.97	0.23-4.08
Pink	13/189	6.9	Reference	
During operation				
Surgeon type (n=232)				
Thai veterinarian	12/188	6.4	0.94	0.28-3.18
Foreign veterinarian	3/44	6.8	Reference	
Prophylaxis (n=252)				
Cefazolin	7/178	3.9	0.36	0.14-0.97
Penicillin/streptomycin	8/74	10.8	Reference	
Type of operation (n=252)				
Castration	5/63	7.9	1.50	0.53-4.22
Ovariohysterectomy	10/189	5.3	Reference	
Midline	4/141	2.8	0.23	0.07-0.77
Flank	6/48	12.5	Reference	
Maintenance frequency (n=252)				
No	9/133	6.8	1.34	0.49-3.66
Yes	6/119	5.0	Reference	
1-5 times	5/100	5.0	0.95	0.12-7.68
>5 times	1/19	5.3	Reference	
Hand scrub (n=252)				
Yes	8/184	4.3	0.42	0.16-1.12
No	7/68	10.3	Reference	
Duration of operation (n=158)				
<30 minutes	4/102	3.9	0.44	0.12-1.57
>30 minutes	5/56	8.9	Reference	
Sterilization (n=252)				
Autoclave	9/199	4.5	0.40	0.15-1.07
Disinfection	6/53	11.3	Reference	
Post-operation				
Post-operative drug (n=252)				
Anti-inflammatory	5/81	6.2	1.06	0.37-2.99
Antimicrobial	10/171	5.8	Reference	
Drug history (n=242)				
Continuous and complete	12/243	4.9	0.15	0.05-0.43
Incomplete	3/9	33.3	Reference	

Oral administration of antibiotic after operation did not reduce the incidence of wound complication, comparing with anti-inflammatory drug in this study.

A previous study also revealed that antimicrobial drug administration did not show effects on the post-operative wound complications if the operations were performed under clean procedures by the experienced surgeons[10]. Hence, giving antibiotics for animals after operation might not be necessary if the operation was performed under appropriate aseptic condition.

In some other studies, the risk factors such as using liquid chemical disinfectant instead of autoclaving instruments[11], operation duration and body weight of animals[12], and anesthesia duration[12-14] were proved to be associated with the post-operative wound complications, however not supported by this study.

The complete drug dosage (either antibiotic or anti-inflammatory) was also identified to be a protective factor for wound complication. This effect might derive directly from the drug itself or a complete dose that served as a proxy for post-operative care which might be a confounder for the association between wound complication and complete drug dosage. However, this issue was not determined in this study.

The information on post-operative care practices by animal owners was not gathered since the information was collected by telephone interview. Thus, post-operative care practices should be studied in more detailed.

This study was performed in complementary to follow up the program of animal health after surgical operation. As the study did not aim to prove specific factors associated with the post-operative wound complications, appropriate randomization was not applied. However, the results revealed useful information that was needed for further interventions.

In conclusion, 6% of post-operative wound complications was found in the animal birth control program of Chiang Mai Municipality. In the future, wound complications could be prevented by administering the appropriate antibiotic just before the operation and applying midline incision in female animals. Owners' compliance with the spay-neuter program to support rabies control relies on a high success rate of the control program and low incidence of post-operative complications. Continuous monitoring of wound complications after the surgical sterilization is necessary to ensure as part of the animal birth control program in Chiang Mai Municipality. Future studies could be carried out to understand the effects of post-operation care by animal owners and wound complications.

Suggested Citation

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References

1. Beal MW, Brown DC, Shofer FS. The effects of perioperative hypothermia and the duration of anesthesia on postoperative wound infection rate in clean wounds: a retrospective study. Vet Surg. 2000 Mar-Apr;29(2):123-7.
2. Brown DC, Conzemius MG, Shofer F, Swann H. Epidemiologic evaluation of postoperative wound infections in dogs and cats. J Am Vet Med Assoc. 1997 May 1;210(9):1302-6.
3. Coe RJ, Grint NJ, Tivers MS, Hotston Moore A, Holt PE. Comparison of flank and midline approaches to the ovariohysterectomy of cats. Vet Rec. 2006 Sep 2;159(10):309-13.
4. Food and Agriculture Organization of the United Nations. Dog population management. Report of the FAO/WSPA/IZSAM expert meeting - Banna, Italy, 14-19 March 2011. Animal Production and Health Report. Rome. p. 43-5.
5. Worldwide Veterinary Service, Thailand. Training Course Manual for the Veterinarians. Bangkok: Worldwide Veterinary Service, Thailand; 2015.
6. Centers for Disease Control and Prevention. Epi Info [cited 2018 Dec 5]. <http://wwwn.cdc.gov/epiinfo/html/prevVersion.htm>.
7. Heldmann E, Brown DC, Shofer F. The association of propofol usage with postoperative wound infection rate in clean wounds: a retrospective study. Vet Surg. 1999 Jul-Aug;28(4):256-9.
8. Kustritz MV. Determining the optimal age for gonadectomy of dogs and cats. J Am Vet Med Assoc. 2007 Dec 1;231(11):1665-75.
9. Muraro L, White RS. Complications of ovariohysterectomy procedures performed in 1880 dogs. Tierarztl Prax Ausg K Kleintiere Heimtiere. 2014;42(5):297-302.
10. Nicholson M, Beal M, Shofer F, Brown DC. Epidemiologic evaluation of postoperative

wound infection in clean-contaminated wounds: A retrospective study of 239 dogs and cats. Vet Surg. 2002 Nov-Dec;31(6):577-81.

11. World Organisation for Animal Health. ASEAN rabies elimination strategy. Jakarta: ASEAN Secretariat; December 2016. p. 18-21.

12. Homkong P, Bender JB, Chutipongvivate P, Punyapornwithaya V, Yano T, Kreausukon K. Detection of multi-drug resistant bacterial recovered in a community animal control setting. Asian Journal of Animal and Veterinary Advances. 2017;12:109-114.

13. Vasseur PB, Levy J, Dowd E, Eliot J. Surgical wound infection rates in dogs and cats. Data from a teaching hospital. Vet Surg. 1988 Mar-Apr;17(2):60-4.

14. Rutala WA, Weber DJ, the Healthcare Infection Control Practices Advisory Committee. Guideline for disinfection and sterilization in healthcare facilities, 2008. 2017 Feb 15 [cited 2018 Dec 5]. <https://www.cdc.gov/infectioncontrol/pdf/guidelines/disinfection-guidelines.pdf>.

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An Enterovirus Outbreak Associated with Probable Rhombencephalitis in a Nursery, Tak Province, Thailand, 2017

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Abstract

On 4 Sep 2017, the Bureau of Epidemiology received a notification from Tak Provincial Health Office on an outbreak of hand, foot and mouth disease (HFMD) at a nursery following one death at the provincial hospital. An investigation was carried out to confirm the diagnosis and identify source of infection. Active case finding was performed in the nursery, index case's house and community. Medical records were reviewed, and children, teachers and household members of the index case were interviewed. Confirmed cases were defined as children or teachers in the nursery, household members and neighbors of the index case who was found to have enterovirus from fresh stool or nasopharyngeal/throat swab by polymerase chain reaction. Total 30 cases were identified, including nine confirmed, one probable (index case) and 20 suspected cases. The overall attack rate was 51.7% and case fatality proportion was 3.3%. There were 26% of enterovirus 71, 13% of coxsackie B4 identified from fresh stool samples of symptomatic cases. Neither samples from asymptomatic close contact or nasopharyngeal/throat swab was positive. No residual chlorine in the supplied water at the nursery was detected. We recommended hand washing with soap, wash the toys more than once a week, chlorinate the water to more than 0.5 ppm and increase awareness of enterovirus infection to early detect the outbreak.

Keywords: Hand, foot and mouth disease, enterovirus, rhombencephalitis, nursery

Introduction

Enteroviruses are ribonucleic acid (RNA) viruses of the family Picornaviridae.[1,2] They are non-enveloped viruses that resist pH 3-10, lipid, ether, chloroform and alcohol. They can be inactivated by temperatures above 50°C, ionizing radiation, formaldehyde and phenol. While enteroviruses are transmitted mainly via the fecal-oral route, it can also be spread by respiratory secretion.[3] At present, no specific treatment is available for an enteroviral infection.[4]

Enteroviruses can cause various clinical manifestations from asymptomatic (50-80%) to respiratory tract infections, hand, foot and mouth disease (HFMD), herpangina, acute gastroenteritis. Severe neurological complications can occur with aseptic meningitis or encephalitis such as rhombencephalitis, especially after enterovirus serotype 71 (EV71) infection [5,6,7].

EV71 has been reported as the causative agent in several outbreaks of HFMD in Asia during 1997-2008.[8-14] In Thailand, EV71 was first isolated during 1998 and as it can cause severe manifestation, a surveillance system for EV71 was established in the Bureau of Epidemiology (BOE) by including HFMD as a notifiable disease since 2001[6]. In addition, severe cases of HFMD who need admission in hospital or fatal cases must be fully investigated and isolated for EV71. On 31 Aug 2017, one suspected enterovirus infection who visited Bantak Hospital was referred and died at Somdejphrajaotaksin Maharaj Hospital. Subsequently, an outbreak of HFMD was detected at a nursery and this event was notified to BOE on 4 Sep 2017. Thus, officers from BOE, Office of Disease Prevention and Control 2 and provincial health office jointly investigated the event during 5-12 Sep 2017. Our objectives were to confirm an outbreak of enterovirus infection, describe epidemiological characteristics of the outbreak, identify the source of infection and provide recommendations to control the outbreak.

Methods

A descriptive study was performed. The situation of HFMD in Thailand during 2012-2016 was retrieved from the national surveillance data in BOE. The HFMD situation in Bantak District, especially in Thong Fah Subdistrict, during 8 Aug-8 Sep 2017 was also assessed in the hospital database by international classification of diseases (ICD) 10 codes of B08.4 (HFMD), B08.5 (Herpangina), B08.8 (Other specified viral infections characterized by skin and mucous membrane lesions), G04 (Encephalitis) and J81 (Pulmonary edema).

Moreover, medical records of the index case in Bantak Hospital and Somdejphrajaotaksin Maharaj Hospital were reviewed for clinical manifestations, disease progression and laboratory findings. Children and teachers at the nursery, and the index case's household members were interviewed for demographic information, clinical manifestation, vaccination, travel history, behavior, sanitation and activities. Active case finding was performed at the nursery and index case's house using a modified investigation form.

The index case was the dead case who was suspected of enterovirus infection on 31 Aug 2017 and led to the investigation. Household members were the index case's family members who had an epidemiological linkage with the index case. Neighbors were people who lived in the neighborhood around 500 meters radius of the index case's house and shared activities with the index case. Contacts were anyone who had shared activities with the index case at home or nursery.

Suspected enterovirus cases were defined as children or teachers in the nursery, household and neighbors of the index case who had at least one of following symptoms during 8 Aug to 8 Sep 2017: rash/vesicles on at least one site of palm, oral cavity, sole or buttock; or upper respiratory infection (URI) symptoms of cough, runny nose or sore throat. Probable cases were suspected cases with severe neurological or cardiopulmonary symptoms, yet with no enterovirus found by polymerase chain reaction (PCR). Confirmed cases were suspected cases who had enterovirus in fresh stool or nasopharyngeal/throat swab specimen tested by PCR for enterovirus.

Fresh stool specimens were collected from all suspected cases, and close contacts of the index case in household and classroom. The stool specimens were stored under four degrees Celsius during transportation and tested by PCR for *enterovirus* spp. The nasopharyngeal/throat swab specimens were also collected from suspected cases who had any symptoms within seven days of onset, transported by viral transport media and tested by PCR for *enterovirus* spp. All specimens were sent and tested at the National Institute of Health, Thailand.

The possible risk factors of enterovirus infection were analyzed by odds ratio (OR) and 95% confidence interval (CI) using Epi Info version 7.2.1.0[15].

In addition, an environmental study was conducted at the nursery and index case's house by a walk-through survey and discussion with teachers in the nursery and household members.

Results

Situation of HFMD in Bantak District and Thailand

Reports of HFMD in BOE[16] were retrieved on 19 Oct 2017, and HFMD reports from Bantak District Hospital in Tak Province were accessed on 6 Sep 2017. The situation of HFMD in Bantak District was similar to the national reports by months during 2012-2017, with the peak in June and July. There were 1-3 deaths per year (Figures 1 and 2).

Investigation of Index Case

The index case lived in Bantak District, Tak Province. She was three years old, with complete vaccination from the national program and no underlying diseases. Prior to her disease onset, she did not go anywhere, except attending classroom 2 at a nursery in Thong Fah Subdistrict. She started to be sick on 29 Aug 2017 and was treated at home by her parents, presenting with fever and chills, headache, myoclonus at extremities, abdominal pain, nausea and vomiting. On 31 Aug 2017, she was treated at Bantak District Hospital and referred to Somdejphrajaotaksin Maharaj Hospital where she was admitted. At night, as she developed vesicles at palms and soles, physician diagnosed as HFMD and gave supportive treatment.

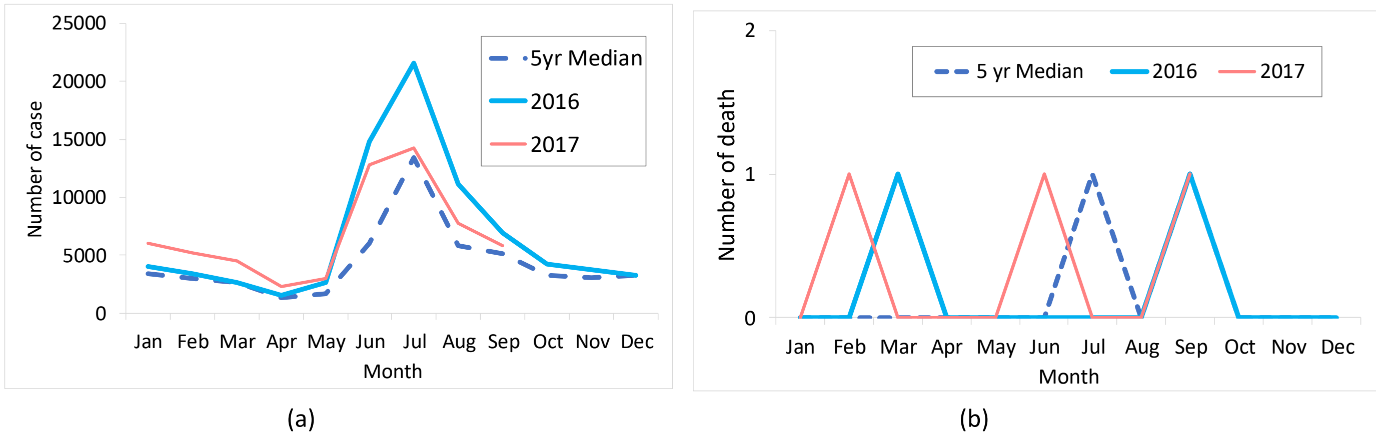


Figure 1. Cases (a) and deaths (b) of hand, foot and mouth disease by months reported to the national disease surveillance system in Bureau of Epidemiology, 1 Jan 2012-19 Oct 2017

On 2 Sep 2017, she suddenly developed dyspnea, tachycardia, hyperglycemia, pink frothy sputum and cardiac arrest, and died. Her chest x-ray finding showed cardiomegaly with patchy infiltration in both lungs. Although the *enterovirus* spp. was not detected by PCR in the stool specimen collected on 2 Sep 2017, her final diagnosis by a pediatrician at the hospital was EV71 infection with HFMD.

Active Case Finding

In the nursery, the children were divided into three classrooms by age groups, with two teachers per classroom. All six teachers and 40 (88.9%) out of 45 children were screened, and 25 suspected cases were identified. Among 12 household members and neighbors, four suspected cases were detected. However, there was no other case in the community. By reviewing ICD10 code at Bantak Hospital, three suspected cases were found. However, they were not linked with the index case.

Out of total 29 suspected cases, 23 fresh stool samples and nine nasopharyngeal/throat swab samples were collected to test for enterovirus. In addition, nine fresh stool samples were collected from asymptomatic household contacts. There were 26.1% (6/23) of EV71, and 13.0% (3/23) of coxsackie B4 confirmed from fresh stool specimens of the suspected cases. Neither fresh stool nor nasopharyngeal/throat swabs from asymptomatic close contact was positive for enterovirus infection (Figure 3).

Epidemiological Characteristics

There were 30 cases identified in this study, including six EV71, three coxsackie B4, one probable case (index case) and 20 suspected cases. The case fatality proportion was 3.3% (1/30).

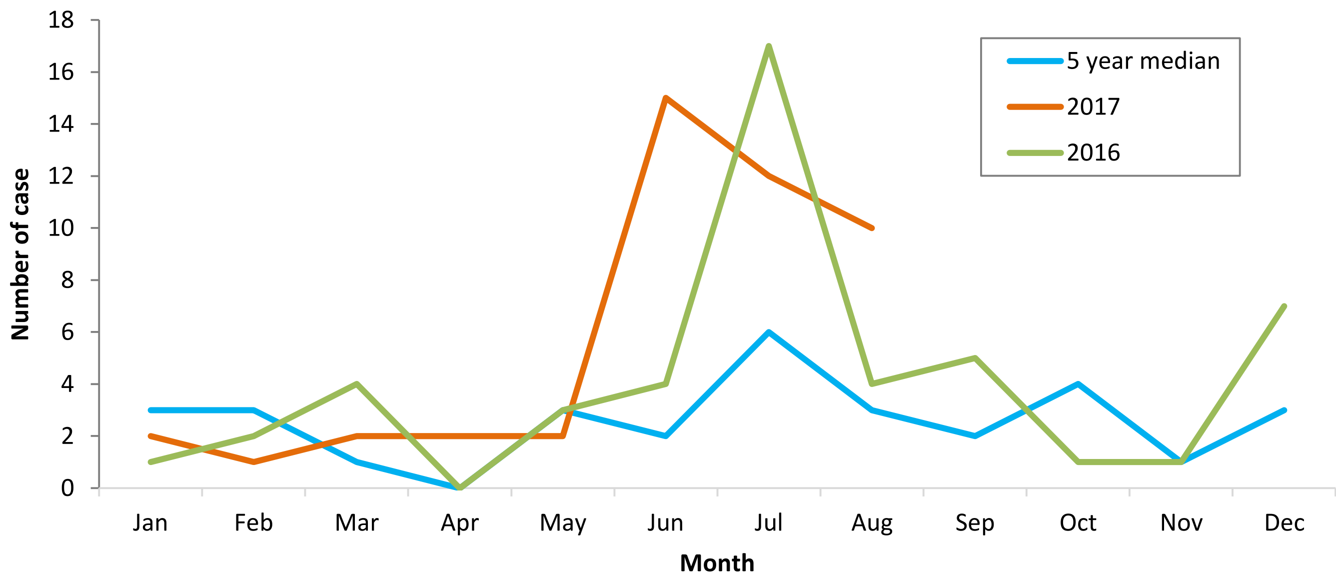
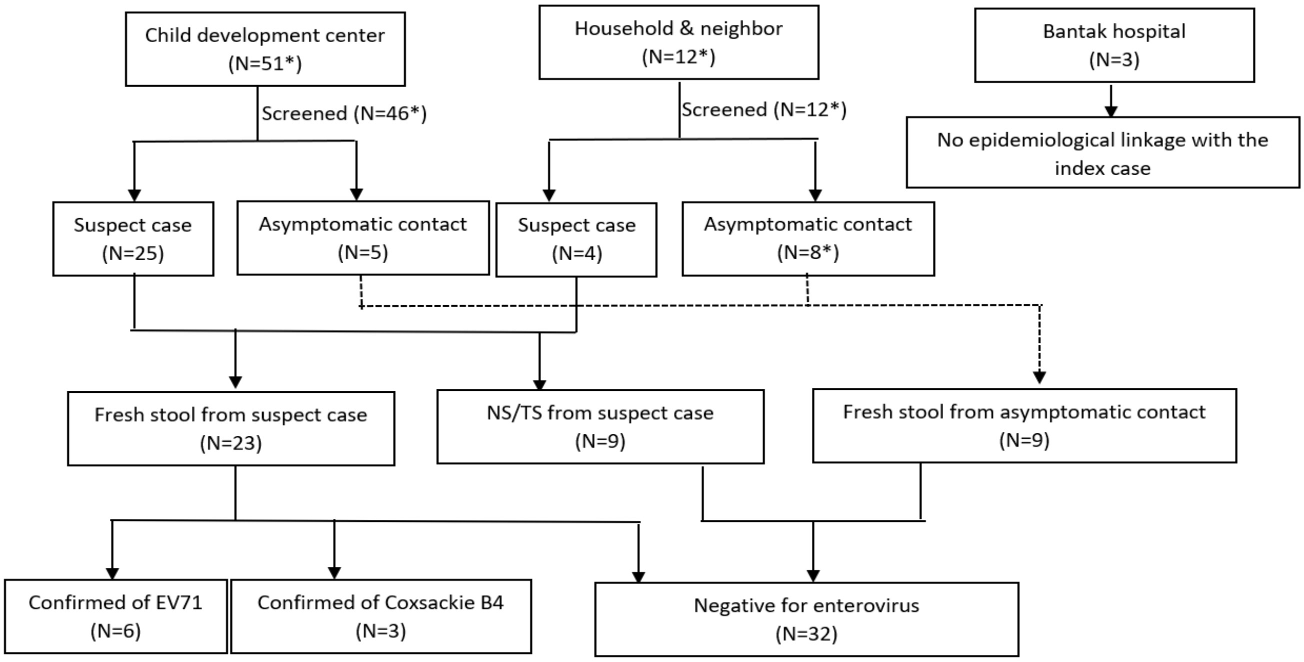


Figure 2. Hand, foot and mouth cases by months identified in Bantak District, Tak Province, Thailand, 1 Jan 2012-6 Sep 2017



* One case was counted as both a student in the nursery and a neighbor.

Figure 3. Active case finding from hand, foot and mouth outbreak in Bantak District, Tak Province, Thailand, 2 Aug-18 Sep 2017

Clinical manifestations of cases were URI symptoms 83.3% (25/30), vesicle/rash 46.7% (14/30) and fever 50.0% (15/30). One third (36.7%) of cases had URI symptoms only. Cardiopulmonary and neurological symptoms were only found in the dead case. All EV71 cases had vesicle/rash (6/6). However, coxsackie B4 cases had URI symptoms (100%), and vesicle/rash (33.3%) (Figure 4).

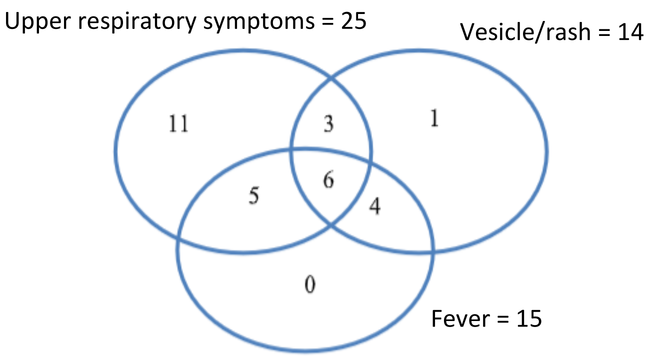


Figure 4. Distribution of enterovirus cases by clinical manifestations in Bantak District, Tak Province, Thaialnd, 2 Aug-18 Sep 2017

The first case in the index case's house had oral ulcer on 8 Aug 2017, yet we could not collect his fresh stool specimen for testing. The first case at the nursery developed fever, vesicle and URI symptoms in classroom 2 on 16 Aug 2017, and subsequently, the infection spread in the nursery with seven more cases. Therefore, the nursery was closed during 24 Aug-10 Sep 2017 to disinfect the contaminated surface by 1% sodium hypochlorite at least 15 minutes and dry the non-washable items under the sun (Figure 5).

The overall attack rate was 51.7% (30/58). The specific attack rate was higher in males (53.3%, 16/30) and children aged 2-5 years old (67.5%, 27/42). The specific attack rate in the classrooms was 72.7% (10/19) for classroom 1, followed by 70.0% (7/10) for classroom 2 and, 52.6% (10/19) for classroom 3 (Table 1). The median age was three years and six months (range 8 months to 60 years). Children aged 2-5 years old had odds of getting the infection for 7.8 times compared with adults over 15 years (95% CI = 1.9-31.8).

Environmental Results

In general, the nursery was observed to be in good sanitation. There were three classrooms: classrooms 1 and 2 were closely located while classroom 3 was in another building. Density of the classrooms included 4.9, 3.3 and 2.8 m^2/person. The residual chlorine in drinking water and water supply was 0.5 ppm and zero respectively. There were four toilets for girls, four toilets for boys and one common washing room.

Interview with teachers revealed that all children had their own drinking glasses. Children washed hands with soap before and after lunch, and after using toilet, yet they used the same towel. They usually washed toys once a week. Alcohol gel was provided by the local public health team as an outbreak response.

The index case lived only with her parents. Although they used the serving spoons for meals, they shared the drinking glass. She played with only one neighbor who was also attending in the same nursery. She went to the nursery with the private vehicle in routine.

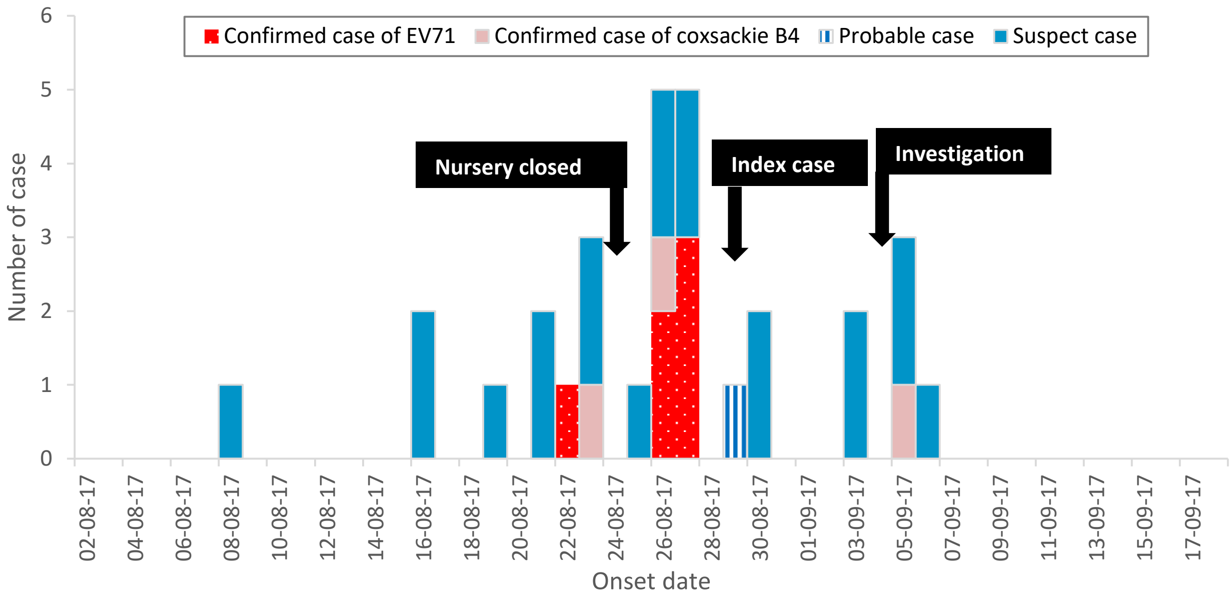


Figure 5. Enterovirus cases by dates of onset in Bantak District, Tak Province, Thailand, 2 Aug-18 Sep 2017

Table 1. Specific attack rates by gender, age and place of an enterovirus outbreak in Bantak District, Tak Province, Thailand, 2 Aug-18 Sep 2017

Characteristic	Total	Number of case	Attack rate (%)
Gender			
Male	30	16	53.3
Female	28	14	50.0
Age (year)			
Child (2-5)	42	27	64.3
Adult (>15)	16	3	18.8
Place			
Nursery	47*	26*	55.3
Index case's house	12*	5*	41.7
Total	58	30	51.7

Discussions

This event was considered as an enterovirus outbreak, as 26.1% of the sampled cases were found to be with EV71 and 13.0% were with coxsackie B4 infection. This implied that multiple species were circulating in the area. This outbreak occurred in August 2017, the rainy season of Thailand, which was consistent with the fact that enteroviral infections appear to peak in the rainy and cold seasons.[17] Our study found that the children aged 2-5 years old posed a higher risk for getting infected with enteroviruses compared to adults, which was consistent with the prior reports[18].

A sensitive case definition, ranged from vesicle or rash to URI, neurological and cardiopulmonary symptoms, was used in this outbreak. As enterovirus infection can demonstrate a wide range of clinical presentations,[3] cases with mere URI symptoms were also included as suspected enterovirus infection. A study by Christy SS and Christine ML remarked that the most common pathogens of respiratory tract infection were rhinovirus and enterovirus, accounting for 25.4%[19].

HFMD outbreaks from EV71 are commonly reported in Thailand. An annual report of Thai National Institute of Health during 2016 showed that 19% of HFMD samples were found to have enterovirus and EV71 was found in 32% of the positive samples.[20] Moreover, there were reports of patients developed rhombencephalitis after experiencing several days of HFMD, herpangina or febrile illness. Some developed cardiopulmonary failure and died rapidly despite intensive management.[21,22] In this event, although six EV71 cases and two coxsackie B4 cases at the nursery developed illness prior to the index case, all cases were mild and went to private clinics. Hence, the outbreak at the nursery was unnoticeable by teachers and health care workers. However, a previous study reported that patients with coxsackie B infection were likely to have a higher hospital admission rate and central nervous system involvement while the most common serotypes were coxsackie A16 and B3.[23]

Rhombencephalitis refers to inflammation of the brainstem and cerebellum. It is a recognized complication of enteroviral infection and patient may progress rapidly from intact mental status to death, experiencing in sympathetic overstimulation associated with tachycardia, hyperglycemia and pulmonary edema due to pulmonary vasoconstriction.[6,24] The index case was classified as a probable case of enterovirus infection due to her clinical manifestations compatible with enterovirus rhombencephalitis as well as epidemiological linkage with the confirmed cases at the nursery. However, the virological etiology of the index case remained unclear as a stool sample was obtained prior to death, instead of throat swab. In the early stage of EV infection like this case, the testing results of rectal swab could be less sensitive[25] while the throat swab samples could provide a higher positive rate[26].

The World Health Organization has recommended intravenous immunoglobulin (IVIG) in patients with encephalitis and acute flaccid paralysis. Although the use of IVIG has not yet been supported with evidences from randomized clinical trials,[27] anecdotal experiences in Asia suggested that if IVIG administered early, it could limit disease progression to affect autonomic nervous system and subsequent pulmonary edema. In Thailand during 2012, two EV71 cases with neurologic involvement were treated with IVIG and both survived.[28] However, in 2015, there was a cluster of echovirus 6 infections with an encephalitis death, to whom IVIG was not administered.[29] According to the national guidelines, administration of IVIG is recommended in the acute phase of Kawasaki disease, severe Guillain-Barré syndrome and myasthenia crisis while application in other indications depends on the physician's judgment and patients must bear the related expenses.[30]

Limitations

There was no specimen available to confirm etiology in the dead case such as pair serum for enterovirus, cerebrospinal fluid for PCR (sensitivity 76-100%)[25], or brain or heart necropsy.

In term of behavioral risk for disease transmission, the information was acquired by interviewing the teachers since the nursery was closed during the investigation. In addition, recall bias on information from parents might exist for clinical illness of their children. Since behavioral risk factors were difficult to be ascertained in toddlers, the analytic study was not performed.

Conclusion and Recommendations

Almost all enterovirus cases found in this outbreak were children. The pathogens were identified as EV71 and coxsackie B4. To control these pathogens, sanitation is crucial[19]. To reduce incidence, control measures should be intensified. Firstly, since alcohol gels cannot inactivate the enterovirus,[1] washing hand with soap at least 20 seconds before and after eating, and after using the toilet should be emphasized[31]. Furthermore, as children with HFMD might have drooling due to painful swallowing, toys should be washed every day to control this disease. Chlorinating the water supply in Tong Fha Subdistrict should be carried out through collaboration with Provincial Waterworks Authority to ensure the residual chlorine level at 0.5 ppm for inactivation of enterovirus[32]. Lastly, serotypes of enterovirus should be isolated to increase awareness on HFMD with neurological complications and administration of IVIG should be considered.

Control Measures and Follow up

The local surveillance and rapid response team provided health education to teachers, household members and villagers about the disease, personal hygiene and hand washing. Isolation of sick children were recommended if their parents could not take them back to home immediately.

Following the recommendations by the investigation team on 6 Sep 2017, screening and control measures were monitored at the nursery until 22 Sep 2017 when no more ill children were detected. For sanitation, the children washed their hands with soap under supervision of the teachers and they had their own towels. The drinking glasses were cleaned and non-washable items (nap mats, toys, books) were dried under the sun to disinfect every day.

Acknowledgement

We thank all staff at the nursery, Bantak District Hospital, Bantak District Health Office, Somdejphrajaotaksin Maharaj Hospital, Tak Provincial Health Office and Office of Disease Prevention and Control 2 for their valuable support in various activities that lead to our accomplishment in the investigation. We are also grateful to Dr. Chuleeporn Jiraphongsa for providing advice and critically reviewing the manuscript.

Suggested Citation

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References

1. Chatproedprai S, Theanboonlers A, Korkong S, Thongmee C, Wananukul S, Poovorawan Y. Clinical and molecular characterization of hand-foot-and-mouth disease in Thailand,

2008-2009. Jpn J Infect Dis. 2010 Jul;63(4):229-33.

2. Shikha J, Bhupeswari P, Girish CB. Enteroviral encephalitis in children: clinical features, pathophysiology, and treatment advances. Pathog Glob Health. 2014 Jul;108(5):216-22.

3. Robert AS. Enteroviruses. 2017 Feb 8 [cited 2017 Oct 19]. <https://emedicine.medscape.com/article/217146-overview#a5>.

4. Nicholas JB. Pediatric enteroviral infections treatment and management. 2017 Jun 16 [cited 2018 Jan 24]. <https://emedicine.medscape.com/article/963637-treatment>.

5. Lo CW, Wu KG, Lin MC, Chen CJ, Ho DM, Tang RB, et al. Application of a molecular method for the classification of human enteroviruses and its correlation with clinical manifestations. J Microbiol Immunol Infect. 2010 Oct;43(5):354-9.

6. Buathong R, Hanshoaworakul W, Sutdan D, Iamsirithaworn S, Pongsuwanna Y, Puthawathana P, et al. Cluster of fatal cardiopulmonary failure among children caused by an emerging strain of enterovirus 71, Nakhorn Ratchasima Province, Thailand, 2006. OSIR. 2008 Aug;1(1):1-3.

7. Kogon A, Spigland I, Frothingham TE, Elveback L, Williams C, Hall CE, et al. The virus watch program: a continuing surveillance of viral infections in metropolitan New York families. VII. Observations on viral excretion, seroimmunity, intrafamilial spread and illness association in coxsackie and echovirus infections. Am J Epidemiol. 1969 Jan;89(1):51-61.

8. Shekhar K, Lye MS, Norlijah O, Ong F, Looi LM, Khuzaiah R, et al. Deaths in children during an outbreak of hand, foot and mouth disease in Peninsular Malaysia--clinical and pathological characteristics. Med J Malaysia. 2005 Aug;60(3):297-304.

9. Wang JR, Tuan YC, Tsai HP, Yan JJ, Liu CC, Su IJ. Change of major genotype of enterovirus 71 in outbreaks of hand-foot-and-mouth disease in Taiwan between 1998 and 2000. J Clin Microbiol. 2002 Jan;40(1):10-5.

10. Fujimoto T, Chikahira M, Yoshida S, Ebira H, Hasegawa A, Totsuka A, et al. Outbreak of central nervous system disease associated with hand, foot, and mouth disease in Japan during the summer of 2000: detection and molecular epidemiology of enterovirus 71. Microbiol Immunol. 2002;46(9):621-7.

11. Shah VA, Chong CY, Chan KP, Ng W, Ling AE. Clinical characteristics of an outbreak of hand, foot and mouth disease in Singapore. Ann Acad Med Singapore. 2003 May;32(3):381-7.

12. Chong CY, Chan KP, Shah VA, Ng WY, Lau G, Teo TE, et al. Hand, foot and mouth disease in Singapore: a comparison of fatal and non-fatal cases. Acta Paediatr. 2003 Oct;92(10):1163-9.

13. Zhang Y, Tan XJ, Wang HY, Yan DM, Zhu SL, Wang DY, et al. An outbreak of hand, foot, and mouth disease associated with subgenotype C4 of human enterovirus 71 in Shandong, China. J Clin Virol. 2009 Apr;44(4):262-7. Epub 2009 Mar 9.

14. Yang F, Ren L, Xiong Z, Li J, Xiao Y, Zhao R, et al. Enterovirus 71 outbreak in the People's Republic of China in 2008. J Clin Microbiol. 2009 Jul;47(7):2351-2. Epub 2009 May 13.

15. Centers for Disease Control and Prevention. Epi Info [cited 2017 Oct 19]. <http://wwwn.cdc.gov/epiinfo/html/prevVersion.htm>.

16. Thailand. Bureau of Epidemiology. Department of Disease Control. Ministry of Public Health. Annual Epidemiological Surveillance Report 2012-2016. Nonthaburi: Bureau of Epidemiology, Thailand; 2017. Thai.

17. Samphutthanon R, Tripathi NK, Ninsawat S, Duboz R. Spatio-temporal distribution and hotspots of hand, foot and mouth Disease (HFMD) in northern Thailand. Int J Environ Res Public Health. 2013 Dec 23;11(1):312-36.

18. Centers for Disease Control and Prevention. Enterovirus. 2015 Nov 9 [cited 2018 Jan 25]. <https://www.cdc.gov/features/evd68/index.html>.

19. Christy SS, Christine ML. The epidemiology of upper respiratory infections at a tertiary care center: prevalence, seasonality, and clinical symptoms. Journal of Respiratory Medicine. 2014 Jun [cited 2018 Jan 30]. <https://www.hindawi.com/journals/jrm/2014/469393/cta/>.

20. Thailand. National Institute of Health. Department of Medical Sciences. Annual report 2016. Nonthaburi: National Institute of Health, Thailand; 2017.

21. Ho M, Chen ER, Hsu KH, Twu SJ, Chen KT, Tsai SF, et al. An epidemic of enterovirus 71 infection in Taiwan. Taiwan Enterovirus Epidemic Working Group. N Engl J Med. 1999 Sep 23;341(13):929-35.

22. Huang CC, Liu CC, Chang YC, Chen CY, Wang ST, Yeh TF. Neurologic complications in children with enterovirus 71 infection. N Engl J Med. 1999 Sep 23;341(13):936-42.

23. Yen FB, Chang LY, Kao CL, Lee PI, Chen CM, Lee CY, et al. Coxsackieviruses infection in northern Taiwan--epidemiology and clinical characteristics. J Microbiol Immunol Infect. 2009 Feb;42(1):38-46.

24. Modlin JF, Dagan R, Berlin LE, Virshup DM, Yolken RH, Menegus M. Focal encephalitis with enterovirus infections. Pediatrics. 1991 Oct. 88(4):841-5.

25. Centers for Disease Control and Prevention. Specimen collection, storage, and shipment. 2018 Jun 26 [cited 2018 Sep 20]. <https://www.cdc.gov/non-polio-enterovirus/lab-testing/specimen-collection.html>.

26. Li JX, Meng FY, Liang ZL, Mao QY, Zhu FC. How to understand the efficacy measurements for enterovirus type 71 vaccine? Hum Vaccin Immunother. 2014;10(3):623-7. Epub 2013 Nov 26.

27. World Health Organization. A guide to clinical management and public health response for hand, foot and mouth disease (HFMD). Geneva: World Health Organization; 2011. p.41.

28. Puenpa J, Chieochansin T, Linsuwanon P, Korkong S, Thongkomplew S, Vichaiwattana P, et al. Hand, foot, and mouth disease caused by coxsackievirus A6, Thailand, 2012. Emerg Infect Dis. 2013 Apr;19(4):641-3.

29. Rattanathumsakul T, Bunthanapat N, Suwanchairob O, Saksirisampan B, Buathong R, Tantiworrawit P. An investigation of a cluster of echovirus 6 infection with an encephalitis death in Samut Prakan Province, Thailand, 2015. OSIR. 2017 Dec;10(4):9-16.

30. Thailand. Food and Drug Administration. Ministry of Public Health. Guideline of using human normal immunoglobulin, intravenous (IVIG). 2012 Feb 09 [cited 2018 Jan 30]. Thai. <http://drug.fda.moph.go.th:81/nlem.in.th/node/5101>.

31. Taiwan Centers for Disease Control. Press releases. 2016 Jul 5 [cited 2017 Oct 19]. <https://www.cdc.gov.tw/english/info.aspx?treeid=bc2d4e89b154059b&nowtreeid=ee0a2987cfba3222&tid=7D0A5B57E6C68859>

32. Melnick JL., Enterovirus. In: Evans AS, editor. Viral infections of humans: epidemiology and control. New York: Plenum Publishing Corporation; 2013 Nov 11. p. 197.

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Systemic Investigation of Dengue Incidence and Control Measures in Surin, Thailand, 2018

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Abstract

This study aimed to explore the situation of dengue outbreak in Surin, a province in the Northeast of Thailand, and its control measures, and determine the association between entomological indices and dengue incidence in 2018. A cross-sectional mixed-methods design was used. Document review, primary survey and in-depth interviews were performed. A survey was conducted in 17 subdistricts. Descriptive statistics and multivariable Poisson regression were exercised in quantitative data. Thematic coding was applied in qualitative data. The attack rate between 1 January 2018 and 28 July 2018 was 72.3 cases per 100,000 population. The outbreak was pronounced during June-July 2018, with no reported deaths. Most cases were children aged below 15 years. Dengue fever was the most common diagnosis. The survey found positive association between Breteau index and attack rate. Regarding control measures, most fogging used a single chemical instead of mixed chemicals. Some local providers flagged difficulties in operationalizing the control measures, resulted from resource-mobilization constraints and opposition from some local inhabitants. Intensifying larva elimination campaigns and switching the fogging method from single chemical to mixed chemicals were recommended. A participatory public policy process should be initiated to identify effective vector-control strategies that are in line with the inhabitants' living norms.

Keywords: Dengue, system investigation, Breteau index, house index, container index, integrated vector management

Introduction

Dengue has been one of the key global public health threats for years.[1,2] It is caused by any of four dengue virus serotypes (DENV 1, 2, 3 and 4) and transmitted by *Aedes* mosquitoes. The most prevalent vector is *Aedes aegypti*, which is usually found in urban environment.[3] The spectrum of illness ranges from a mild non-specific febrile syndrome to classic dengue fever (DF), to more severe forms like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[4] The World Health Organization (WHO) estimated that about 100 million dengue infections occurred annually.[5]

For Thailand, the first case of dengue was reported in 1949. The reported cases increased enormously, varying around 50,000-150,000 each year.[6] With the increasing trend, dengue surveillance was later incorporated into the national surveillance system led by the Bureau of Epidemiology (BOE), the Ministry of Public Health (MOPH). Providers in public facilities are obliged to report all suspected and confirmed cases to the national R506 surveillance system.[7]

One of the most widely recognized dengue-control strategies is the '3/3/1 measures', proclaimed by the MOPH in 2013.[8] The term '3/3/1' denotes timely notification to local providers within 'three hours' after diagnosis, early elimination of sources within 'three hours' after notification, and cutting transmission by various means within 'one day' after notification. Moreover, currently, it is recommended that all control measures should be in line with the integrated vector management (IVM), proposed by the WHO in 2001, which focuses on optimal use of resources on the bases of social mobilization and mutual participation amongst stakeholders.[9]

The success of larva control can be assessed by several indicators. House index (HI) and Breteau index (BI) have been the most widely used indices worldwide.[10] Some literature recommends container index (CI) to assess transmission risk.[11] In Thailand, CI and HI are more recognized than BI in the wider public. The Thai MOPH sets the cutoffs at 10% for HI and 50 for BI to identify high risk areas, and recommends the cut-off at 0% for CI in highly populated areas, such as schools and temples.[12,13]

In 2018, Thailand faced dengue outbreaks in many provinces. As of July 2018, total number of cases nationwide was 37,793 (attack rate 57.8 cases per 100,000 population).[14] Surin, a province in the northeast, is one of the most affected areas. The outbreak was pronounced in six districts (Buachet, Chumpolburi, Kapchoeng, Prasart, Samrongthap and Thatum), especially during June-July 2018 (epidemiological weeks 23-30). The Office of Disease Prevention and Control Region 9 (ODPC 9) reported the BOE about the uncontrolled dengue epidemic in Surin. The BOE then initiated the investigation for dengue outbreak in Surin. This investigation was not performed on a case-by-case basis. In contrast, the study performed as a systemic investigation over the whole province. Hence, the objectives of this study were to describe the situation of dengue epidemic and its control measures in Surin, determine association between larva indices and dengue epidemic, and identify challenges in implementing dengue control measures through local providers' perspectives.

Methods

A cross-sectional mixed-methods design (comprising qualitative and quantitative approaches) was used. The study was conducted in Surin between 30 Jul and 4 Aug 2018 by the joint investigation team, comprising staff from the BOE, the District Health Office, the Provincial Health Office, and the ODPC 9.

The first objective was achieved through document review and secondary data analysis. The analysis was divided into outbreak situation and control measures. For outbreak investigation, individual records diagnosed with dengue (either DF, DHF or DSS) since 1 Jan 2018 were obtained from the R506 report. The case definition followed the reporting guideline of BOE.[15] Demographic data were analyzed by descriptive statistics. For control measures, the main data collection technique was document review on prior reports of the Vector Borne Diseases Control Center (VBDC), ODPC 9. The report was part of the routine operations in VBDC, comprising control-measures data in 16 target subdistricts. The target subdistricts were areas where cases within a week outnumbered the last 5-year median; and when counted back to the past four consecutive weeks, there was no any single week containing the case volume smaller than the last 5-year median. Moreover, Mueang (headquarter) district was used as a case study to assess the relationship between IVM and the outbreak. Of 21 subdistricts in Mueang district, four of them implemented IVM. Univariable Poisson regression was applied to determine the effect of IVM on the outbreak. Attack rate during June-July 2018 served as a dependent variable. The presence of IVM served as independent variable. Incidence rate ratio (IRR) and 95% confidence interval (95% CI) were presented.

The second objective involved both primary and secondary data collections. The fieldwork was conducted in six epidemic districts. The term epidemic was defined as the number of cases during epidemiological weeks 27-30 larger than the last 5-year median. Unit of analysis was subdistrict. The number of selected subdistricts was basically set at 17 based on feasibility of human resources and time. Within these six districts, there were 59 subdistricts. Thirty five of them met the epidemic definition. Then simple random sampling with probability proportional to size was applied. As a result, 11 out of 35 epidemic subdistricts and six out of 24 non-epidemic subdistricts were randomly selected. In each subdistrict, reports of dengue cases at the health center and prior larva survey by village health volunteers were explored.

The research team also conducted on-site survey on larva indices in 20 randomly selected households per subdistrict. The survey started from the subdistrict center. Then the team performed a random walk towards the edge of each subdistrict. The households were selected in alternate fashion. Descriptive statistics and multivariable Poisson regression were applied. The dependent variable was attack rate between 1 and 30 Jul 2018, while the independent variables were BI reported a month earlier (3-30 Jun 2018) and BI from the fieldwork (spot survey). BI was used instead of CI and HI because it captures information from containers and households altogether.[16] The analysis was adjusted for prior attack rate, one month before the survey. Adjusted IRR and 95% CI were displayed.

For the third objective, unstructured informal interviews with local health staff in each subdistrict were performed plus in-depth interviews with two local providers from two epidemic subdistricts. Each interview lasted around 30 minutes and took place at the Surin Provicial Health Office. The question guides focused on challenges and experiences in implementing control measures from providers' experiences. The interviews were analyzed by inductive thematic coding. Summary of the methods is demonstrated in figure 1.

As this study was part of the regular operation of the BOE, it did not require approval from the Ethics Committees of the MOPH and consent to participate was not needed. However, the study had strictly followed confidential requirement as per conventional ethical standards.

Results

Situation of Dengue Epidemic and Control Measures

A total of 1,009 cases were diagnosed with dengue in Surin, between 1 Jan and 28 Jul 2018 (attack rate 72.3 cases per 100,000 population). Dengue cases were distributed all over Surin and especially in Meung District (Figure 2). No patients passed away from dengue.

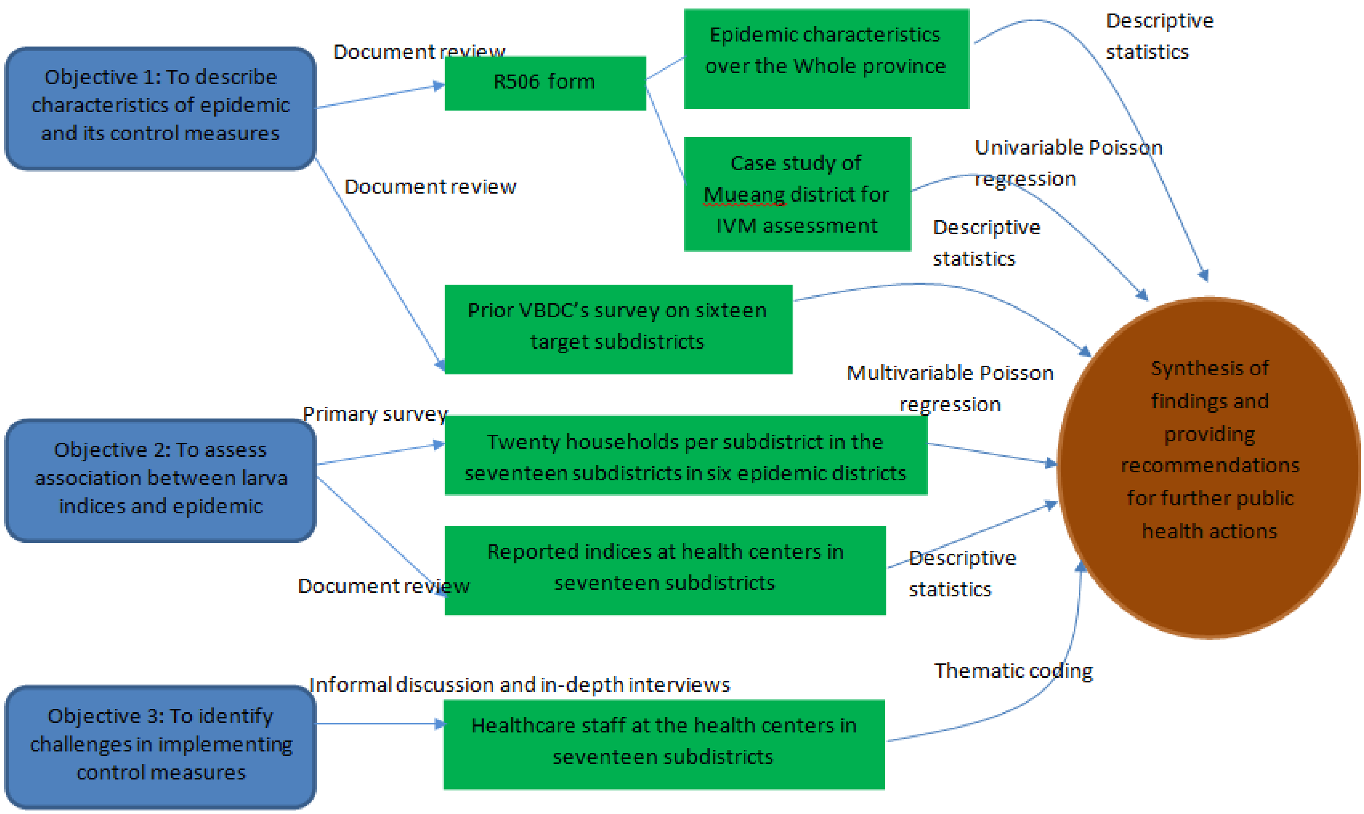

Figure 1. Summary diagram of the data collection techniques and data analysis

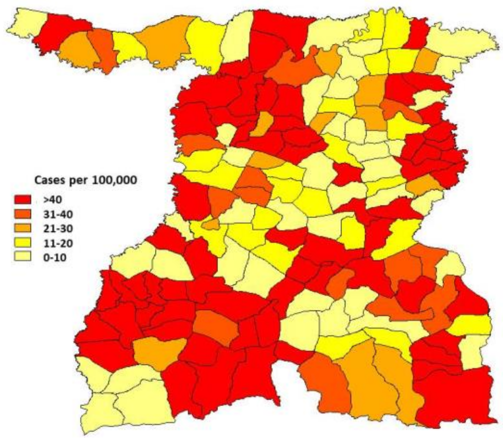

Figure 2. Distribution of dengue cases in subdistricts of Meuang District, Surin Province, Thailand, June-July 2018

The outbreak was pronounced during June-July 2018. That period accounted for about 67.1% (677/1,009) of the total cases (Figure 3).

About three-quarters (757/1,009) of the cases were diagnosed with DF. Inpatient care was the most common treatment type. Almost all (1,007/1,009) cases were Thai. Males slightly outnumbered females. Mean age and median age of the cases were 15 years and 11 years respectively (range 6 months - 89 years). The majority of cases (707/1,009) were below 16 years old. Students and children under guardian accounted for over 82.5% (832/1,009) of total cases. Gap between onset date and treatment date was three days on overage (Table 1).

Control Measures

The recent survey by the VBDC, ODPC 9 found a great variation in the completeness of each action listed in the '3/3/1 measures'. After excluding one health center with missing information, only nine (56.3%) from 16 health centers received a timely notification and performed mosquito spraying within three hours. The action completeness reduced by time as reflected by the decline of health centers performing fogging, from 75.0% (12/16) to 62.5% (10/16) in days 3 and 7 respectively. There appeared difficulty in assessing the completeness of community education. Some providers insisted that they did provide community education. However, this was done informally, instead of mass public campaign—and this was assessed as 'undetermined'. The assessment of health centers' performance in reaching CI and HI targets on day 7 also faced much difficulty due to data incompleteness and contradiction between data reported by the health centers and those reported by the VBDC (Table 2).

Concerning mosquito fogging, only three (18.8%) from 16 health centers used mixed chemicals such as deltamethrine 0.5% and piperonyl butoxide 10% while other 13 applied a single chemical. Deltamethrine 0.5% was the most commonly used (Figure 4).

Table 1. Characteristics of dengue cases in Surin Province, Thailand, January-July 2018 (n=1,009)

Characteristic	Number	Percent
Diagnosis		
Dengue fever	757	75.0
Dengue hemorrhagic fever	250	24.8
Dengue shock syndrome	2	0.2
Treatment type		
In-patient	650	64.4
Out-patient	358	35.5
Unknown	1	0.1
Race		
Thai	1,007	99.8
Non-Thai	2	0.2
Gender		
Male	510	50.5
Female	499	49.5
Occupation		
Student	676	67.0
Under guardian	156	15.5
Agriculturist	75	7.4
Manual labor	56	5.5
Others	46	4.6
Age group (year)		
Under 16	707	70.1
16-30	195	19.3
31-45	50	4.9
46-60	37	3.7
Above 60	20	2.0
Gap between dates of onset and treatment (day)		
≤1	280	27.8
>1-2	107	10.6
>2-3	223	22.1
>3-4	196	19.4
>4-5	126	12.5
>5	77	7.6

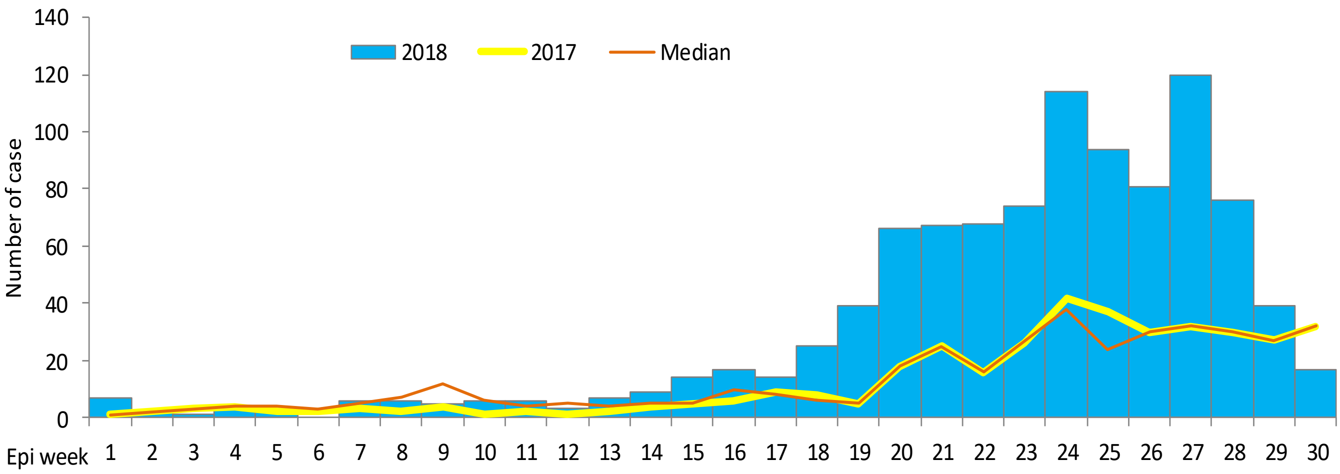

Figure 3. Epidemic curve of dengue cases in Surin Province, Thailand, January-July 2018

Table 2. Completeness of each action in the '3/3/1 measures' from the survey on 16 dengue-epidemic subdistricts, Meuang District, Surin Province, Thailand (n=16)

Day	Hour	Action	Number of health center (%)		
			With actions	Without actions	Undetermined
0	3	Reporting the presence of new case(s) to local health center's staff	9 (56.3)	1 (6.2)	6 (37.4)
0	3	Mosquito spraying at patient's house	9 (56.3)	4 (25.0)	3 (18.7)
1	-	Larva control within 100 meters from the patient's house	15 (93.8)	1 (6.2)	0 (0)
1	-	Mosquito fogging within 100 meters from the patient's house	15 (93.8)	1 (6.2)	0 (0)
1	-	Summoning villagers to undertake health education	0 (0)	0 (0)	16 (100)
3	-	Mosquito fogging within 100 meters from the patient's house	12 (75.0)	1 (6.2)	3 (18.8)
3	-	Summoning villagers to undertake health education	16 (100)	0 (0)	0 (0)
7	-	Mosquito fogging within 100 meters from the patient's house	10 (62.5)	6 (37.5)	0 (0)
7	-	Assessing CI and HI (target HI = 0 and target CI = 0)	0 (0)	0 (0)	16 (100)

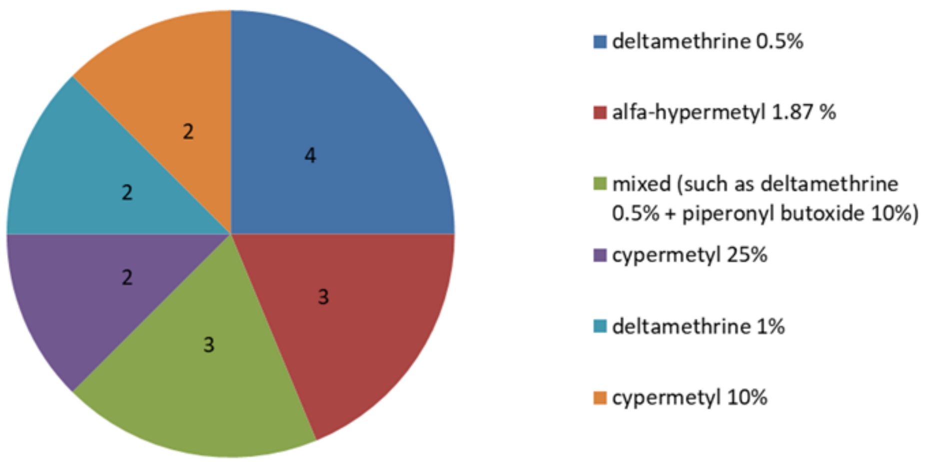

Figure 4. Number of health centers tallied by fogging chemicals in Mueang District, Surin Province, Thailand, June-July 2018 (n=16)

The case study of Mueang District revealed that smaller attack rate was found in IVM-implemented subdistricts than non-IVM subdistricts. Univariate Poisson regression showed that the presence of IVM was significantly associated with lower dengue incidence by around 28% (IRR = 0.720, 95% CI = 0.569-0.912) (Table 3).

Larva Indices and Association with Dengue Epidemic

According to the survey in 17 subdistricts, amongst all indoor containers, tile fragments had the largest CI (CI = 40.4%). For outdoor containers, garden pot saucers had the largest CI (CI = 40.0%), followed by non-specific containers and water jars (Figure 5).

Table 1. Attack rate of dengue and integrated vector management (IVM) implementation in Mueang District, Surin Province, Thailand, June-July 2018

Case per 100,000 population	IVM implemented (n=4)	Non-IVM implemented (n=17)
Mean (Standard deviation)	20.1 (15.2)	28.0 (40.6)
Median (Interquartile range)	15.2 (19.4)	13.0 (24.1)
Minimum-Maximum	8.0-42.1	0-154.0
Incidence rate ratio (95% CI) Ref = Non-IVM	0.720 (0.569- 0.912)*	

** P-value = 0.006*

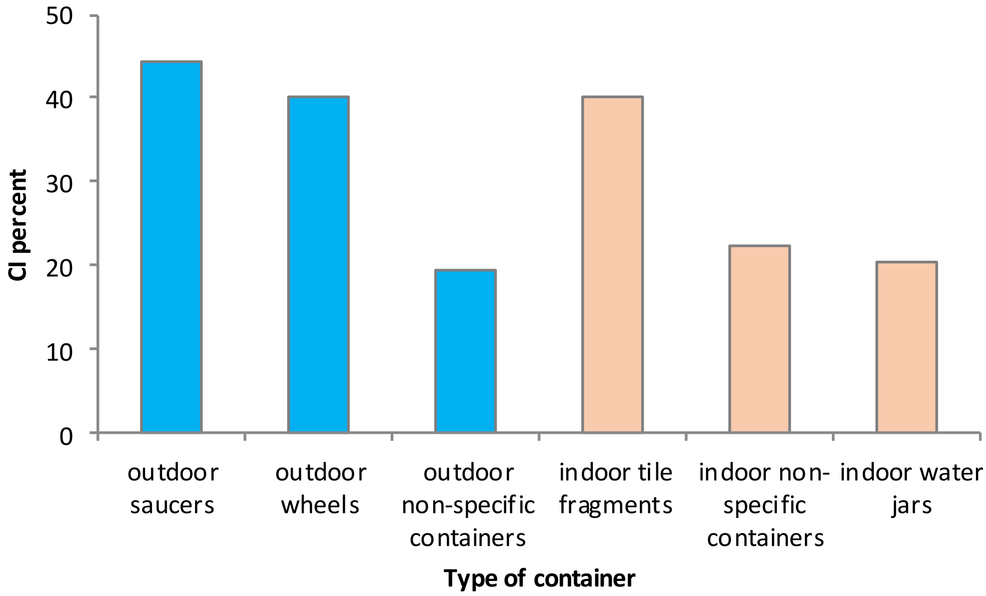

Figure 1. Top 3 containers with largest container index from the spot survey in 17 subdistricts from 6 epidemic districts, Surin Province, Thailand, July 2018

Concerning larva indices, the indices from spot survey were larger than those reported by village health volunteers. For instance, the mean spot BI was 113.1 while the mean reported BI was 25.6. The multivariable Poisson regression suggested that every unit increase in prior BI tended to enlarge the incidence in the following month by 0.4% with statistical significance (adjusted IRR = 1.004, 95% CI = 1.002-1.007). The spot BI also yielded nearly the same effect size (adjusted IRR = 1.005, 95% CI = 1.004-1.006) (Tables 4 and 5).

Challenges in Implementing Control Measures

Two main themes emerged from the interviews: resources constraints, and dissonance between control measures and living norms of inhabitants. In the first theme, most health care staff voiced their concerns towards resources mobilization and human resources constraint. Some health centers had only one professional nurse, plus few public health officers responsible for a wide range of task (not only dengue control). In addition, materials and budget are amongst the crucial issues. At present, there existed the District Health Board, serving as the main policy platform in the communities. The Board members consisted of representatives from all relevant authorities, including health facilities. This also meant a pooling of resources, including budget. Thus, the mobilization of budget to buy fogging chemicals and temephos (organophosphate larvicide) did not solely depend on the discretion of health staff. In practice, budget mobilization required approval from the Board. Thus, at times, the fogging could not be done promptly. This was because staff who initiated the fogging was local government officers whom the health sector did not have authority over.

"When there were new cases during weekend, sometimes we could not force them (local government officers) to do the fogging immediately…" a male provider in a health center, 40-50 years old

Table 4. Entomological indices (June 2018 and on-site survey) in 17 subdistricts from 6 epidemic districts, Surin Province, Thailand, July 2018 (n=17)

Index	Mean percentage (Standard deviation)	Median percentage (Interquartile range)	Range
From prior report (June 2018)			
Container index	4.5 (3.3)	4.0 (4.4)	0.7-12.0
House index	14.1 (8.7)	12.9 (12.2)	3.0-31.5
Breteau index	25.5 (23.1)	17.4 (33.4)	0.0-76.0
From spot survey			
Container index	16.2 (6.7)	16.1 (9.7)	3.2-26.9
House index	51.8 (20.0)	50.0 (30.0)	15.0-95.0
Breteau index	113.1 (57.1)	107.5 (80.0)	25.0-250.0

Table 5. Multivariable Poisson regression on the association between entomological indices and dengue attack rate in 17 subdistricts from 6 epidemic districts, Surin Province, Thailand, July 2018

Variable	Adjusted incidence rate ratio (95% CI)	P-value
Prior Breteau index (June 2018)	1.004 (1.002-1.007)	0.001
Spot Breteau index	1.005 (1.004-1.006)	<0.001
Previous attack rate (June 2018)	1.012 (1.011-1.014)	<0.001

In the second theme, the interviewees voiced that they experienced opposition from some local villagers against fogging or temephos addition. One of the key reasons flagged by local inhabitants was fogging might harm their silkworms. Some households gained revenue from raising silkworms. Thus, those villagers feared that fogging might jeopardize the worms. Moreover, some subdistricts were promoted to be 'green/organic' tourism spots. This made some villagers reluctant to accept the use of temephos and fogging.

"There are households raising silkworms for living. And the district is promoted for green tourism. So some people deny fogging for fear that this might harm the silkworms." a female provider in a health center, 40-50 years old

Discussion

This study confirmed the presence and magnitude of dengue outbreak in Surin. The majority of cases were students aged less than 15 years. This finding corresponds with previous study by Chareonsook et al[19] and Nagao et al[20], suggesting that since late 1990s the mean age of dengue cases shifted from early childhood (0-4 years) to late childhood (10-14 years). Nevertheless, some positive sides from this event were noted. First, no deaths were reported; and second, most patients received care in a timely manner (within three days after disease onset).[17]

Another potential factor of the burgeoning trend of dengue in Surin was the use of single-chemical fogging in some subdistricts. The mixed chemicals mostly contain piperonyl butoxide, which provides synergistic toxicity effect on mosquitos. The use of single pyrethroid agent likely creates pyrethroid resistance.[18] Chuaycharoensuk et al reported a wide degree of physiological response (~4-5.6%) to permethrin in *Ae. aegypti* in different regions of Thailand.[19]

Moreover, positive relationship between entomological indices and dengue attack rate was highlighted. Every unit increase in BI tended to magnify dengue incidence in the following month by 0.4%.

From public health point of view, this discovery warrants prompt public health actions. Larva eliminating campaigns should focus on containers that appeared to have high CI, which are likely to be overlooked, such as saucers, wheels and tile fragments. At present, the MOPH recommended the BI-cutoff at 50.[12,13] Yet, some international literature suggested different cutoffs, varying around 4-50[20,21] Thus, the MOPH's recommendation for BI-cutoff should be revisited.[21]

Another worth-mentioning point is the reported indices seemed to be lower than those from on-site survey. This phenomenon likely leads to complacency in dengue control. Stringent measurement and close supervision during routine larva controls are recommended. Nevertheless, monitoring local health staff's performance in larva control is not straightforward as their performance did not necessarily conform to every detail written in the guideline. Further discussions between local providers, academics and policy formulators should be initiated to fine-tune appropriate assessment methods and implementation details.

Qualitative findings also confirmed difficulty in exercising the 3/3/1-measure, especially in terms of fogging and temephos introduction in light of resource pooling under the District Health Board. Though in principle this approach aims at seamless collaboration among all sectors, it de facto creates difficulty to local health staff as they did not have absolute authority in resource mobilization. It does not mean that the Board is to be blamed. The bottom line is the function of each authority should be streamlined to allow timely mobilization of resources. Collaboration among authorities should be strengthened. Besides, local villagers should be included in the participatory public policy process. This will help raise awareness towards dengue situation and in the same time help increase compliance to the control measures, particularly among those with negative views towards fogging. All of these notions are indeed in line with the IVM concept and evidence shows that areas with IVM (which includes 3/3/1 measures) appeared to have better protection against dengue.[9,22,23] However it seems that this concept has not been fully utilized amongst all relevant stakeholders.

Limitations

This study encountered some limitations. Firstly, the fieldwork was confined to only one province. In addition, the number of subdistricts in the primary survey was quite limited. There were also other unobserved factors that might affect the incidence of dengue; for instance, seasonal influence, entomological indices in public places, and populations' immunity. Nevertheless, influence from those factors was, to some degree, captured by adding attack rate in the month prior as a variable in the model. Lastly, views of other stakeholders were still lacking.

Public Health Actions and Recommendations

Health care providers were advised to change their fogging method, from single-chemical fogging to mixed-chemicals fogging. Campaigns to get rid of larva sources in communities, especially areas with high entomological indices, should be promoted. A participatory public policy process that engages all stakeholders, including policy makers, health care providers, and local inhabitants, should be initiated to identify effective vector-control strategies that are suitable to the living norms of the inhabitants. Processes to mobilize dengue-control resources should be simplified and streamlined among different authorities to ensure a timely response towards the incidence.

Conclusion

During June-July 2018, Surin faced severe dengue outbreak. The use of single-chemical fogging was probably a contributory factor, coupled with inadequate larva control as reflected by high entomological indices. Dissonance between chemical-use strategies and living norms of the inhabitants and resource-mobilization constraints were noted. Intensifying larva-elimination campaigns and shifting fogging means were recommended. A participatory public policy process should be initiated to identify vector-control strategies that are effective and in the same time acceptable to the living norms of the inhabitants. Processes to mobilize dengue-control resources should be simplified and streamlined among different authorities.

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References

1. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, et al. Dengue: a continuing global threat. Nat Rev Microbiol. 2010 Dec;8(12 Suppl):S7-16.

2. Simmons CP, Farrar JJ, Nguyen v V, Wills B. Dengue. N Engl J Med. 2012 Apr 12;366(15):1423-32.

3. Powell JR, Tabachnick WJ. History of domestication and spread of *Aedes aegypti* - A Review. Memórias do Instituto Oswaldo Cruz. 2013;108(Suppl 1):11-7.

4. Srikiatkhachorn A, Rothman AL, Gibbons RV, Sittisombut N, Malasit P, Ennis FA, et al. Dengue—how best to classify it. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2011;53(6):563-7.

5. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496:504.

6. Limkittikul K, Brett J, L'Azou M. Epidemiological trends of dengue disease in Thailand (2000-2011): a systematic literature review. PLoS Neglected Tropical Diseases. 2014;8(11):e3241.

7. Chareonsook O, Foy HM, Teeraratkul A, Silarug N. Changing epidemiology of dengue hemorrhagic fever in Thailand. Epidemiol Infect. 1999 Feb;122(1):161-6.

8. Thailand. Bureau of Vector Borne Diseases. Department of Disease Control. Ministry of Public Health. Dengue control measures: 3,3,1–7–14–21–28. Nonthaburi: Department of Disease Control, Thailand; 2013 [cited 2018 Sep 14]. <http://www.thaivbd.org/n/contents/view/325289>.

9. World Health Organization. Handbook for integrated vector management. Geneva:

World Health Organization; 2012 [cited 2018 Sep 14]. <http://apps.who.int/iris/bitstream/handle/10665/44768/9789241502801_eng.pdf;jsessionid=F994FC4765D80E6A920D58C6BF685761?sequence=1>.

10. Focks D. A review of entomological sampling methods and indicators for dengue vectors. Geneva: World Health Organization; 2003 [cited 2018 Sep 14]. <http://apps.who.int/iris/bitstream/handle/10665/68575/TDR_IDE_DEN_03.1.pdf?sequence=1>.

11. Bowman LR, Runge-Ranzinger S, McCall PJ. Assessing the relationship between vector indices and dengue transmission: a systematic review of the evidence. PLoS Negl Trop Dis. 2014 May;8(5):e2848.

12. Wongbutdee J, Saengnill W. *Aedes aegypti* larval habitats and dengue vector indices in a village of Ubonratchathani in the North-East of Thailand. Res J. 2015;20(2):254-9.

13. Thailand. Bureau of Vector Borne Diseases. Department of Disease Control. Ministry of Public Health. Dengue: container index and house index. Nonthaburi: Department of Disease Control, Thailand; 2016. Thai [cited 2018 Sep 14]. <https://phdb.moph.go.th/phdb2017/force_down.php?f_id=194>.

14. Epidemiology Unit. Dengue situation during epidemiological week 29. Surin: Surin Provincial Health Office; 2018.

15. Thailand. Bureau of Epidemiology. Department of Disease Control. Ministry of Public Health. Reporting of priority diseases guideline, Thailand. Nonthaburi: Department of Disease Control, Thailand; 2012. Thai.

16. Thailand. Bureau of Vector Borne Diseases. Department of Disease Control. Ministry of Public Health. Larva survey for dengue vector control. Nonthaburi: Department of Disease Control, Thailand; 2013 [cited 2018 Sep 14]. <http://www.thaivbd.org/n/contents/view/324792>.

17. Srikiatkhachorn A, Krautrachue A, Ratanaprakarn W, Wongtapradit L, Nithipanya N, Kalayanarooj S, et al. Natural history of plasma leakage in dengue hemorrhagic fever: a serial ultrasonographic study. Pediatr Infect Dis J. 2007;26(4):283-90.

18. Kasai S, Komagata O, Itokawa K, Shono T, Ng LC, Kobayashi M, et al. Mechanisms of pyrethroid resistance in the dengue mosquito vector, *Aedes aegypti*: target site insensitivity, penetration, and metabolism. PLoS Negl Trop Dis. 2014 Jun;8(6):e2948.

19. Chuaycharoensuk T, Juntarajumnong W, Boonyuan W, Bangs MJ, Akratanakul P, Thammapalo S, et al. Frequency of pyrethroid resistance in *Aedes aegypti* and Aedes albopictus (Diptera: Culicidae) in Thailand. J Vector Ecol. 2011 Jun;36(1):204-12.

20. Basker P, Kolandaswamy KG. Study on the behavior of dengue viruses during outbreaks with reference to entomological and laboratory surveillance in the Cuddalore, Nagapattinam, and Tirunelveli Districts of Tamil Nadu, India. Osong Public Health and Research Perspectives. 2015 Jun 1;6(3):143-58.

21. Sanchez L, Vanlerberghe V, Alfonso L, Marquetti MdC, Guzman MG, Bisset J, et al. *Aedes aegypti* larval indices and risk for dengue epidemics. Emerging Infectious Diseases. 2006;12(5):800-6.

22. Murray NEA, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clinical Epidemiology. 2013;5:299-309.

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Epidemiological Features of Japanese Encephalitis among Acute Encephalitis Syndrome Cases in Myanmar, 2014-2016: Implications to the Vaccination Program

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Abstract

Japanese encephalitis (JE) was confirmed in Myanmar since 1974 and sporadic outbreaks have been reported. A descriptive study was conducted to determine the epidemiological characteristics of JE among acute encephalitis syndrome (AES) cases during 2014-2016 and identify potential risk factors for JE infection. The reported AES cases increased from 252 in 2014 to 1,911 in 2016. The annual proportion of JE among AES cases were 22.1-22.6% during 2014-2016. The highest proportion of JE among AES case was found in Rakhine State (44.6%) in 2016. Proportions of JE among AES cases were high in the rural areas, and in children aged 1-14 years. None of AES cases had previous JE vaccination prior to onset. JE infection was confirmed in 53.4% of serum and 47.0% of cerebrospinal fluid specimens obtained 3-7 days after onset of illness. In multivariate analysis, people aged one year and above, living in rural areas (Adjusted odds ratio = 2.9, 95% CI = 2.2-4.0) and having chickens and/or ducks in/nearby house (Adjusted odds ratio = 1.4, 95% CI = 1.0-1.9) were significantly associated with JE positivity among AES cases. An effective immunization campaign should be implemented nationwide, with prioritization given to the most affected areas and those aged 1-14 years.

Keywords: Japanese encephalitis, AES, vaccination, Myanmar

Introduction

Japanese encephalitis (JE) is a vector-borne zoonotic viral disease. It is transmitted to humans through the bite of infected *Culex* species mosquitoes, particularly *Culex tritaeniorhynchus*. Pigs, ducks and chickens are the amplifier hosts and humans are the incidental or dead-end hosts.[1-4] Less than 1% of people develop clinical illness after they are infected with JE virus (JEV). The case fatality rate, however, can be as high as 30% and permanent neurologic or psychiatric sequelae can be found in 30-50% of those with encephalitis.[1-3]

Globally, it has been estimated that approximately 68,000 cases of JE occur annually. In Asia and the Western Pacific, endemic JEV transmission can be observed in 24 countries, including Myanmar, with over three billion people exposed to risk of infection.[5] In Myanmar, the first confirmed outbreak of JE occurred in eastern Shan State in 1974. By 1979, 198 cases, with 98 deaths (CFR 49.5%), were reported in 11 townships in six states and regions. A JE outbreak was also detected in 1977 among 13 horses and one donkey in the animal breeding center in southern Shan State.[6,7] In 2016, JE outbreaks were reported from Rakhine State.[8,9]

JE primarily affects children and people living in rural areas.[6] Since approximately 70% of the population residing in the rural areas and 28.6% of total population are children 0-14 years, a high risk of JEV transmission exists in Myanmar.[10-11]

Myanmar is divided administratively into Nay Pyi Taw Council Territory, seven states and seven regions.[10] Hospital based AES surveillance has been initiated in limited places since 2007. The Central Epidemiology Unit (CEU) is the responsible unit for the surveillance of JE and AES. In 2016, the CEU developed national guideline on AES surveillance and modified the case definition of JE. Laboratory facilities for AES surveillance are only available at the National Health Laboratory (NHL) where a sample of serum and/or cerebrospinal fluid of an AES case should be tested for JE. Training of volunteers for vector control is implemented by the vector-borne diseases control (VBDC) program. The expanded programme on immunization (EPI), Myanmar, also provides technical advice and training to the health workers.[6]

Analysis of trends and distribution would be useful for implementation of prevention and control activities in high risk geographical areas. Hence, this study aimed to describe the morbidity and mortality trends of JE infected cases, determine the epidemiological characteristics of JE among AES cases, and identify the potential risk factors for JE infection.

Methods

Descriptive Study

A descriptive study was performed by reviewing the AES surveillance data in the CEU. The information from case investigation forms reported during 2014-2016 in the NHL was retrieved. Descriptive characteristics in the case investigation forms included age, gender, residence, clinical features, JE vaccination, and dates of onset and specimen collection. In addition, geographical distributions of JE among AES cases in 2014-2016 were presented. Seasonal patterns during 2014-2016 were described by onset.

An AES case in this study was defined as a person with acute onset of fever (Temperature >100.4°F or 38°C), change in mental status (confusion, disorientation, coma, or inability to talk), with or without new onset of seizures (excluding simple febrile seizure), and tested for JE virus immunoglobulin M (IgM) in NHL in 2014-2016. A JE case was defined as an AES case confirmed to have JEV IgM in serum or CSF by enzyme-linked immunosorbent assay (ELISA).[6]

Analytical Study

We used Epi Info version 7.2.1.0[12] to analyze and identify the potential risk factors using the information from the case investigation forms. The chi-square test was used to compare proportions. Multiple logistic regression analysis was used to identify factors associated with JE among AES cases and all variables were controlled at the same time in the final model. All factors from the univariate analysis with p-value equal to or less than 0.2 were included in final model. Adjusted odds ratio (OR) and their 95% confidence intervals (CI) were calculated to indicate the strength of association.

Results

JE among AES cases in 2014-2016

The annually reported AES cases started to increase from 252 in 2014 to 1,911 in 2016 and JE cases increased from 57 in 2014 to 424 in 2016. The proportion of JE among AES cases was approximately 22.2-22.6% in 2014-2016. JE proportions among AES cases were found to be the highest during and after the rainy season, i.e. June to August, throughout 2014-2016 (Figure 1).

JE cases were identified among AES cases in two states and five regions, with the highest in Mandalay Region and Kachin State in 2014. However, in 2015, JE cases were reported from six states and six regions. In 2016, 13 out of total 15 states and regions, except Kachin and Kayah States, reported JE cases, with the highest in Rakhine State (Figure 2).

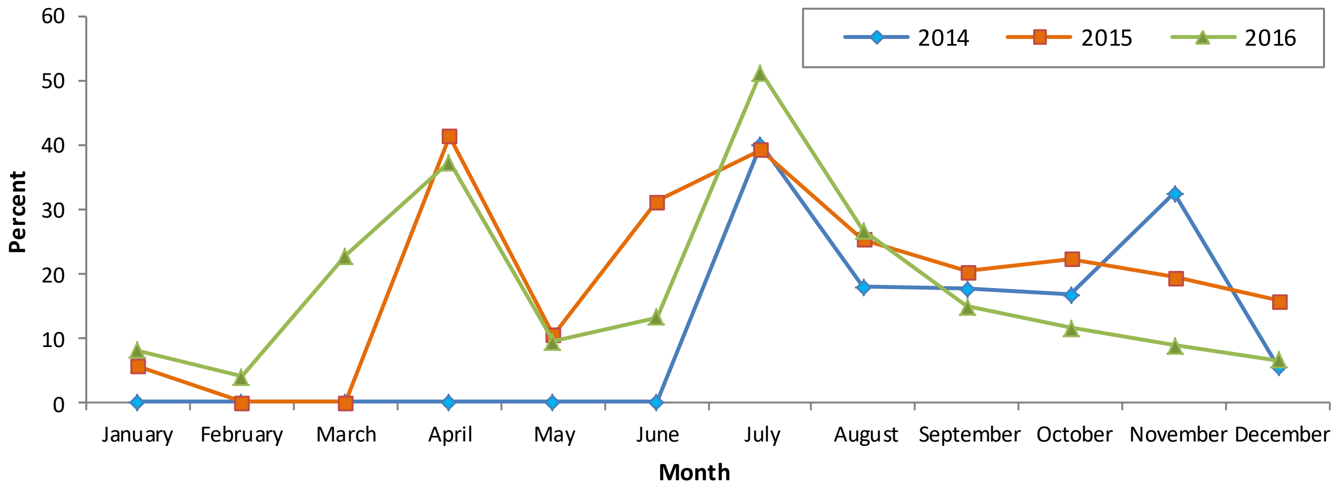

Figure 1. Distribution of Japanese encephalitis among acute encephalitis syndrome cases by months in Myanmar, 2014-2016

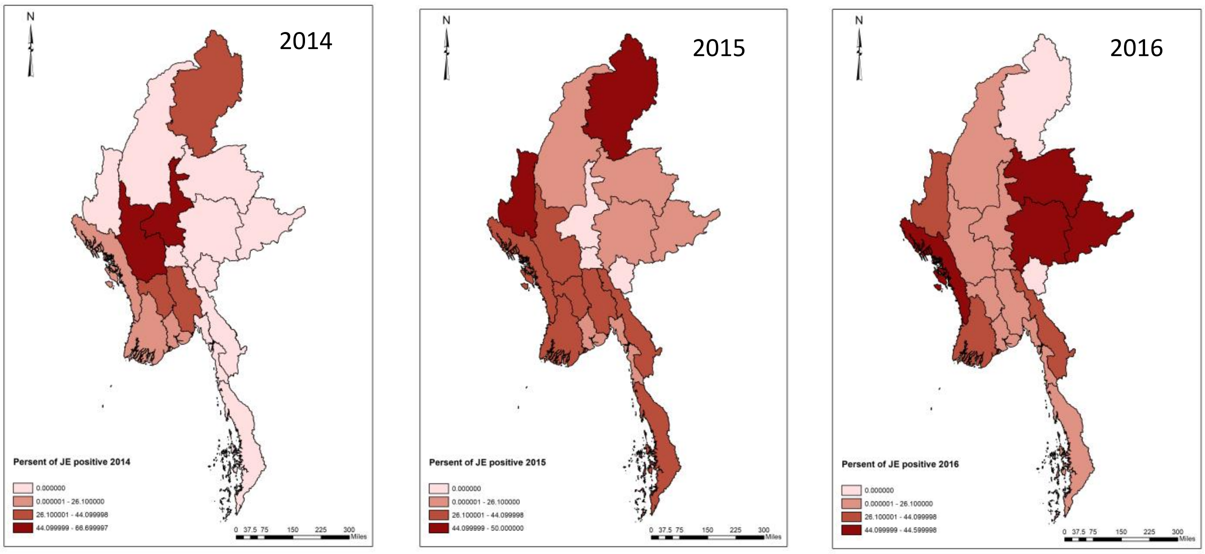

Figure 2. Percent distribution of Japanese encephalitis among acute encephalitis syndrome cases by states and regions of Myanmar, 2014-2016

Proportions of JE among AES cases were high in the rural areas, from 26.8% in 2014, 31.7% in 2015 and 31.5% in 2016 (Table 1). In 2016, high JE proportions among AES cases were in children 1-14 years old (30.9%), particularly in those 5-9 years of age, with 43.1% in 2014, 36.3% in 2015, and 33.8% in 2016. The lowest proportion (2.0%) was seen among under one year of age (Figure 3). Moreover, higher proportion of JE cases was seen in males during 2014-2016. The most common clinical manifestations of JE cases were neck stiffness (35.0%) in 2014 and unconsciousness in 2015-2016 (55.0% and 50.5% respectively) (Figure 4).

Table 1. Distribution of Japanese encephalitis (JE) and acute encephalitis syndrome cases (AES) in rural and urban areas of Myanmar, 2014-2016

Area	2014		2015		2016	
	AES case examined	JE positive case (%)	AES case examined	JE Positive case (%)	AES case examined	JE positive case (%)
Rural	127	34 (26.8)	328	104 (31.7)	1,007	317 (31.5)
Urban	82	10 (12.2)	206	21 (10.2)	688	90 (13.1)
Unknown	43	13 (30.2)	114	21 (18.4)	216	17 (7.9)
Total	252	57 (22.6)	648	146 (22.5)	1,911	424 (22.2)

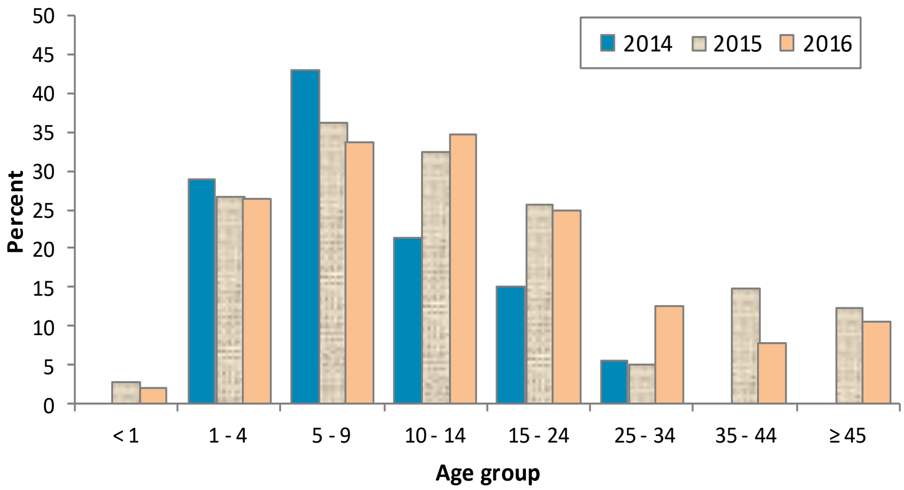

Figure 3. Distribution of Japanese encephalitis among acute encephalitis syndrome cases by age groups in Myanmar, 2014-2016

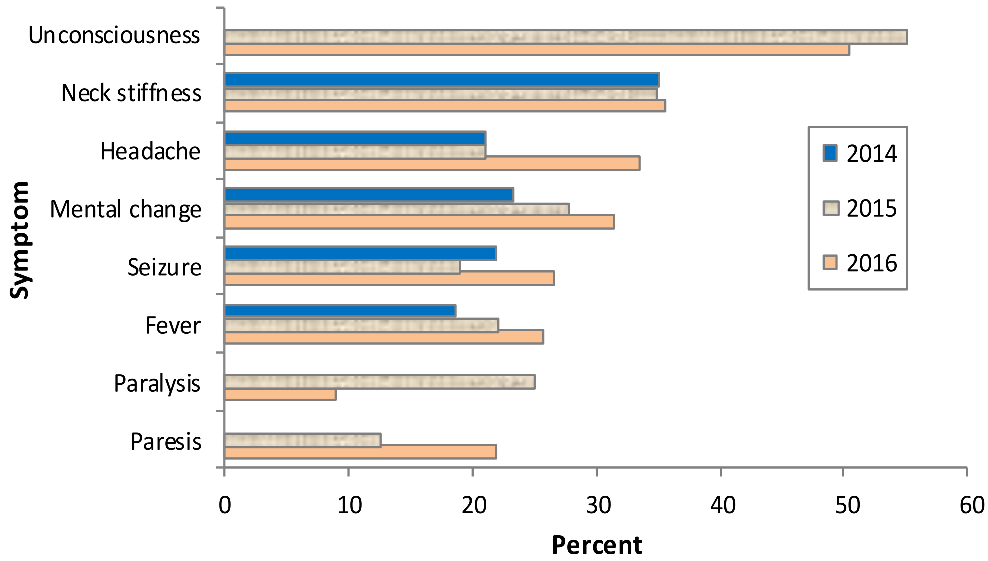

Figure 4. Clinical manifestations of Japanese encephalitis cases in Myanmar, 2014-2016

Description on JE among AES cases in 2016

Most of the AES cases (1,431/1,911, 74.9%) were initially diagnosed as viral encephalitis/meningitis or fever with central nervous system (CNS) symptoms while about 22.2% of all the AES cases were confirmed as JE cases. The highest proportion of JE was found in the cases with diagnosis of viral encephalitis/meningitis or fever with CNS symptoms (25.8%). Bacterial encephalitis or meningitis were the initial diagnosis in 113 of AES cases, of whom 26 (23.0%) were confirmed by laboratory testing. None of the AES cases had previous JE vaccination history before their onset of AES.

Among total 1,503 serum samples tested, 388 (25.8%) were positive for JE. Of the JE positive cases, 207 (53.4%) had a specimen obtained 3-7 days after onset of illness. Another 75 (19.3%) cases had all specimens collected between 8-14 days of illness onset. Only 57 (14.7%) cases were collected within two days of disease onset. Out of 784 CSF tested samples, 151 (19.3%) had positive JE results. Although 71 (47.0%) of the positive cases had a specimen obtained 3-7 days after onset of illness, only 18 (11.9%) cases were collected within two days of illness onset.

Analytical Study

From the univariate analysis, the characteristics significantly associated with JE were age, residence, distance between rice field and home, and having pigs, chickens and/or ducks, sheep and/or goats in/nearby the house (Table 2). The highest proportion of JE was in children 5-14 years old (34.2%), followed by those 1-4 years old (26.5%). The proportion decreased with increasing age in adults and was very low in children under one year old. Those living in rural areas and near the rice fields less than one kilometer away from the home had the highest proportion of JE. Clinical manifestations significantly associated with JE were presence of fever, seizure, mental change, headache, neck stiffness and unconsciousness (Table 3).

From the multivariate analysis, the factors significantly associated with JE were age groups: 1-4 years old (Adjusted OR = 40.7, 95% CI = 12.7-130.5), 5-14 years old (Adjusted OR = 52.0, 95% CI = 16.4-165.5), 15-24 years old (Adjusted OR = 31.1, 95% CI = 9.1-106.1) and 25 years old and above (Adjusted OR = 14.7, 95% CI = 4.3-50.2), living in rural areas (Adjusted OR = 2.9, 95% CI = 2.2-4.0) and having chickens and/or ducks in/nearby the house (Adjusted OR = 1.4, 95% CI = 1.0-1.9) (Table 4).

Discussion

In Myanmar, the annual reported AES and JE cases was found to be increasing over a three-year period from 2014-2016. This increasing trend could reflect the heightened awareness of the clinicians to send samples for laboratory diagnosis, the increase utilization of health facilities by patients and the development of national guidelines in 2016. However, the incidence of JE among AES cases has remained unchanged, from 2014-2016. Additional risk factors include children aged 1-14 years, people those living in rural areas and having chickens and/or ducks in/nearby the house.

JE cases were reported sporadically throughout the year with peaks from June to August which coincides with the rainy season and potentially an increase in the prevalence of the mosquito vectors. JE incidence declined significantly with the onset of winter.[13] The occurrence of JE cases increased from seven states/regions in 2014 to almost all states/regions of Myanmar in 2016.

Table 2. Distribution of Japanese encephalitis (JE) among acute encephalitis syndrome cases (AES) by demographic characteristics in Myanmar, 2016

Characteristic	Number of AES case examined	Number of JE positive case (%)	P-value
Total	1,911	424 (22.2)	
Age (year)			
<1	343	7 (2.0)	<0.001
1-4	490	130 (26.5)	
5-14	640	219 (34.2)	
15-24	152	38 (25.0)	
≥25	275	29 (10.5)	
Gender			
Male	1,052	246 (23.4)	0.163
Female	859	178 (20.7)	
Residence			
Rural	1,007	317 (31.5)	<0.001
Urban	688	90 (13.1)	
Environmental factors			
Distance between rice field and home (km)			
< 1	327	98 (30.0)	0.019
1-5	119	27 (22.7)	
> 5	1,041	229 (22.0)	
Pig in/nearby the house	408	138 (33.8)	<0.001*
Chicken and/or duck in/nearby the house	468	156 (33.3)	<0.001*
Sheep and/or goat in/nearby the house	33	13 (39.4)	0.040*
Cattle and/or buffalo in/nearby the house	232	68 (29.3)	0.051*

* Comparison between those reporting: yes and no

Table 3. Distribution and univariate analysis of Japanese encephalitis (JE) among acute encephalitis syndrome (AES) cases by clinical manifestation in Myanmar, 2016

Clinical manifestation	Number of AES case examined	Number of JE positive case (%)	P-value
Total	1,911	424 (22.2)	
Fever	1,432	369 (25.8)	<0.001*
Seizure	878	234 (26.7)	0.014*
Mental change	483	152 (31.5)	<0.001*
Headache	402	135 (33.6)	<0.001*
Neck stiffness	227	81 (35.7)	<0.001*
Unconsciousness	99	50 (50.5)	<0.001*
Paresis	50	11 (22.0)	0.707*
Paralysis	11	1 (9.1)	0.477*

* Comparison between those reporting yes and no

Table 4. Multiple logistic regression analysis on possible risk factors for Japanese encephalitis infection among acute encephalitis syndrome cases in Myanmar, 2016 (n=1,911)

Characteristic	Adjusted odds ratio	95% CI
Personal factors		
Age under 1 year	Reference	
Age 1-4 years	40.7	12.7-130.5
Age 5-14 years	52.0	16.4-165.5
Age 15-24 years	31.1	9.1-106.1
Age ≥25 years	14.7	4.3-50.2
Gender (male/female)	1.1	0.8-1.4
Environmental factors		
Residence (rural/urban)	2.9	2.2-4.0
Distance between rice field and home (km)		
No field	Reference	
Distance (<1)	0.9	0.6-1.4
Distance (1-5)	0.7	0.4-1.2
Pig in/nearby the house	1.0	0.7-1.4
Chicken and/or duck in/nearby the house	1.4	1.0-1.9
Sheep and/or goat in/nearby the house	1.4	0.6-3.3
Cattle and/or buffalo in/nearby the house	0.9	0.6-1.3

Despite that, JE and AES cases might still be under reported if hospitals from remote areas were unable to send specimens of suspected AES cases for laboratory confirmation of JEV IgM due to laboratory facilities for AES surveillance being only available at the NHL.[6] Among the AES cases, majority of JE positive cases were found in those living in rural areas, one-third were those living near rice fields of less than one kilometer where the main case occupation was farming and about one-third were those having domestic animals in/nearby the house. This finding was similar to the findings of a study in India which postulated that this may be due to an expansion of irrigated rice production systems which increase mosquito vector density.[13]

JEV infection could be detected in chickens, ducks and pigs.[4,14,15] One study in Indonesia found that 25 (20.6%) out of 121 sera samples of ducks, 72 (36.7%) out of 196 sera samples of chickens and 65 (32.2%) out of 202 sera samples of pigs were JEV antibodies positive by ELISA.[4]

In our study, a high proportion of JE case was found in children with AES cases aged 1-14 years, in 2014-2016. This finding is similar to what was found in a similar study in China by Zundong Yin et al in 2010, where 45-77% of JE cases were found in children under 15 years of age.[16] This could reflect that the children under 15 years were more susceptible to JE infection than adults for a lack of immunity and may have been exposed to mosquito vectors due to frequent visits to the rice fields with their parents. Those with clinical symptoms of fever, seizure, mental change, headache, neck stiffness and unconsciousness were found in a higher percentage of JE positive cases than among AES cases.

Although most of the JE positive cases had an initial clinical diagnosis such as viral encephalitis/meningitis, other encephalitis or other diagnosis, 74.9% of AES cases were initially diagnosed as viral encephalitis/meningitis or fever with CNS symptoms. In other studies, of the 2,815 AES cases identified at sentinel hospitals, 1,194 (42%) were initially diagnosed as viral encephalitis/meningitis.[17] This difference might be due to a local physician preference to assign a diagnosis of viral encephalitis or other encephalitis rather than JE if there were no supporting laboratory results. A significant proportion of cases found to be positive for JE were also detected among those who were initially diagnosed as bacterial meningitis/ encephalitis (23.0%).

Confirmed JE cases were found in 53.4% of serum specimens and 47.0% of CSF specimens, which were obtained 3-7 days after illness onset. Besides, 11-14% of the specimens were collected within two days of illness. There might have been false-negative results because about 75% of samples would be JEV IgM positive at four days after onset of illness.[6] Had we obtained follow-up specimens, additional JE cases might have been identified from AES cases. Moreover, there may have been incorrect information about date of illness onset provided by health care providers.

In multivariate analysis, the proportion of JE among AES cases was significantly higher among people aged between 1-80 years old. The persons who lived in rural area and who had the family or neighbor own domestic animals such as chicken and/or duck were significantly associated with JE positive. This is consistent with another study in Vietnam which found the proportion of JE positivity among AES cases was significantly higher among children aged 6-15 years compared with aged five years or less and adults over 15 years of age (p-value <0.01).[17]

There were some limitations with this study. We found that there was missing information in AES case investigation forms and therefore the residual neurological sequelae and outcomes were not studied because of incomplete clinical notes in these surveillance forms.

We recommended that all suspected AES cases undergo laboratory testing for JEV and monitoring of disease situation should be pursued by public health authorities. Responsible persons for AES surveillance should complete case investigation forms starting from township hospital following the national guideline. JEV immunization campaigns should prioritize those aged 1-14 years, especially people living in rural areas, family members of confirmed cases and those who own or are neighbors to those who own domestic animals such as chickens and/or ducks.

The reported annual incidence of JE among AES has increased over a three-year period from 2014-2016 and poses an important public health threat in Myanmar. An immunization campaign should be initiated to target the most affected areas including rural areas and those aged 1-14 years given the increase in risk revealed by this study.

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References

1. World Health Organization. Meeting of the strategic advisory group of experts on immunization, October 2014 – conclusions and recommendations. Wkly Epidemiol Rec. 2014;89(50):561-76.

2. World Health Organization. A global brief on vector-borne diseases. Geneva: World Health Organization; 2014.

3. World Health Organization. Japanese encephalitis vaccines: WHO position paper, February 2015 – recommendations. Wkly Epidemiol Rec. 2015;90(9):69-88.

4. Ayu Mirah Adi AA, Astawa NM, Asri Damayanti PAA, Kardena IM, Krisna Erawan IGM, Suardana IW, et al. Seroepidemiological evidence for the presence of Japanese encephalitis virus infection in ducks, chickens, and pigs, Bali-Indonesia. Bali Medical Journal. 2016;5(3):533-7.

5. Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, Hombach JM, et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ. 2011;89(10):766-74.

6. Myanmar. Central Epidemiology Unit. Department of Public Health. Ministry of Health and Sports. Acute encephalitis syndrome surveillance field guide. Nay Pyi Taw: Central Epidemiology Unit, Department of Public Health; 2016.

7. Saw-Lwin, Kyaw-Zeya. Epidemiology of Japanese encephalitis in Myanmar. Myanmar J Curr Med Pract. 1999;3:438-40.

8. Oo PM, Hlaing T,Lwin S, Pittyawonganon C, Sirichaisinthop J, Khine SK. A large outbreak of Japanese encephalitis in Rakhine State, Myanmar: implication for vaccine policy. OSIR 2016;9(2):8-15.

9. Khine SK, Swaddiwudhipong W, Tha KK, Aung TH, Naing NW, Than T, et al. Adult Japanese encephalitis outbreak following an immunization campaign in children, Shwe Pyi Tha Village, Sittwe Township, Rakhine State, Myanmar, 2016. OSIR 2018;11(1):1-5.

10. Myanmar. Ministry of Health. Health in Myanmar 2014. Nay Pyi Taw: Ministry of Health; 2014.

11. Myanmar. Vector Borne Disease Control Program. Department of Public Health. Ministry of Health and Sports. Annual report. Nay Pyi Taw: Vector Borne Disease Control Program, Department of Public Health; 2010.

12. Centers for Disease Control and Prevention. Epi Info. [cited 2018 Jan 22]. <http://wwwn.cdc.gov/epiinfo/html/prevVersion.htm>.

13. Bandyopadhyay B, Bhattacharyya I, Adhikary S, Mondal S, Konar J, Dawar N, et al. Incidence of Japanese encephalitis among acute encephalitis syndrome cases in West Bengal – India. BioMed Research International volume 2013;896749.

14. Cleton NB, Bosco-Lauth A, Page MJ, Bowen RA. Age-related susceptibility to Japanese encephalitis virus in domestic ducklings and chicks. Am J Trop Med Hyg. 2014;90(2):242-6.

15. Bhattacharya S, Basu P. Japanese encephalitis virus (JEV) infection in different vertebrates and its epidemiological significance: a review. International Journal of Fauna and Biological Studies. 2014;1(6): 32-7.

16. Yin Z, Wang H, Yang J, Luo H, Li Y, Hadler SC, et al. Japanese encephalitis disease burden and clinical features of Japanese encephalitis in four cities in the People's Republic of China. Am. J. Trop. Med. Hyg. 2010; 83(4):766-73.

17. Yen NT, Duffy MR, Hong NM, Hien NT, Fischer M, Hills SL. Surveillance for Japanese encephalitis in Vietnam, 1998–2007. Am J Trop Med. Hyg. 2010; 83(4):816-9.

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Grammar of Science: Engines of Statistical Models

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Introduction

An engine or motor is a machine designed to convert one form of energy into mechanical energy[1]. Heat engines burn a fuel; electric motors convert electrical energy; pneumatic motors compressed air; then the energy conversion from those engines is used to do the work. The same principle applies in biological systems; for example, molecular motors (e.g. myosins in muscles) use chemical energy to create forces and motion[1]. In statistics, I would say that there are two mathematical engines which are the driving forces underneath almost all statistical methods/models: "regression" and "correlation".

There are varieties of regression and correlation. But we will focus on the classic engines of all, the "Linear regression" and the "Pearson's correlation". It is important to understand the mechanism of these engines because they are the foundations or driving forces of all other types of regression and correlation and used as basis for several other statistical models. We will take a close look at the development of linear regression model, the steps in derivation of Pearson's correlation coefficient, and the mathematical linkage between the two statistical terms.

What are Correlation and Regression?

The two statistics are both similar and different. Regarding the meaning, correlation determines co-relationship or association of two variables while regression describes how an independent variable is numerically related to the dependent variable[2]. Correlation quantifies the degree to which two variables (say, x and y) are related. Regression identifies the "best" equation that predicts y from x. We can say that correlation does not distinguish the dependent variable (y) and Independent variable (x) but regression tends to do so[3-4].

Both statistics are based on linear relationship. Correlation assumes that the association is linear, that one variable increases or decreases a fixed amount for a unit increase or decrease in the other. Regression, on the other hand, involves estimating the best straight line to summarize the association between the variables. Therefore correlation coefficient infers the extent to which two variables are associated with each other while regression coefficient estimates the impact of a unit change in the variable (x) on the variable (y)[2,4].

A Brief History

The name "Pearson's correlation" leads to believe that Karl Pearson (1857-1936) developed this statistical measure himself. Although he is the one who made correlation as currently known today, but history went back before his time.

Sir Francis Galton (1822-1911) is commonly regarded as the founder of the statistical techniques of correlation and linear regression[5-7]. Galton, a cousin of Charles Darwin (1809-1882) was a distinguish scientist in biology, psychology and applied statistics. His works on genetics and heredity provided the initial inspiration that led to regression and correlation[5,6]. As Galton's biographer, Pearson described interesting story of the discovery of the regression analysis. In 1875, Galton had distributed packets of sweet pea seeds to seven friends to harvest the seeds and return the next generations to him. Each friend received seeds of uniform weight but there was substantial variation across different packets. Galton then plotted the weights of the daughter seeds against the weights of the mother seeds, and he discovered a straight line relationship with positive slope of the two weights[5].

But Pearson also credited Auguste Bravais (1811-1863), a professor of astronomy and physics, as a founder of initial mathematical formulae for regression and correlation concepts. As noted by Pearson, Bravais wrote about "mathematical analysis on the probability of errors of a point" which is the fundamental theorems of the correlational calculus[7].

Some argued that regression and correlation went even further back to the legendary mathematician Carl Friedrich Gauss (1777-1855) and Adrien-Marie Legendre (1752-1833) who independently discovered the method of "least squares", the essential feature of linear regression[8].

Basics of Regression

A simple way to explore relationships between the two variables is to construct a scatter diagram with one variable on the vertical scale and the other on the horizontal scale. In regression model the "dependent variable" is usually plotted on the vertical axis while the "independent variable" on the horizontal axis, or baseline[4]. The main purpose of regression analysis is to obtain an equation explaining the relationship between variables. Such equation is frequently used to predict the future (or unknown) value of the dependent variable, or to understand which factors (independent variables) cause or associate with an outcome (dependent variable)[8].

Back to the history of regression, in studying data on relative sizes of parents and their offspring in various species of plants and animals, Galton noted that a larger-than-average parent tends to produce a larger-than-average child, but the child is likely to be less large than the parent in terms of its relative position within its own generation[9]. Galton termed this phenomenon a "regression towards mediocrity", which in modern terms is a "regression to the mean". Regression to the mean can be expected in natural settings, for example, relative to others in the same class, your final exam score could be expected to be less good or bad than your midterm score[9]. However, the term "regression" later evolved and changed to the concept of slope determining the relationship between the independent variable(s) and dependent variable.

Regression is a statistical technique for estimating the change in the dependent variable (y) due to the change in one or more independent variables (x). The decision of which variable is dependent or independent variable must be pre-determined as the best-fit line will be different if you swap the two[3]. The simple regression line of y on x is expressed as: $\hat{y} = \beta_0 + \beta_1 x$ where, β_0 = constant (intercept), β_1 = regression coefficient (slope). The β_0 and β_1 are the two regression parameters in the equation. As shown in the hypothetical scenario (steps of a walking baby), in figure 1 (a); at Day 0 (baseline) a baby is able to walk 5 steps, and then 8, 11, 14 steps on Days 1, 2, and 3, respectively. This is one sample with a perfect linear relationship; the linear regression equation here is $\hat{y} = 5 + 3x$ where β_0 = 5 steps (intercept: when x=0) and β_1 = 3 (slope when x changes 1 unit-day, y changes 3 unit-steps). So, if this linear pattern holds, you can expect that the baby will walk 17 steps on Day 4.

But when the researcher collects data on walking steps from many babies with "not so perfect" linear relationship, the numbers will vary for each baby as shown in figure 1 (b), i.e. not all observed values fall on the straight line. "Error" as used in mathematical/statistical sense since 1726 is defined as "any deviation from accurate determination (or true value)" assuming that the accurate determination is obtainable[7]; see figure 1 (b), the distances from each of the observed values (y) collected from the study samples to its predicted value ($\hat{y}$) on the regression line. In order to find the best straight line that will represent the relationship between the two variables, the equation should be the one that gives the least "errors" of prediction.

There are many ways to minimize the error of your guess (prediction), but the "least squares" method optimizes by minimizing squared error. According to Pearson's approach, for linear regression if the slope is calculated from the least square method, then the observed x values predict the observed y values with the minimum possible sum of squared errors of prediction, $\sum(y-\hat{y})^2$[5]. The slope created from the

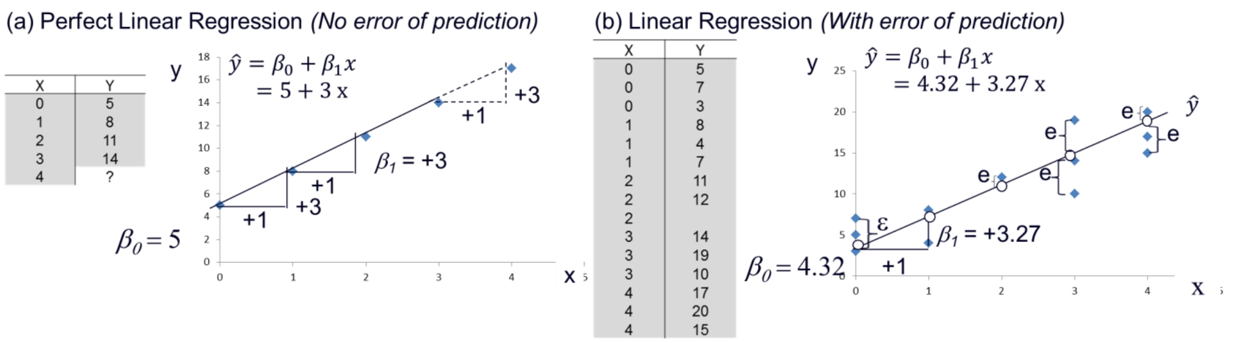


Figure 1. Simple regression concept

least (minimum) errors is then considered as the best regression line with the best estimates of β_0 and β_1. This method is quite popular because it was comparatively easy to compute even manually to get the best guess for minimizing the squared error with the major assumption that the error is normally distributed[8].

Basics of Correlation

The term correlation composes of 'Co' (together) and relation (connection) between two quantities[2]. "Correlation coefficient", denoted by r. is measured on a scale that varies between +1 and -1. Complete correlation between two variables is expressed by either positive direction (+1) or negative direction (-1). Positive relationship occurs when one variable increases as the other increases; while negative relationship occurs when one decreases as the other increases. When there is no connection between the two variables, the correlation is 0[2,4].

The Pearson's correlation is calculated using statistics variance and covariance. Variance refers to the spread of data points around its mean, while a covariance refers to the measure of the directional relationship between two random variables[11,12]. Variance is the average of the squared deviations from the expected value (mean) for a single variable (x): $\sigma_x^2 = \sum(x-\bar{x})^2/n = [\sum(x-\bar{x})(x-\bar{x})]/n$. The larger the variance means the data scatter widely and at large distance from the mean[11]. A covariance refers to the measure of how two random variables (x and y) will change when they are compared to each other. In other words, covariance is an average measure of the deviations from both means $\sigma_{xy} = \sum(x-\bar{x})(y-\bar{y})/n$.

A positive covariance means the two variables move upward or downward in the same direction at the same time, while a negative covariance means the values of the two variables move in opposite direction from each other. Note that covariance is the measure that indicates the direction, but not the degree of the movements of two variables[11].

Correlation coefficient is the comparison of covariance with the variances of the two variables. That is, $r = Covariance\ xy \,/\, \sqrt{Variance\ x \times Variance\ y}$.

Figure 2 illustrates how correlations are calculated using this formula.

Major assumptions of the Pearson correlation coefficient are: (1) both variables are normally distributed; (2) the sample is randomly selected; (3)

(a) Perfect Positive Correlation

$(x-\bar{x})^2$	$(x-\bar{x})$	x	y	$(y-\bar{y})$	$(y-\bar{y})^2$	$(x-\bar{x})(y-\bar{y})$
4	-2	1	10	-20	400	40
1	-1	2	20	-10	100	10
0	0	3	30	0	0	0
1	1	4	40	10	100	10
4	2	5	50	20	400	40
$\sum(x-\bar{x})^2$ ***10***		$\bar{x} = \sum x/n$ ***3***	$\bar{y} = \sum y/n$ ***30***		$\sum(y-\bar{y})^2$ ***1000***	$\sum(x-\bar{x})(y-\bar{y})$ ***100***
Variance $\sum(x-\bar{x})^2/n$ ***2***					***Variance*** $\sum(y-\bar{y})^2/n$ ***200***	***Co-variance*** $\sum(x-\bar{x})(y-\bar{y})/n$ ***20***
Std.Dev. $\sqrt[2]{\sum(x-\bar{x})^2/n}$ ***1.414***					***Std.Dev.*** $\sqrt[2]{\sum(y-\bar{y})^2/n}$ ***14.141***	
$r = Covariance\ xy \,/\, \sqrt{Variance\ x \times Variance\ y}$ = 20 / $\sqrt{2 \times 200}$ = +1						

(b) Perfect Negative Correlation

$(x-\bar{x})^2$	$(x-\bar{x})$	x	y	$(y-\bar{y})$	$(y-\bar{y})^2$	$(x-\bar{x})(y-\bar{y})$
4	-2	1	50	20	400	-40
1	-1	2	40	10	100	-10
0	0	3	30	0	0	0
1	1	4	20	-10	100	-10
4	2	5	10	-20	400	-40
$\sum(x-\bar{x})^2$ ***10***		$\bar{x} = \sum x/n$ ***3***	$\bar{y} = \sum y/n$ ***30***		$\sum(y-\bar{y})^2$ ***1000***	$\sum(x-\bar{x})(y-\bar{y})$ ***-100***
Variance $\sum(x-\bar{x})^2/n$ ***2***					***Variance*** $\sum(y-\bar{y})^2/n$ ***200***	***Co-variance*** $\sum(x-\bar{x})(y-\bar{y})/n$ ***-20***
Std.Dev. $\sqrt[2]{\sum(x-\bar{x})^2/n}$ ***1.414***					***Std.Dev.*** $\sqrt[2]{\sum(y-\bar{y})^2/n}$ ***14.141***	
$r = Covariance\ xy \,/\, \sqrt{Variance\ x \times Variance\ y}$ = -20 / $\sqrt{2 \times 200}$ = -1						

(c) Positive Correlation

$(x-\bar{x})^2$	$(x-\bar{x})$	x	y	$(y-\bar{y})$	$(y-\bar{y})^2$	$(x-\bar{x})(y-\bar{y})$
27.04	-5.2	1	3	-6.0	36.0	31.2
10.24	-3.2	3	8	-1.0	1.0	3.2
0.64	0.8	7	6	-3.0	9.0	-2.4
3.24	1.8	8	10	1.0	1.0	1.8
33.64	5.8	12	18	9.0	81.0	52.2
$\sum(x-\bar{x})^2$ ***74.80***		$\bar{x} = \sum x/n$ ***6.20***	$\bar{y} = \sum y/n$ ***9.00***		$\sum(y-\bar{y})^2$ ***128.00***	$\sum(x-\bar{x})(y-\bar{y})$ ***86.00***
Variance $\sum(x-\bar{x})^2/n$ ***14.96***					***Variance*** $\sum(y-\bar{y})^2/n$ **25.60**	***Co-variance*** $\sum(x-\bar{x})(y-\bar{y})/n$ ***17.2***
Std.Dev. $\sqrt[2]{\sum(x-\bar{x})^2/n}$ ***3.868***					**Std.Dev.** $\sqrt[2]{\sum(y-\bar{y})^2/n}$ ***5.059***	
$r = Covariance\ xy\ /\ \sqrt{Variance\ x \times Variance\ y}$ = 17.2 / $\sqrt{14.96 \times 25.60}$ = -0.879						

Figure 2. Calculation of Pearson Product Moment Correlations

each pair of the observations are independent of one another; (4) two variables is linearly related[4,12]. Note that other types of correlation (e.g., Spearman correlation, Biserial correlation) slightly relax some of these assumptions. Moreover, you should avoid common misconception stating that correlation implies causation. Actually correlation does not imply causation but it could be a pre-condition, but not necessary, for measuring causation[12].

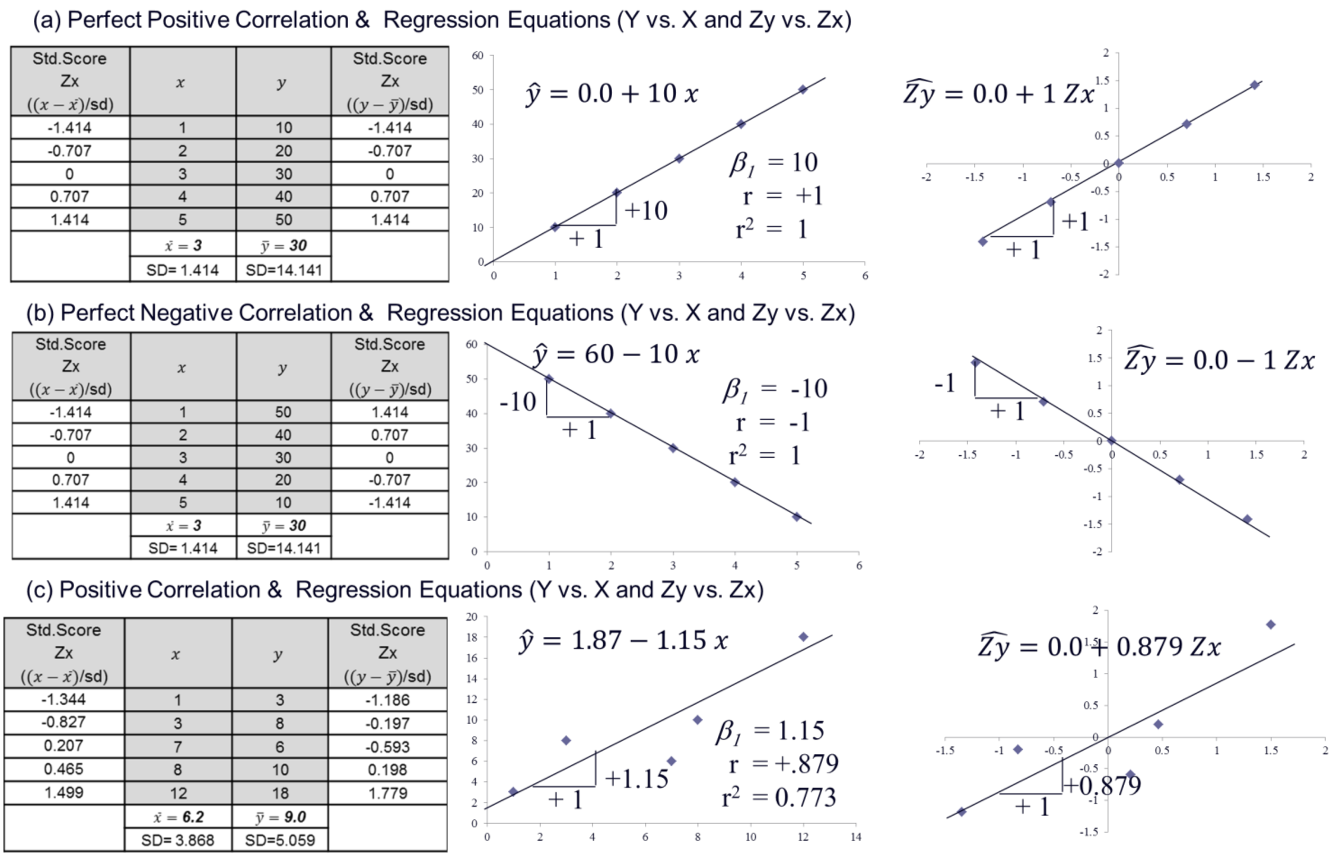
Mathematical Link between Regression and Correlation

Using the same data to calculate correlation and linear regression, you will get different statistics. Based on regression equation, you will get β_1 which is the slope indicating association between x and y (i.e., when x changes one unit of x, y will change β_1 unit of y). But correlation will give you the r which is the degree of linear association; r is simply a coefficient without unit attached. However, if you convert x and y to standard scores (Z-scores) and regress Zy from Zx, then β_1 calculated from the least square method will be the same value as correlation r while β_0 becomes 0. As shown in figure 3, β_1 the slope of Zx is equal to the correlation coefficient (r).

As for a note about Z-score, the Z-score is the number of standard deviations from the mean where a data point is located [i.e., Z-score = $(x-\bar{x})/\ sd$]. It is a measure of how many standard deviations below or above the population mean; it ranges from +3 standard deviations on the normal distribution curve[13]. Z-score is a useful way to compare observed data collected from a "normal" population. With raw score data, the values and units sometimes may not be informative. For example, your exam score of 80 from a total mark of 100 might sound good but where your position is when comparing your score to the average of the class is unknown; calculating your Z-score [(your score of 80 – average score of the class) / SD of the class] can then tell you where you are, compared to the rest of the class. That is, the Z score tells you how many standard deviations from the mean to where your score is[13]. Z-score has no unit attached, so does correlation r.

When you perform linear regression analysis, the model will quantify its goodness of fit with the coefficient of determination (r^2) which will be the same number as the square of correlation coefficient (r). In fact, the concept behind r^2 in linear regression is not quite the same as r from correlation analysis but interpretation of r^2 is useful to consider, in both regression and correlation context. The r^2 is a proportion (unlike r) as it is in effect measuring the proportion of explained/predicted variation compared to the total variation[3]. When all the observed variation is accounted for by the predicted portion (the line of best fit which is equivalent to perfect correlation), the r^2 is 1[12].

Many statistical models are based on correlation coefficient (r) among variables collected in the study. The interpretation of the r in those statistical models may not always be quantified as r^2, the coefficient of determination for the goodness of fit of the model. However, it is possible to provide a readily understandable interpretation by using the square of the correlation as the determinant of best fit of regression model. A correlation of 0.5 could mean that only 25% of the variability is accounted for by the correlation model[12].



(a)

Std.Score Zx $((x-\bar{x})/sd)$	x	y	Std.Score Zx $((y-\bar{y})/sd)$
-1.414	1	10	-1.414
-0.707	2	20	-0.707
0	3	30	0
0.707	4	40	0.707
1.414	5	50	1.414
	$\bar{x} = 3$	$\bar{y} = 30$	
	SD= 1.414	SD=14.141	

(b)

Std.Score Zx $((x-\bar{x})/sd)$	x	y	Std.Score Zx $((y-\bar{y})/sd)$
-1.414	1	50	1.414
-0.707	2	40	0.707
0	3	30	0
0.707	4	20	-0.707
1.414	5	10	-1.414
	$\bar{x} = 3$	$\bar{y} = 30$	
	SD= 1.414	SD=14.141	

(c)

Std.Score Zx $((x-\bar{x})/sd)$	x	y	Std.Score Zx $((y-\bar{y})/sd)$
-1.344	1	3	-1.186
-0.827	3	8	-0.197
0.207	7	6	-0.593
0.465	8	10	0.198
1.499	12	18	1.779
	$\bar{x} = 6.2$	$\bar{y} = 9.0$	
	SD= 3.868	SD=5.059	

Figure 3. Regression and correlation models

Final Thought

It is not overstated to say that both correlation and regression are the engines of statistical models. Several models (e.g., factor analysis, structural equation model, generalized linear models, etc.) are based on these two engines[14-15]. A historian of statistics, Stephen M. Stigler (1941-) calls them the "automobile" of statistical analysis, though he also stated that "... despite its limitations, occasional accidents, and incidental pollution, it and its numerous variations, extensions, and related conveyances carry the bulk of statistical analyses, and are known and valued by nearly all"[8].

Knowing your engines, now you are up to speed on your journey wisely.

Suggested Citation

Kaewkungwal J. Grammar of science: engines of statistical models. OSIR. 2019 Mar;12(1):32-7.

References

1. Wikipedia. Engine. 2019 Feb 22 [cited 2019 Mar 2]. <https://en.wikipedia.org/wiki/Engine>.

2. Surbhi S. Difference between correlation and regression. 2016 May 3 [cited 2019 Mar 2]. <https://keydifferences.com/difference-between-correlation-and-regression.html>.

3. Graphpad. What is the difference between correlation and linear regression? 2009 Jan 1 [cited 2019 Mar 2]. <https://www.graphpad.com/support/faq/what-is-the-difference-between-correlation-and-linear-regression/>.

4. The BMJ. 11. Correlation and regression [cited 2019 Mar 2]. <https:/www.bmj.com/about-bmj/resources-readers/publications/statistics-square-one/11-correlation-and-regression>.

1. Stanton JM. Galton, Pearson, and the Peas: a brief history of linear regression for statistics instructors. Journal of Statistics Education. 2001;9:3.

2. Gillard JW. An historical overview of linear regression with errors in both variables. 2006 October [cited 2019 Mar 2]. <http://mathsdemo.cf.ac.uk/maths/resources/Gillard_Tech_Report.pdf>.

5. Denis DJ. The origins of correlation and regression: Francis Galton or Auguste Bravais and the error theorists? Proceedings of the 61st Annual Convention of the

Canadian Psychological Association; 2000 Jun 29; Ottawa, Canada [cited 2019 Mar 2]. <https://www.york.ac.uk/depts/maths/histstat/bravais.htm>.

6. Kopf D. The discovery of statistical regression. 2015 Nov 6 [cited 2019 Mar 2]. <https://priceonomics.com/the-discovery-of-statistical-regression/>.

7. Nau R. Introduction to linear regression analysis [cited 2019 Mar 2]. <http://people.duke.edu/~rnau/regintro.htm>.

8. Wikipedia. Moment (mathematics). 2019 Feb 7 [cited 2019 Mar 2]. <https://en.wikipedia.org/wiki/Moment_(mathematics)>.

9. Hall M. Variance vs. Covariance: What's the Difference? 2019 Feb 20 [cited 2019 Mar 2]. <https://www.investopedia.com/ask/answers/041515/what-difference-between-variance-and-covariance.asp>.

10. Beaumont R. An introduction to statistics correlation. 2012 Sep 19 [cited 2019 Mar 2]. <http://www.robin-beaumont.co.uk/virtualclassroom/contents.html>.

11. Theme Horse. Z-Score: definition, formula and calculation - statistics how to [cited 2019 Mar 2]. <https://www.statisticshowto.datasciencecentral.com/probability-and-statistics/z-score/>.

12. Schumacker RE, Lomax RG. A beginner's guide to structural equation modeling. 3rd ed. New York: Routledge Taylor & Francis Group; 2010.

13. McCullagh P, Nelder JA. Generalized linear models. 2nd ed. London: Taylor & Francis Group; 1989.