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Two-year Survival Outcomes among Patients with Cholangiocarcinoma Diagnosed during 2010 in Roi-et Province, Thailand

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Abstract

Cholangiocarcinoma (CCA) is a common cancer in Thailand. This study aimed to describe epidemiological characteristics and survival outcomes of patients diagnosed with CCA at Roi-et Cancer Center during January and December 2010. Cox proportional hazard regression analysis was used to analyze data from 119 patients diagnosed with imaging techniques. The median survival time was found to be 4.4 months and the 2-year survival rate was 14.5%. From multivariate analysis by Cox proportional hazard regression, carcinoembryonic antigen (CEA) level >5 µg/l and alkaline phosphatase (ALP) >150 IU/l were found to be indicators of decreased survival time while having surgery led to longer survival time. To improve survival outcome, early detection through screening program and early diagnosis must be organized. Prognostic values of CEA and ALP should be considered.

Keywords: survival, cholangiocarcinoma, prognosis, Thailand

Introduction

In 2008, 7.8 million people died from cancer worldwide, resulting in 13% of all causes of death.[1,2] About 70% of all cancer deaths during 2008 occurred in low and middle-income countries. Cholangiocarcinoma (CCA) accounts for about 10-25% of primary liver cancers in many parts of the world, with age-standardized incidence rates (ASR) between 0.3 to 1.5 per 100,000 population in the western countries.[3-5] Most CCA patients had unresectable diseases at presentation and died within 12 months. Overall survival rate, including resected patients, was poor with less than 5% of patients survived up to five years, which has not changed significantly over the past 30 years.[6] However, many other factors might affect a patient's prognosis such as location of cancer, whether it is removable by surgery (resectable) and general health condition.[7]

In 2010, hepatobiliary cancer was one of the top five cancers in Thailand.[8] The CCA incidence in Thailand was exceedingly high, with ASR of 33.4 per 100,000 population in men and 12.3 in women.[9] Over 75% of hepatobiliary cancer in the northeastern region were found to have CCA while in other regions, proportion of CCA ranged about 25-40%.[10]

Roi-et, a province in the northeastern region of Thailand, was selected to be the study site since a high prevalence of CCA was found in the province[10] and Roi-et Hospital was upgraded to be the Regional Cancer Center of the northeastern region in May 2012. Survival time for each stage of CCA reflects severity of the disease as well as accessibility to early screening and quality of treatment received. Hence, this study focused on the survival outcome of CCA patients and factors affecting survival time of the patients.

Methods

A retrospective cohort study was designed to describe the characteristics of CCA patients, and demonstrate the survival analysis among CCA patients having different findings and receiving treatment procedures. The studied population included all patients who were diagnosed with CCA according to international classification of diseases (ICD-10) code of C269 in Roi-et Hospital during January-December 2010. All the medical charts were retrieved by nurses and statistician in the hospital. Those charts were copied with concealing name, hospital number and address. The records with evidence of computerized tomography (CT) scan, magnetic resonance imaging

(MRI) and any cholangiography were collected to confirm the diagnosis. The study process received the certificate of approval by the Committee for Research Ethics (Social Sciences) in Mahidol University, Thailand.

Data of all confirmed CCA patients were recruited from several sources, and reviewed by trained health officers, nurses and physicians. Profile and demographic data of CCA patients were accessed from Hos-XP, an application program for hospital service data. Date of CT scan examination was accounted as the diagnosis date. In addition, patients' symptoms and laboratory results were reviewed from medical records in outpatient department (OPD) and inpatient department (IPD). Records with blood tests done within 30 days before or after the date of CT scan or MRI were included in the analysis. Blood tests included testing for carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, alkaline phosphatase (ALP) and total bilirubin (TB).

All the interventions given to patients were reviewed from Hos-XP program, OPD and IPD charts, and included in the study, regardless of whether alternative treatments were received in other hospitals such as Udon Thani Cancer Center, Khon Kan Provincial Hospital and Srinagarind Hospital. Survival status of patients was obtained from database in the annual population survey of Roi-et Hospital and records in National Health Security Office. To identify the dead patients, birth date, gender and sub-district were matched. Since the information of deaths was retrieved for the period from 1 Jan 2010 to 31 Dec 2012, patients diagnosed as CCA during 1 Jan 2010 to 31 Dec 2010 were included in the study to calculate 2-year survival rate among these patients.

Afterwards, the data were checked for completion, coded and entered into a computerized database. The 25^{th}, 50^{th} and 75^{th} percentile of survival time and cumulative survival at 24^{th} month of patient with any types of CCA were calculated by Kaplan-Meier method.

Univariate analysis was conducted using log-rank test to compare the survival curve by variables in each group. Certain variables were selected purposively for multivariate model. Cox proportional hazard regression, explaining hazard ratio between patients who exposed to the given factors and those who had not exposed, was fitted. Significant level was considered at p-value less than 0.05. The given assumption was that no patient had lost to follow-up during two years. As for Cox proportional hazard regression, ratio of hazards for persons with different patterns of covariates was constant over time. The model assumption was checked by graphical approach, including hazard functions and log-minus-log plots of the baseline survival.

Results

There were total 427 patients diagnosed with CCA in the year 2010. Among them, only 271 (63.5%) records had imaging results showing suspected or confirmed CCA in either OPD or IPD chart, which included 269 CT scan, one MRI and one magnetic resonance cholangiopancreatography (MRCP). However, only 269 records were included in the study as death date was not available in two records (Figure 1).

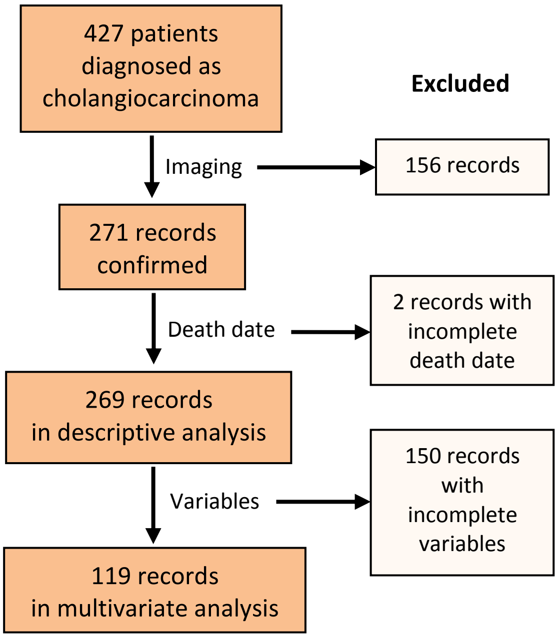

Figure 1. Recruitment of cholangiocarcinoma patient records in Roi-et Hospital for descriptive and multivariate analyses, 2010

Roi-et Hospital had started hepatic resection by one surgeon since the beginning of 2010 and thus, some patients were referred to other tertiary care hospitals. During 2-year follow up, there were 174 patients receiving any kinds of treatment only in Roi-et Hospital (not referred), seven with hepatic resection, six with cholecystectomy, six with exploratory laparoscopy, one with core needle liver biopsy and 57 with palliative surgery (Endoscopic retrograde cholangiopancreatography, bypass, stent and percutaneous transhepatic biliary drainage). Only one patient was receiving chemotherapy as an adjuvant therapy.

Among all 269 CCA patients with imaging, the median age at diagnosis was 62 years (range 40-90 years). The case distribution by demographic data, clinical presentation and treatment procedure are shown in table 1.

Table 1. Demographic characteristics, clinical presentation, treatment and outcomes of patients with cholangiocarcinoma diagnosed at Roi-et Hospital in Roi-et Province, Thailand, 2010 (n=269)

Factor	Number of case (%)	Number of death (% CFR)	Median survival time (Month)	P-value (Log-rank test)
Gender				
Male	179 (66.5)	155 (86.6)	4.3	0.52
Female	90 (33.5)	75 (83.3)	4.6	
Age (year)				
<u><</u>60	92 (34.2)	76 (82.6)	5.3	0.12
>60	177 (65.8)	154 (87.0)	3.8	
Occupation				
No	79 (29.4)	68 (86.1)	3.6	0.47
Government officer	13 (4.8)	8 (61.5)	4.4	
Farmer	155 (57.6)	137 (88.4)	4.4	
Monk	6 (2.2)	5 (83.3)	12.5	
General employee	16 (5.9)	12 (75.0)	4.1	
Health insurance				
No	3 (1.1)	3 (100.0)	1.1	0.25
Civil servants' medical benefit scheme	21 (7.8)	16 (76.2)	4.4	
Universal coverage	221 (82.2)	190 (86.0)	4.6	
Social security service	4 (1.5)	4 (100.0)	2.6	
Others	20 (7.4)	17 (85.0)	3.2	
Abdominal pain				
No	50 (18.6)	43 (86.0)	4.6	0.25
Yes	219 (81.4)	187 (85.4)	3.6	
Tumor markers				
Cancer antigen (CA) 19-9 (U/ml)				
≤200	74 (27.5)	54 (73.0)	6.4	0.058
>200	61 (22.7)	56 (91.8)	4.8	
No result	134 (49.8)	120 (89.6)	3.8	
Carcinoembryonic antigen (CEA) (µg/l)				
<5	56 (20.8)	38 (67.9)	9.9	<0.001
≥5	78 (29.0)	70 (89.7)	3.8	
No result	135 (50.2)	122 (90.4)	3.8	
Total bilirubin levels (mg/dL)				
<5	121 (45.0)	93 (76.9)	6.6	<0.001
≥5-10	23 (8.6)	21 (91.3)	3.2	
≥10	54 (20.1)	50 (92.6)	3.0	
No result	71 (26.4)	66 (93.0)	3.4	
Alkaline phosphatase level (IU/L)				
<150	50 (18.6)	31 (62.0)	13.2	<0.001
≥150-400	84 (31.2)	76 (90.5)	4.3	
≥400	64 (23.8)	59 (92.2)	2.8	
No result	71 (26.4)	64 (90.1)	3.6	
Surgery including hepatic resection, cholecystectomy, liver biopsy, and exploratory surgery				
No	239 (88.8)	207 (86.6)	4.1	<0.005
Yes	30 (11.2)	23 (76.7)	11.9	

Following the matched database of National Health Security Office and death certificate registry during 1 Jan 2010 and 31 Dec 2012, 230 CCA patients had already died without any injuries. The survival rate among 269 CCA patients during 2-year follow-up was 14.5%, in other word, the fatality rate was 85.5%. The Kaplan-Meier survival estimation showed that the median overall survival time was 4.4 months and 25% of the cases died within the first 1.9 months since the date of diagnosis (Figure 2) and no one died within one month after having therapeutic surgery (hepatic resection, cholecystectomy, liver biopsy and exploratory surgery), despite with or without palliative surgery.

Factors of CEA, CA 19-9, TB, ALP and having surgery were significantly associated with the disease prognosis (Table 1). These factors and age more than 60 years were employed in Cox proportional hazard regression model.

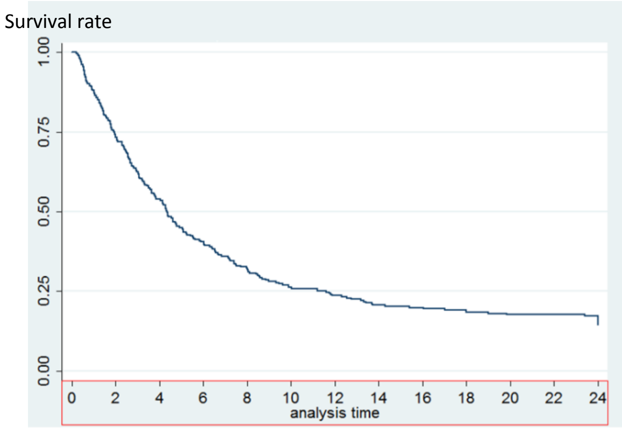

Figure 2. Kaplan-Meier survival curve of cholangiocarcinoma patients during 24 months after imaging diagnosis in Roi-et Hospital, Roi-et Province, Thailand, 2010 (n=269)

All the selected variables were re-categorized into two categories and tested for proportional hazard assumption. Eventually, all the variables met the assumption. When these variables were calculated for the hazard ratio, only three factors (CEA >5 µg/l, ALP >150 IU/l and having surgery) were significantly associated with the death outcome in 2-year follow up, with the hazard ratios of 1.7, 2.0 and 0.5 respectively (Table 2).

Table 2. Two-year follow-up hazard ratios of patients diagnosed as cholangiocarcinoma by multiple Cox proportional hazards regression in Roi-et Hospital, Roi-et Province, Thailand, 1 Jan to 31 Dec 2010 (n=119)

Clinical characteristic	Hazard ratio	95% CI
Carcinoembryonic antigen CEA ≥5 µg/l	1.7	1.10 - 2.72
Age >60 years old	1.1	0.58 - 1.53
Total bilirubin TB ≥5 mg/dl	1.3	0.78 - 2.07
Alkaline phosphatase ALP ≥150 IU/L	2.0	1.14 - 3.42
Cancer antigen CA 19-9 >200 U/ml	1.0	0.61 - 1.62
Undergoing surgery	0.5	0.27 - 0.87

Remark: log-likelihood ratio = (-375.79), p-value = 0.0001

Discussion

Two-third of all CCA cases had an evidence of CT scan or any imaging following the inclusion criteria. In other words, one-third (37%) were diagnosed without any imaging support, reflecting that accessibility to CT scan should be assessed and using ultrasonography as a diagnostics tool should be further evaluated.

The 2-year overall survival rate was 15% which was same as the result of a study in Malaysia during 1997-2007[15] and higher than the study in Cluj-Napoca during 2005-2009 (3%)[16]. However, most CCA patients (83%) from the study in Malaysia were extrahepatic CCA whereas over 99% of CCA patients in Thailand were intrahepatic type[17]. The median survival time was 4.4 months which was very close to the median survival time from the 10-year study in Malaysia[15]. Unfortunately, the survival curve could not be displayed for each type of CCA as most CCA patients were diagnosed by CT scan without specifying type of CCA. The number of deaths after surgery within 30 days was likely due to complications from surgery[18]. Nevertheless, no CCA patient in this study died within 30 days after having surgery.

In analysis by log-rank test, although demographic factors such as gender, age, occupation and health insurance did not associate with the survival outcome, TB, ALP, tumor marker and having surgery revealed a statistically affect to the survival outcome. Actually, another factor which might affect the death outcome of CCA was nutritional status that could be measured by body mass index (BMI). Despite that, information on height and weight on the date of diagnosis could not be retrieved, and BMI could not be calculated. Hence, a prospective study with a proper data collecting system should be considered.

CCA patients with different types of health insurance and occupation had the same mortality within two years, which reflected the equity to access to care in the government hospitals. This study showed that using results of CA 19-9 and serum bilirubin could not forecast the prognosis of CCA within two years, which was not consistent to a meta-analysis study in China[19].

According to the regression, six factors were included in the model, including age, CEA, CA 19-9, ALP, having surgery and TB. The sample size was decreased to 119 cases due to incomplete data. The only three factors which significantly associated with the survival outcome were CEA, ALP and receiving surgery. This could be possibly concluded that the CCA patients with CEA level more than five microgram per liter posed the hazard of 1.7 times higher than those with lower level. This could be possibly explained by positive correlation between tumor stage and CEA[20]. Hence, level of CEA could indicate treatment planning since higher cancer staging could possibly associate with higher level of CEA. However, some studies showed that both CEA and CA 19-9 could be elevated in CCA[21-23] and simply the level of CEA might not sensitive or specific for CCA[24]. One study showed 100% sensitivity and 100% specificity of using CEA (>5.2 ng/ml) and CA 19-9 (>180 U/ml)[24] while other investigators did not obtain such outstanding results[25,26].

Abdominal pain as well as levels of TB and ALP could also be used to identify type and severity of the disease. The most common physical indications are abnormal liver function tests, jaundice, abdominal pain, generalized itching, and changes in stool or urine color.[27,28] To some extent, the symptoms depend upon location of the tumor. Patients with CCA in the extrahepatic bile ducts are more likely to have jaundice while those with tumors of intrahepatic bile duct more often have pain without jaundice.[28] Nevertheless, this study showed the significance only for ALP and thus, type of CCA and location of tumor should be further explored to explain the disease stage related to symptoms and laboratory findings.

Prognosis of CCA was generally poor with a 5-year survival of less than 5%.[29,30] As most patients initially presented with advanced stage, they were not well treated by surgical resection and 75% of them died within one year after diagnosis. Focusing on treatment intervention, the patients received surgical treatment had longer survival time, yet it was hard to conclude that the surgery could prolong the life of CCA patient since physicians normally provide merely supportive care to patients in advanced stages and do not perform surgery[31].

Conclusion

The median survival time among 269 CCA patients diagnosed by CT imaging in Roi-et Hospital during 2-year follow-up was 4.4 months. The fatality rate in two years following diagnosis was 85.5% which implied that diagnosis was too late. Thus, early screening and diagnosis should be emphasized. Accessibility to disease screening and more sensitive techniques to detect the precancerous stage should be innovated as well. In addition, sensitivity and specificity of the current screening tool should be further evaluated. As the factors of CEA (>5 µg/l), ALP (>150 IU/l) and having surgery showed statistically significant affect to 2-year survival time, levels of CEA and ALP could be important information for physicians.

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Suggested Citation

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Behavioral Factors and Work-related Illnesses among Animal Traders in the Largest Night Market in Thailand

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Abstract

People who keep animals for trade or as pets are groups that encounter one of the highest risks for zoonotic diseases through close contact. This issue needs attention because zoonosis has been an important health problem around the world. The objective of this study was to investigate the behavioral factors associated with work-related illnesses among animal keepers and pet sellers in the largest night market of Thailand, located in Nakhon Ratchasima Province. A cross-sectional study was conducted using a questionnaire and a walk-through survey in the market during 1 Jan and 28 Feb 2015. Out of 75 animal traders, 60 responded to our questionnaire. Common injuries were animal scratches (56.7%), and bites (26.7%). Results from the multiple logistic regressions revealed a relationship between direct contact with animals and illnesses (odds ratio = 11.56, 95% CI = 1.16-115.20). Adequate education and promoting awareness among the animal traders who had prolonged exposure and direct contact with animals should be a main control strategy for prevention of work-related illnesses.

Keywords: Occupational infection, surveillance, work-related illnesses, zoonosis

Introduction

Diseases transmitted from animals to humans, zoonoses, pose a significant public health impact worldwide. More than 75% of the infectious disease epidemics around the world were transmitted from animals to humans through skin lesions, consumption or breathing.[1-5] Emerging zoonotic diseases can also occur by increasing people interaction with animals such as intruding into wildlife areas, keeping wild animals as pets, and bringing wild animals closer to domestic animals.[1] Epidemic could happen at any time as long as humans expose to infectious pets, and animals used for experiments and commercials.[1-5]

Zoonotic diseases have been a challenge for both veterinarians and public health professionals in Thailand as well. People who keep animals for trade or as pets have one of the highest risks for zoonotic diseases through close contacts. Study on illnesses caused by contact between animals and humans would be helpful for development of a surveillance system that can detect the diseases even before an outbreak occurs in the community. Therefore, this study was conducted to determine types of illnesses and factors contributing to the illnesses among pet sellers at the largest night market in Thailand.

Methods

The study was carried at a night market called "Save One Market" in Nakhon Ratchasima Province, in the northeastern region of Thailand. We conducted a cross-sectional survey using a questionnaire among animal traders who keep and sell animals in the market from 1 Jan to 28 Feb 2015.

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, approved the study and all participants provided a written informed consent prior to participation (COA No. 144/2015, IRB No. 479/57).

Data on animal keeping and selling practices, chances of contact with animals and risk of infecting the contagious diseases between animals to humans was collected by face-to-face interview. Sick people were defined as animal sellers or care-takers who felt sick or had fever and sought medical attention for any reasons, except chronic diseases or accidents, during the previous 12 months.

Statistical Analysis

Illnesses of all respondents were described as distribution of acute illnesses, chronic illnesses and injuries from working with animals. Acute illnesses during the previous year were used as a dependent variable for further analyses. Univariate analyses were employed using logistic regression. Key variables, based on literature and biological possibility, and variables with statistical significance using alpha value equal 0.05 from the univariate analyses were included in multivariate analysis. Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated to examine the relationship between exposures and illnesses.

Results

Nakhon Ratchasima is a northeastern province in Thailand, with 2,614,552 population in 2015. There are approximately 4,000 stores in the night market on 14 hectares of land (Figure 1). Approximately 8,000 sellers and visitors were in the market every night. There were about 120 stores selling pets.

Sixty (80.0%) out of 75 animals sellers and keepers in the night market responded to the questionnaire. Median age of the participants was 37.5 years, ranged 15-75 years, and 53.3% were male. About half (51.7%) of them had been working with animals for more than five years and 35.0% of them had educated up to high school. Majority (73.3%) of them kept the animals in their own houses while others raised or stocked the animals in rented houses (18.3%), row houses (6.7%) and apartments (1.7%). A total of 34 persons (56.7%) reported acute illness during the previous year, and most of them had dermatitis (61.8%) and acute diarrhea (61.8%) during the previous year (Table 1).

About 43.3% of participants had chronic diseases that needed continuous medication, including allergies (50.0%), hypertension (50.0%), dyslipidemia (23.1%), diabetic mellitus (11.5%) and asthma (7.7%). Most common injuries from animal attack were scratches (56.7%), followed by bites (26.7%) (Table 1).

Results from the univariate analyses showed an association between acute illnesses of animal traders and characteristics of animal keepers or sellers who worked with animals for more than five years (OR = 4.70, 95% CI = 1.38-16.45). Types of exposure that were significantly associated with illnesses include direct contact (OR = 17.47, 95% CI = 2.03-788.13), contact with sick animals (OR = 3.46, 95% CI = 1.05-11.64), and contact with animal feces (OR = 4.66, 95% CI = 1.27-18.15). Although contact with dead animals without protective equipment had a strong association, it was not statistically significant (OR = 4.18, 95% CI = 0.93-25.61). Similarly, although wearing gloves regularly when contact with animals did not show a statistically significant association, it appeared to be a factor that could promote disease prevention (OR = 0.28, 95% CI = 0.06-1.10) (Table 2).

The multiple logistic regression analysis revealed a significant relationship between direct contact with animals and illnesses (adjusted OR = 11.56, 95% CI = 1.16-115.20) (Table 3). The total number of analyzed population (n) in the final model was 60.

Discussion

Analyses of the illnesses among animal keepers and sellers showed that people who were directly exposed to animals were at higher risk of getting sick. There were incidences showing that direct exposure with animals was a primary source of infections such as in

Figure 1. Atmosphere of the "Save One Market" in Nakhon Ratchasima Province, Thailand, during 17:00 to 21:00 on 1 Jan to 28 Feb 2015

Table 1. Types of illnesses of the respondents at the "Save One Market" in Nakhon Ratchasima Province, Thailand, 1 Jan to 28 Feb 2015

Variable	Number of people	Percent
Acute illnesses during the previous year (n = 34) *(Remark: some persons had more than 1 disease)*		
Dermatitis	21	61.8
Acute diarrhea	21	61.8
Conjunctivitis	8	23.5
Pyrexia of unknown origin	3	8.8
Influenza-like illness	2	5.9
Pneumonia	1	2.9
Chronic diseases that needed continuous medication (n = 26) *(Remark: some persons had more than 1 disease)*		
Allergy	13	50.0
Hypertension	13	50.0
Dyslipidemia	6	23.1
Diabetic mellitus	3	11.5
Asthma	2	7.7
Injuries from animal (n = 60)		
Scratch	34	56.7
Bite	16	26.7
Muscle strain from handling animal	6	10.0
Jostle and stabbed	3	5.0
Gored	1	1.7

Table 2. Univariate analyses showing associations between acute illnesses and characteristics of animal keepers and sellers at the "Save One Market" in Nakhon Ratchasima Province, Thailand, 1 Jan to 28 Feb 2015

Variable	Number of sick people (%) (n=34)	Number of healthy people (%) (n=26)	Crude odds ratio	95% CI
Characteristics				
Male gender	19 (55.9)	13 (50.0)	1.27	0.40-3.99
Education lower than bachelor degree	14 (41.2)	7 (26.9)	1.90	0.56-6.80
Having a chronic disease	18 (52.9)	8 (30.8)	2.53	0.77-8.57
Working with animals for >5 years	23 (67.6)	8 (30.8)	4.70	1.38-16.45
Types of exposure with animals				
Direct contact	33 (97.1)	17 (65.4)	17.47	2.03-788.13
Contact with sick animal	22 (64.7)	9 (34.6)	3.46	1.05-11.64
Contact with dead animal without protective equipment	12 (35.3)	3 (11.5)	4.18	0.93-25.61
Contact with animal mucous or blood	15 (44.1)	8 (30.8)	1.77	0.54-6.06
Contact with animal feces	28 (82.4)	13 (50.0)	4.66	1.27-18.15
Washing and cleaning animal keeping equipment	26 (76.5)	14 (53.8)	2.78	0.81-9.80
Factors that promote disease prevention				
Wearing gloves regularly when contact with animals	5 (14.7)	10 (38.5)	0.28	0.06-1.10
Frequently using a protective mask when expose to animals	10 (29.4)	8 (30.8)	0.94	0.27-3.35
Wearing proper clothing: long sleeves, long pants	3 (8.8)	4 (15.4)	0.53	0.07-3.53
Routinely wearing boots while working	7 (20.6)	5 (19.2)	1.09	0.25-5.01
Routinely washing hands after working with animals	20 (58.8)	13 (50.0)	1.42	0.45-4.59
Sharing a drinking glass with others (compared to never share)	6 (17.6)	7 (26.9)	0.58	0.14-2.40
Inadequate zoonosis disease proficiency	26 (76.5)	24 (92.3)	3.69	0.63-38.33

an outbreak of severe encephalitis in Malaysia during 1998-1999[7]. Q fever is considered primarily as an occupational disease among workers who are in close contact with farm animals as well.[8]

Table 3. Multiple logistic regression estimating relationships between exposures and illnesses among animal keepers and sellers at the "Save One Market" in Nakhon Ratchasima Province, Thailand, 1 Jan to 28 Feb 2015 (n=60)

Factors related to illnesses	Adjusted odds ratio*	95% CI
Direct contact with animals	11.56	1.16-115.20
Duration of work >5 years	3.13	0.86-11.36
Contact with sick animals	2.10	0.57-7.73
Contact with animal feces	1.13	0.23-5.65

**Odds ratio of each variable was adjusted for all other variables in the table.*

The most common injuries resulted from animal attack in animal keepers and sellers were scratches and bites. Close contact between animal keepers and sellers and animals in the market zone offers favorable conditions for transmission of diseases by both direct contact (petting, licking or physical injuries) and indirect contact through contaminated food and domestic environments.[1-5] Risk of misdiagnosis and potential development of severe infections in immune-compromised patients are also the main concern. *Bartonella* bacteremia is most frequent in stray cats, cats in shelters/catteries and young cats infested with fleas.[9] Being bitten is potentially dangerous too because dogs and cats harbor diverse microbiota and multiple potential zoonotic pathogens in their oral cavities[10].

The exposure to dead animals without wearing protective equipment significantly increased the risk of getting sick. Although this study showed strong association by crude analysis, it was not statistically significant in multiple logistic regression, which might be due to small sample size and broad definition of the illness. In addition, those who worked with animals for more than five years also had high risk in getting sick compared with those who had less experience. It might be due to inadequate use of personal protective equipment among keepers and sellers as they were being less careful or longer exposure to animals. Although the awareness on risk factors among workers increased with longer work experience, it was determined that they did not have adequate information on occupational risk factors. Prolonged and unprotected exposure to environmental factors could constitute a risk for illness.[11] A protective equipment, especially gloves, is very crucial. Continuous education and training on using personal protective equipment appropriately should be a main control strategy for prevention of occupational infection among animal sellers. In addition to vaccination, standard and additional precautions (also known as universal precautions), and hand-washing should be followed. Awareness on occupational infection in people who are in close contact with animals should be increased for physicians as well.

Even though the market was orderly divided into zones, the risk of disease outbreak was still high due to crowdedness of the market. If an epidemic started at any point of the market, it could be spreading quickly throughout the market and would be difficult to control or investigate the causes. Consequently, developing a system to prevent a disease outbreak as a whole would be difficult. The group with the highest risk should be identified and tracked for early detection of the outbreaks. Furthermore, a routine animal-human health surveillance system should be developed in a population at risk, especially among those who directly expose to animals as part of the occupation to reduce or prevent outbreaks of zoonotic diseases in Thailand. Etiology of illnesses should be explored by further studies to provide basic information for the surveillance system.

Conclusion and Recommendation

Keeping or selling animals in the night market posed a high risk of getting ill through direct contact with animals. Thus, when those people were getting sick, their work information should be informed to the medical practitioner to highlight zoonosis as one of the possible causes for the illness. Wearing gloves, boots and masks while touching animals could reduce the risk of illnesses. Adequate education and promoting awareness among the sellers should prevent occupational zoonotic diseases. The information acquired from this study could be used to develop a passive surveillance system for zoonoses in both sellers and visitors to pet markets in Thailand.

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Malaria Surveillance at Thai-Myanmar Border, Mae Sot District, Tak Province, Thailand, July 2013

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Abstract

Malaria epidemic along Thai-Myanmar border is still an ongoing occurrence. We explored malaria surveillance systems in Mae Sot District in order to improve the detection and response efforts in the region. The main objective was to study effectiveness of the malaria surveillance systems at Thai-Myanmar border. Data were collected by reviewing medical records, interviewing personnel at operation levels and observing the surveillance sites. The reporting system under Bureau of Epidemiology (BOE) was hospital-based, with 76% coverage, 100% positive predictive value and 100% timeliness. It was acceptable and stable, yet less flexible. The reporting system of Bureau of Vector Borne Disease (BVBD), existed from the village level, was used to obtain information for malaria prevention and control. The reports were sent via online malaria database system. Its sustainability could be affected by withdrawal of the Global Fund. Information of both systems was closely linked at the hospital (district) level. At border areas, health personnel regularly shared information through buddy health volunteers from both countries. Collaboration between epidemiology and information technology units should be strengthened in BOE and the reporting forms should be simplified by BVBD. The central Thai government should consider how to sustain the malaria surveillance and response system in the long run.

Keywords: malaria, surveillance, cross-border

Introduction

Malaria has been a leading cause of morbidity and mortality in Thailand for many decades. All four types of malaria are prevalent in the country. Malaria epidemics occurred periodically in high risk areas, especially along Thai-Myanmar and Thai-Cambodia borders. Non-immune migrant workers are the most vulnerable and most affected.[1]

In 2010, annual parasite index was 0.4 per 1,000 population, and total 22,342 Thai cases and 21,969 non-Thai cases were reported. About 68.0% of Thai cases and 96.0% of non-Thai cases were from Thai-Myanmar border.[2]

An effective malaria surveillance system is useful and important for identifying trends of malaria cases and deaths, early detection and respond to outbreaks, and planning prevention and control activities.[3,4]

The malaria surveillance system in Thailand composes of two reporting systems, including the national notifiable disease surveillance system of the Bureau of Epidemiology (BOE), and the national malaria control program of the Bureau of Vector

Borne Disease (BVBD) (Figure 1). Malaria data at the community level were reported to the systems by health volunteers.[5]

This study on malaria surveillance systems was conducted by the International Field Epidemiology Training Program (IFETP)-Thailand, in collaboration with the ASEAN Plus Three Field Epidemiology Training Network[6], at a border district.

The objectives of this study were to study effectiveness of the malaria surveillance systems by describing quantitative and qualitative attributes of the national disease surveillance system of BOE, and qualitative attributes of the BVBD reporting system; exploring the linkage between BOE and BVBD systems; and the collaboration for malaria surveillance between Thailand and Myanmar.

Methods

Study Design

A cross-sectional study was performed, with description on purposes, population under surveillance, resources, processes, operations, information dissemination and usefulness of the systems.

Assessment included estimation of coverage or sensitivity, positive predictive value (PVP), timeliness, simplicity, flexibility, stability, data quality and duplication. The coverage and PVP were described as percent.[7] According to the BOE guideline, timeliness of malaria reporting, the duration from date of diagnosis in hospital or health center to date of data received in the bureau, should be within one week.[8]

Data Collection

The study site was in Mae Sot District, Tak Province, Thailand. A malaria case was a patient who visited Mae Sot Hospital during January to December 2012, was diagnosed (ICD-10) and confirmed as malaria by blood smear or rapid diagnostic test.[9]

Medical records and reports from Mae Sot Hospital, Tak Provincial Health Office (PHO) and notified database were reviewed. Regarding quantitative attributes of the BOE system, sample size for coverage estimation was 240 medical records and PVP estimation was 76 reports.[10,11]

For qualitative assessment of both systems, total 26 persons were interviewed, including staff from Mae Sot Hospital, district health office, health center and port health office, provincial vector borne disease control center (VBDC 9.3), district vector borne disease control unit (VBDU 9.3.1), malaria clinic (MC), malaria post (MP), border malaria post (BMP) and health office at border checkpoint.

Results

Mae Sot District is located in western Thailand and borders with Myawaddy Township of Kayin State, Myanmar. Total area is 1,986 km^2, with the population of about 119,835 Thai and over 100,000 migrants.

There were 88 villages in total 10 sub-districts. One general hospital (420 beds), 22 health centers, eight MC, 10 MP, three BMP, one private hospital (120 beds) and 18 private clinics were situated in the district.

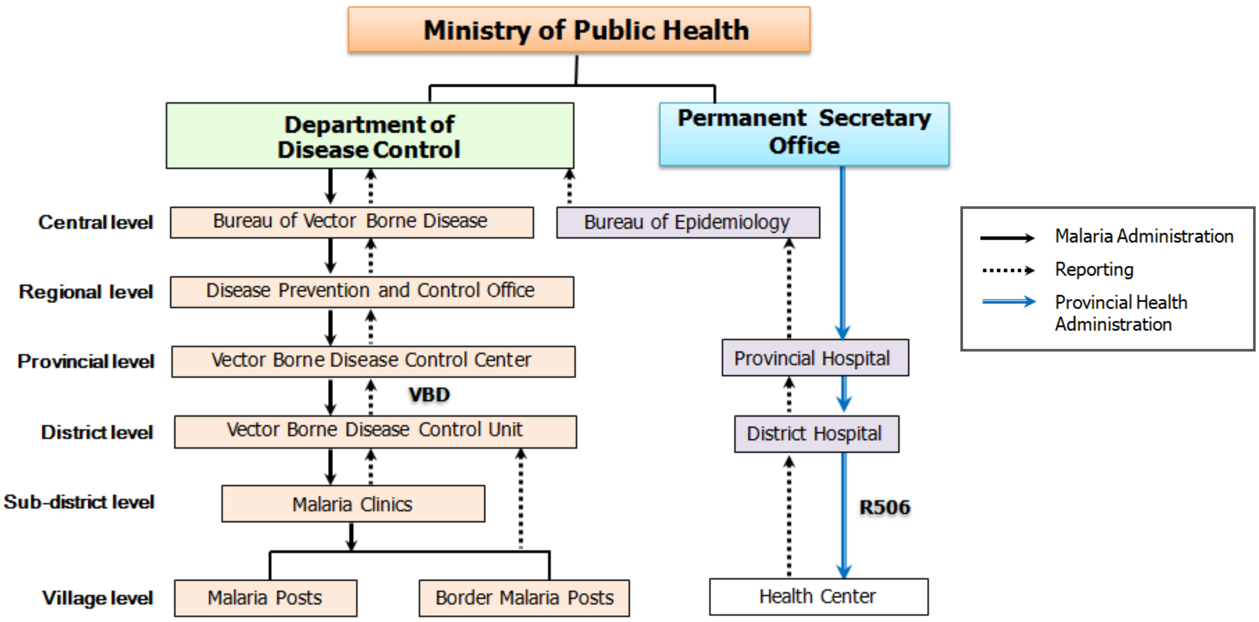

Figure 1. Description of malaria surveillance systems in Thailand[4], 2012

Reported Malaria Cases

During 2012, total 122 malaria cases from Mae Sot were reported in the BOE system while majority of them were Thai. The total number of cases reported in the BVBD system was 1,034, and 82.1% of them were reported from MC and MP (Table 1). Of 1,034 cases, 265 cases were Thai and 769 were foreigners.

Table 1. Malaria cases reported in district hospital (R506) and district vector borne disease control unit (VBDU), Mae Sot District, Tak Province, Thailand, 1 Jan to 31 Dec 2012

Source	R506	VBDU
Hospital	117	119
Health center	5	0
Malaria clinic	-	623
Malaria post/ Border malaria post	-	226
Active case detection	-	66
Total	122	1,034

About 76.0% of cases reported in the BOE system were infected with *P. vivax* and 24.0% were *P. Falciparum*. In the BVBD system, 811 (78..4%) cases with *P. vivax*, 220 cases (21.3%) with *P. falciparum* and three cases (0.3%) with *P. malariae were reported*. Proportion of *P. falciparum* and *P. vivax* from 2008 to 2012 showed a reversing trend in both surveillance systems (Figures 2 and 3).

The BOE System

Purpose and Usefulness

In the reporting system of BOE, information on diagnosis, treatment and follow-up was used to describe the epidemiology of malaria in Mae Sot District and guide actions in reducing malaria burden, complications and deaths. In addition, data of in-patients were filled in the epidemiological reporting form 3 (EP-3) and sent to VBDC for timely response.

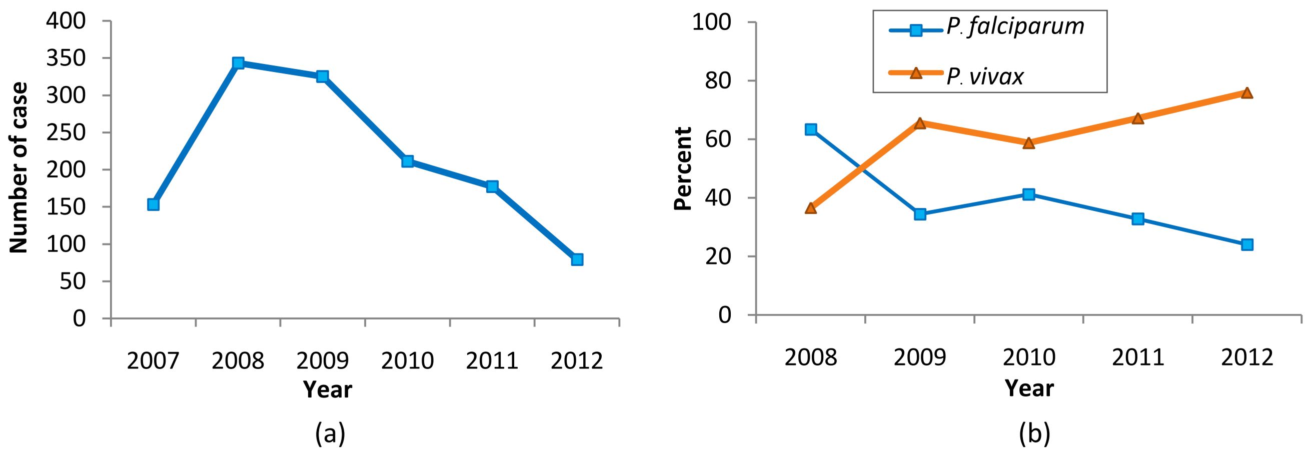

Figure 2. Malaria cases (a) and proportion of malaria species (b) reported from Mae Sot District, Tak Province to Bureau of Epidemiology, Thailand, 2007-2012

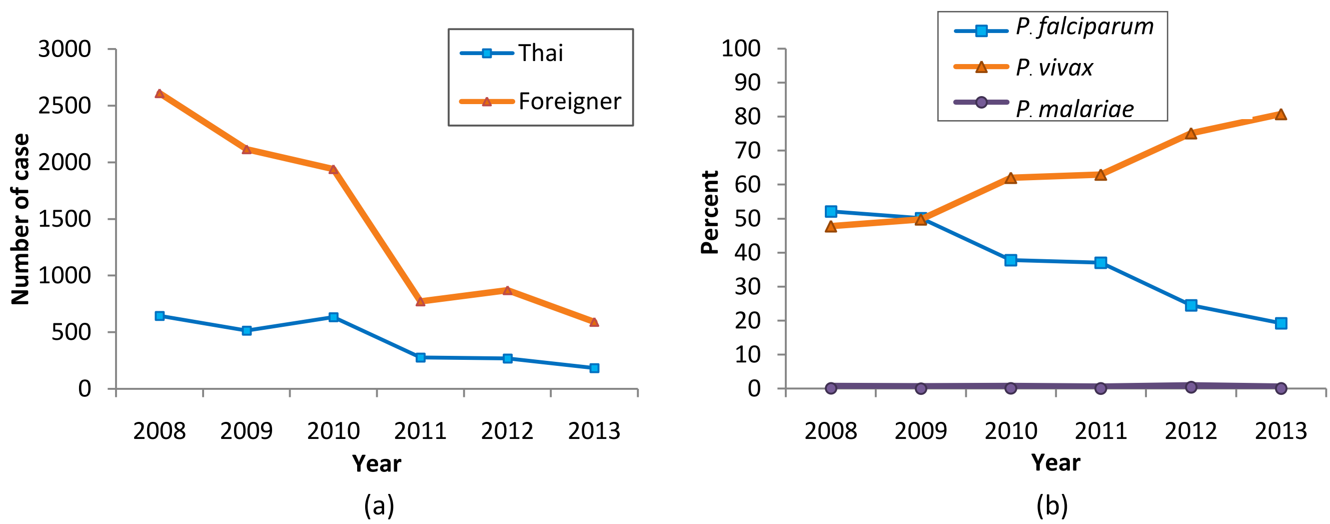

Figure 3. Malaria cases (a) and proportion of malaria species (b) reported from Mae Sot District, Tak Province to Bureau of Vector Borne Disease, Thailand, 2008-2013

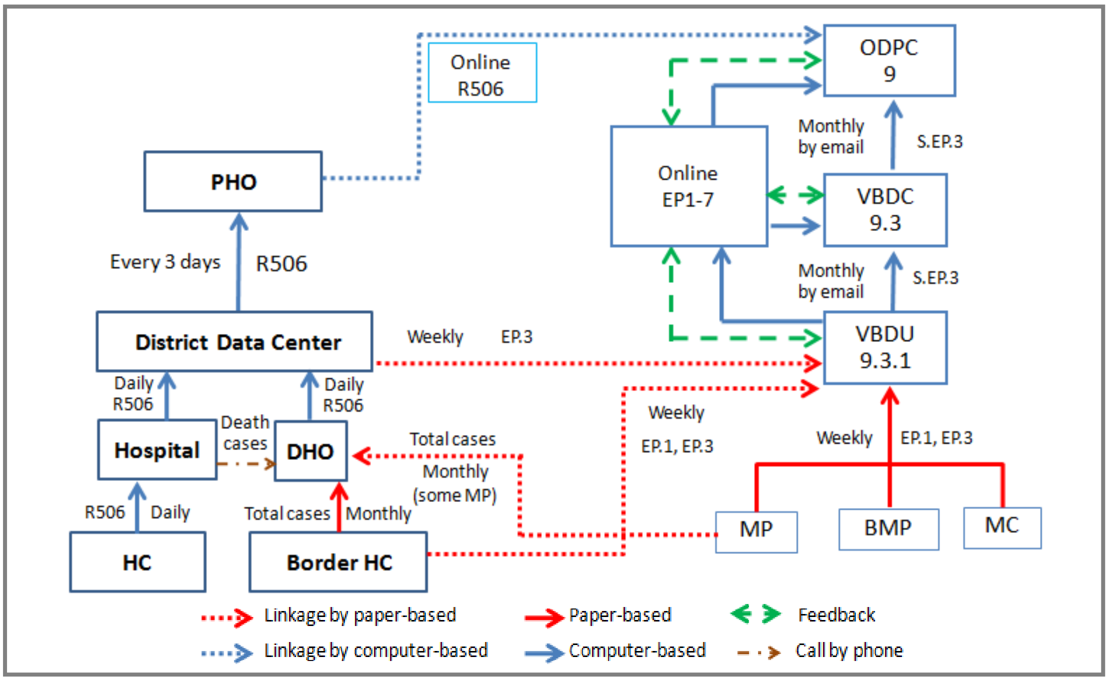

Figure 4. Description on reporting and data dissemination of malaria surveillance systems in Bureau of Epidemiology and Bureau of Vector Borne Disease, Thailand, 2012

Process and Operation

The BOE reporting system was based in health facilities. When patients visited Mae Sot Hospital, they were registered using HOSxP software, including information on diagnosis and treatment. The epidemiologist in the hospital extracted data from the HOSxP database by E1 form and reported in the BOE system. Afterwards, data were entered in EP-3 forms for malaria cases, which were collected by a staff from VBDU every Friday. If an admitted patient was found to have *P. falciparum*, the case was immediately reported to VBDU 9.3.1 to initiate an investigation.

In case a malaria patient who was living out of Mae Sot District was identified, the epidemiologist in the hospital reported to the respective VBDC office in the area where the patient was residing. After data were cleaned and entered into a notification form of BOE, information was sent to district data center and submitted to PHO every three days (Figure 4).

Data from health centers at the sub-district level were sent to the district health office (DHO) using the online BOE system in daily basis. Data from MP situated in mountainous or hard-to-reach areas were sent to DHO through epidemiological reporting forms, EP-1 and EP-3, on monthly basis. In DHO, the data were collected, checked, finalized and sent to the district data center every day by BOE system. Data in BOE[12] were accessible by the regional offices of disease prevention and control (ODPC) and other VBDC.

Coverage and PVP

Total 173 malaria cases from the inpatient department (IPD) were identified from ICD-10 database of Mae Sot Hospital. A total of 168 medical charts were reviewed and 138 cases met the case definition (CD).

Out of 62 cases from the outpatient department (OPD), there were 30 cases with available OPD cards and laboratory confirmation. Therefore, total 168 malaria cases were confirmed. Out of 154 cases met the reporting criteria, 117 cases were reported at the hospital level and coverage was76.0% (Figure 5).

During the study period, BOE received 103 reports of malaria cases from Mae Sot District. Out of them, 76 medical records were available for review and all met the case definition. Thus, calculated PVP of the BOE system was 100% at the central level.

Timeliness and Data Quality

Out of 76 cases reported to BOE, two cases reported before date of diagnosis were excluded. About 93.0% of cases were reported in one day while 100% were reported to BOE within one week, which was aligned with the timeframe indicated in the BOE guideline.[8]

Gender, age, onset date (+/-2 days) and nationality were compared between medical records and information at the hospital, provincial and central. Data quality was 100% for gender, 96.0% for age and 87-91% for nationality. Discrepancies of onset date between medical charts and the notification records existed, with 52.0% accuracy of the onset date.

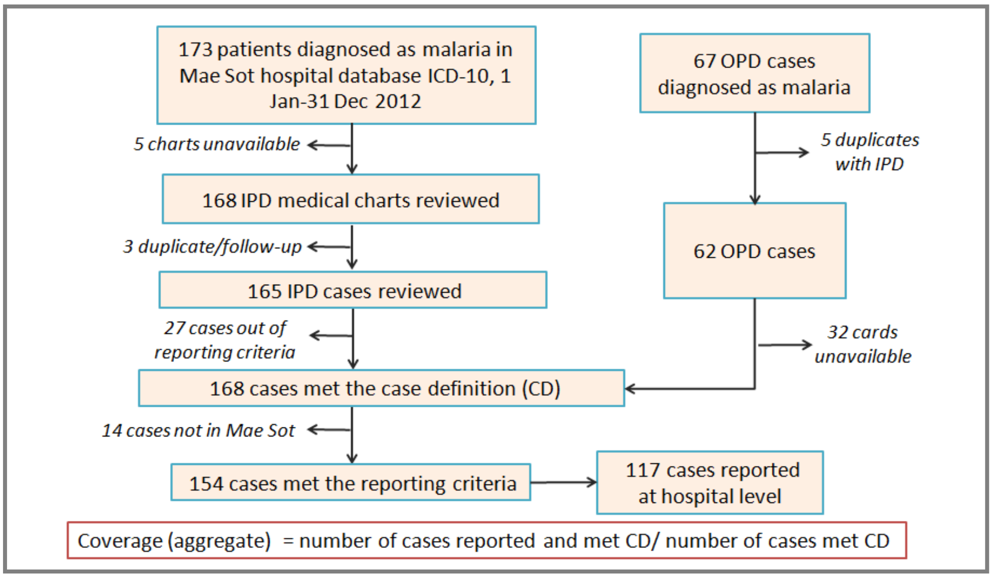

Figure 5. Process on estimating coverage of the malaria surveillance system in Bureau of Epidemiology, Thailand, 2013

Simplicity and Flexibility

According to information from interviews, the reporting forms of the BOE system were easy to fill in and utilize the information. As the online reporting software of the BOE system was linked to HOSxP, the data recorded were automatically reported and was able to analyze easily.

In addition, results were disseminated weekly through the BOE website[12]. However, it was not easy to add new information in the reporting forms due to limitation of the software which was designed at the national level.

Stability

Manpower was adequate to operate the BOE system at the hospital (4 officials), DHO (3 officials) and health center (2 officials). Budget and materials were supplied by the government at all levels. Data back-up system existed at the surveyed reporting units of all levels. In addition, there were external funding sources from World Health Organization (WHO) and European Union (EU) to support the special projects. Although annual training was provided to officials in the hospital, only two out of three sites at the DHO received training.

The BVBD system

Purpose and Usefulness

Information in the BVBD system was used mainly for malaria prevention and control. Villages in Mae Sot were classified for malaria risk[13] in 2012 and resulted as 32 villages in A1, 27 in A2, 29 in B1 and 20 in B2. In addition, information was used to develop plan for annual relocation of medical staff and MP to endemic areas, entomology survey and health education before the epidemic season.

The VBDC weekly compared the reported cases with data from the previous year for outbreak detection and response. If higher number of cases was reported in A1 and A2 areas, or one indigenous case was found in B1 and B2 areas, VBDU was informed to conduct an investigation in the affected village. Subsequently, a special case detection official from VBDU was dispatched with a mobile malaria clinic for screening, testing and providing health education in the communities.

Process and Operations

In the BVBD system, information collected in villages were sent as case reports to VBDU 9.3.1 weekly, with EP-1/EP-3 from MP, EP-1 from BMP and EP-1/EP-3 from MC. In VBDU 9.3.1, data were collected from all sites, including the district hospital, consolidated by computer-based forms (S.EP-3) and sent to provincial VBDC 9.3 by email monthly (Figure 4).

In VBDC 9.3, malaria data from nearby districts were also aggregated and sent to ODPC 9 in Phitsanulok Province using S.EP-3 forms on monthly basis. There were seven types of epidemiological reporting forms in VBDC 9.3 (Table 2).

The VBDU 9.3.1, VBDC 9.3 and ODPC 9 uploaded and shared all malaria data (EP-1-7) on the website of BIOPHICS (the centre of excellence for biomedical and public health informatics) at <www.biophics.org/malaria/r10>.[14] The website was a project under Mahidol University in cooperation with BVBD and supported by Global Fund (GF).

Table 2. Types of epidemiological reporting forms in Bureau of Vector Borne Disease, Thailand, 2012

Form	Description	Type of data
EP-1	Blood record form	Individual
EP-2	Monthly report of malaria case detection	Aggregate
EP-3	Investigation and radical treatment of malaria cases	Individual
EP-4	Monthly report of investigation and radical treatment of malaria cases	Aggregate
EP-5	Report of malaria focus investigation	Individual
EP-6	Malaria case registration	Individual
EP-7	Summary of surveillance operations	Aggregate

Simplicity and Flexibility

Case definition of malaria was known at every level. The reporting forms of BVBD were easy to be used by personnel in BMP and VBDU. However, at VBDC, there were many forms with many variables to fill in while some of these variables were duplicated. Laboratory and information technology (IT) staff could not fill data in the forms since they did not have enough information or knowledge on epidemiology, surveillance system and the malaria control program.

In VBDU, data were filled in manually and entered into the "Malaria off-line" software. Data were easy to analyze, interpret and disseminate by IT staff in VBDU and VBDC; and easy to generate new reports using the online system. Despite that, users of BVBD reporting system could not add new information into the standard questionnaires.

Stability

Sustainability of resources supported by GF could be an important issue to be considered when the support was likely to terminate at the end of 2016. At the village level, when the responsible staff was absent, there was no additional staff for replacement. In VBDU and VBDC levels, although some workers were available to assist in laboratory and IT, there was no additional staff to replace the epidemiologist.

For the resources, two major stakeholders, the Thai government and GF, were providing support to the sub-district level. However, MP, BMP, MC at the village level received support only from GF through Tak PHO and ODPC 9 (Table 3). Trainings on epidemiology and surveillance were provided for epidemiologists regularly. Nevertheless, laboratory and IT staff were trained less frequently.

Cross-border Malaria Surveillance System

The port health office for the border area between Mae Sot and Myawaddy Districts was located in Thailand. The main function of the office was to detect sick migrants who were provided with a screening form and asked to bring the forms back to the office after they got diagnosis and treatment from health facilities. The office sent a summary report to ODPC 9 and the international disease section in Bureau of General Communicable Disease, Ministry of Public Health. If needed, the office contacted staff in Myawaddy Hospital for detailed case investigation by phone or via Myanmar village chief.

In addition, there were buddy health volunteers at 33 informal ports along the river border with many parallel villages in both sides. Myanmar buddy health volunteers shared information with Thai buddy health volunteers who then reported to health center and DHO. DHO was prompted to inform and response if abnormal events occurred. DHO also shared and verified information with Myawaddy Hospital via a Myanmar coordinator in the port office. Afterwards, staff in Myawaddy Hospital would verify data through the line of management. Normally, hospitals in Myawaddy and Mae Sot shared information via phone call.

Table 3. Resources utilized for the malaria surveillance system in Bureau of Vector Borne Disease, Thailand, 2012

Type of resource	Malaria post/ Border malaria post	Malaria clinic	Vector borne disease control unit	Vector borne disease control center
Incentive	-	-	GF	GF
Salary	GF	Gov	Gov, GF (IT)	Gov, GF (IT)
Laboratory equipment	GF	Gov	Gov, GF, others	Gov, GF
Material	GF	Gov	Gov, GF, others	Gov, GF
Medicines	Gov	Gov	Gov	Gov

Remark: Gov = Government, GF = Global Fund

Discussion

The BVBD system revealed a decreasing trend of malaria cases among non-Thai during 2010 to 2011, which could be due to intensified malaria control activities in Myanmar under the support of GF[15]. In addition, effective treatment might lead to lower *P. falciparum* cases when compared to those with *P. vivax*, with intensive intervention and better patient compliance[16].

Data from the BVBD system were collected from both health facilities and communities. The system provided more representative information for magnitude of malaria problem as non-Thai cases and patients from MC and MP were included in the system. Surveillance offices covered most sub-districts, enabling early detection and treatment. Furthermore, the malaria online component allowed public to access to data which could be useful for rapid responses. However, the BVBD system was mainly supported by GF. Once the support from GF was terminated, sustainability could be affected, especially the IT system. In the BOE system, as malaria was included together with other notifiable diseases, the sustainability revealed higher despite less flexibility and lower sensitivity.

Incomplete coverage of the BOE system in malaria reporting was likely to be related to technical (software) issues, and coordination between IT and surveillance staff. Connection problems existed occasionally between HOSxP and the software of BOE. During 2012, different numbers of malaria cases were reported at district data center, Tak PHO, and BOE.

High PVP of the BOE system might be due to simple definitions for case diagnosis and reporting which were understandable at all levels. Clearly established criteria for timeliness and schedule for data submission might contribute to the satisfying timeliness as well. Data quality in general was acceptable, except accuracy of onset date. Discrepancy of onset date between medical charts and hospital notifiable records could be caused by language barrier or inconsistency of patient responses at OPD and IPD.

As VBDC and VBDU were the main sectors to respond to malaria outbreaks, functioning of the BOE system relied on the BVBD system as well. While reports in the BOE system reflected hospital-based situation, the BVBD system indicated malaria situation in both hospitals and communities.

Involvement of Thai and Myanmar community volunteers across the border as buddy health volunteers rendered wider coverage of malaria surveillance, led to early detection and prompt response of abnormal events, and enhanced disease control and prevention activities.

Limitations

The geographical scope was limited in this study as it only focused on a border district. Although all staff from the district level were interviewed, only a few offices in sub-district and villages were reached out for information. Moreover, coverage, PVP, timeliness and data quality were estimated only for the BOE reporting system.

Conclusion

Two malaria surveillance systems in Mae Sot District, the BOE and the BVBD, perform well as border surveillance systems. Review on both systems provided a comprehensive description of malaria situation in this area. Acceptable performance of the BOE surveillance system was observed while the BVBD system was useful for providing a more complete picture of malaria situation. However, sustainability might be affected by termination of resources from the GF.

Recommendations

In the BOE surveillance system, close collaboration between epidemiology and IT units for routine checking on data validity of the automatic program was recommended. In addition, optional case finding after completing IPD medical records should be considered, especially after long holidays or power outage, to increase the reporting coverage.

Reporting forms in the BVBD system should be simplified to reduce workload. In addition, feedbacks from users should be periodically reviewed to improve reporting and control actions. Sustainable support for the malaria online database and local MP should be seriously considered. Training of laboratory and IT staff for epidemiology and the surveillance system should be conducted as well.

The officials working on both systems should be encouraged to carry out regular internet-based data cross-checking and validation using online databases from the websites of BOE[12] and BIOPHICS[14] to avoid data discrepancies between the two systems. Formal or informal communication between cross-border checkpoints, local health offices and community-based buddy health volunteers should be supported and strengthened further.

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