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Zoonotic and vector borne agents causing disease in adult patients hospitalized due to fever of unknown origin in Thailand

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ABSTRACT

Objective: To determine the etiologic agents of fever of unknown origin among populations in agricultural communities and to assess the possible risk factors for zoonotic infections.
Methods: Hospitalized patients with fever of unknown origin under physician care were asked to participate and provide blood samples for laboratory tests and screening for endemic diseases at the hospitals. Samples were stored at –80 ˚C until they were tested at Chulalongkorn University to identify additional pathogens.
Results: We were able to identify the etiologic agents in 24.6% of the 463 enrolled patients. Zoonotic and vector borne agents were confirmed in 59 cases (12.7%). Dengue virus (7.3%) was the most frequently detected disease followed by scrub typhus (3.2%). There were two cases of comorbidities of scrub typhus and dengue fever. The other six cases of zoonoses were leptospirosis, melioidosis, and *Streptococcus suis* infections. Patients with zoonotic/vector borne agents noticed rats in their houses and reported having contact with livestock feces more frequently than those patients without zoonotic/vector borne agents.
Conclusions: Dengue virus and scrub typhus were mostly detected in the rainy season. During this specific season, clinicians should raise awareness of those diseases when any patients are admitted to the hospital with fever of an unidentified source.

1. Introduction

Emerging infectious diseases (EIDs) comprise those infectious diseases whose incidence in humans has increased in the past two decades and threatens to increase in magnitude in the future[1]. EIDs include new or unrecognized diseases, those that are spreading to new geographic areas and hosts, as well as those that are re-emerging. More than 60 percent of EIDs have zoonotic origins[2]. Zoonotic EIDs in livestock pose a significant risk to farmers and others in the agricultural production supply chain[3]. Some examples of important zoonoses occurring among Thai livestock farmers and wildlife hunters/butchers that have been notified under the National Communicable Disease Surveillance System in Thailand include anthrax, food poisoning, hepatitis E, leptospirosis, melioidosis, brucellosis, campylobacteriosis, leptospirosis, rabies, salmonellosis, taeniasis, trichinellosis, tuberculosis, toxoplasmosis, *Streptococcus suis*, and *Streptococcus equi* infection[4]. In recent years, zoonoses have been recognized as increasing public health problems in Thailand. This is also evident in the detection of outbreaks of emerging zoonoses at different localities in the world. If surveillance, detection, prevention, and response among these at-risk population groups are lacking or inadequate, an EID can result in far-reaching and severe global consequences. Surveillance, detection, prevention, and response among these at-risk population groups are essential to avert severe global consequences from deadly EIDs. Early detection of infectious

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All study procedures were reviewed and approved by the Thai Ethical Review Committee for Research in Human Subjects, Ministry of Public Health Thailand (35/2555 and 76/2557). Written informed consent was obtained from individual study subjects at enrollment for both the interview and specimen collection.

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diseases in high-risk populations is also vital for limiting the spread of EIDs. Disease surveillance by gathering and generating data on disease incidence and prevalence in high-risk populations, as proposed here, can provide the basis of evidence for early detection and prompt response to EIDs in Thailand. The objectives were to determine etiologic agents of fever of unknown origin (FUO) among populations in agricultural communities and to assess the possible risk factors for zoonotic infections.

2. Materials and methods

We conducted the study from November 2013 to August 2015 in agricultural communities in Chiang Mai, Nakorn Ratchasima, and Sa Kaeo Provinces with a total of seven participating community hospitals (two hospitals each in Chiang Mai and Nakorn Ratchasima Provinces and three hospitals in Sa Kaeo Province). This population-based surveillance represented seven agriculture districts of the provinces. Hospitalized patients with fever of unknown etiology were asked to participate in the study if they met the inclusion criteria including 1) fever of more than 38 ℃ for 48 h or more, or 2) fever of more than 38 ℃ either continuous or intermittent for 14 days or more, or 3) fever of more than 38 ℃ with no known cause even after extensive diagnostic testing, and 1) aged 18 years or greater, and 2) resident of Chiang Mai, Nakorn Ratchasima or Sa Kaeo Provinces.

Written informed consent was obtained from individual study subjects at enrollment for both the interview and specimen collection. Patients were excluded if they declined to participate in the study, had an HIV infection, or were unable to respond to the questionnaire. All study procedures were reviewed and approved by the Thai Ethical Review Committee for Research in Human Subjects, Ministry of Public Health Thailand (35/2555 and 76/2557).

After a written informed consent was obtained, all participants answered a standardized questionnaire. A direct person-to-person written informed consent was obtained from all participants (adults ⩾ 18 years old) at enrollment. Occupational exposure to livestock or wildlife was assessed by project staff at the participating hospitals through patient interviews. The participants were examined and received treatment by attending physicians who made the decision to collect blood samples, cerebrospinal fluid (CSF), or nasopharyngeal (NP) swabs for laboratory tests at each hospital. Initial screening for endemic diseases including influenza, dengue, leptospirosis, scrub typhus, salmonellosis, typhoid, and malaria was done at the surveillance hospitals. Undiagnosed specimens were transported to a central laboratory where testing for several infectious agents was performed.

All interviews and the collection of blood specimens were conducted in the study hospitals. All blood specimens were centrifuged and separated serum was stored at –80 ℃ until they were tested at the WHO Collaborating Center for Research and Training on viral zoonoses, Chulalongkorn University for further investigation to identify the pathogens, including potential newly emerging pathogens.

2.1. Nucleic acid extraction

Nucleic acids were extracted from 200 μL of the NP or CSF samples or 100 μL of whole blood using an easyMAG automation (bioMérieux, France) and eluted in 50 μL of elution buffer, according to the manufacturer's recommendations.

2.2. Pathogen detection by molecular technique

2.2.1. 2014

Nucleic acids from NP or whole blood samples were tested by conventional reverse transcription-PCR for detection of 16 viral families including Adeno-, Alpha-, Arena-, Astro-, Bunya-, Corona-, Flavi-, Hanta-, Henipa-, Herpes-, Influenza-, Lyssa-, Paramyxo-, Phlebo-, Rhabdo-, Seadorna- viruses and 16S rRNA for bacteria detection. The positive PCR product was confirmed by sequencing. Nucleic acids from NP were tested for respiratory virus by 2 platforms including Anyplex™ FluA/B Typing Real-time for detection of 2009 pandemic H1N1, influenza A virus and influenza B virus and Anyplex™ II RV16 detection assay for adenovirus, influenza A virus, influenza B virus, parainfluenza virus 1–4, rhinovirus A/B/C, respiratory syncytial virus A-B, bocavirus 1/2/3/4, metapneumovirus, coronavirus 229E, -NL63, -OC43, and enterovirus. Nucleic acids from CSF samples were tested by real-time PCR assays for detection of 8 human herpes virus (ARGENE®, bioMérieux, France). PCR results were interpreted according to the manufacturer's recommendations.

2.2.2. 2015

Nucleic acids from NP samples were tested by FTD Respiratory Pathogens 21 (Fast Track Diagnostics, Luxembourg, Belgium) a multiplex real-time PCR assay for the detection of 21 respiratory pathogens [influenza A, influenza A (H1N1), influenza B, coronaviruses NL63, 229E, OC43 and HKU1, parainfluenza 1, 2, 3 and 4, human metapneumovirus A and B, rhinovirus, respiratory syncytial viruses A and B, adenovirus, enterovirus, *Parechovirus*, bocavirus, *Mycoplasma pneumonia*]. Nucleic acids from whole blood samples were tested by two platforms of multiplex real-time PCR including FTD Tropical fever core (Fast Track Diagnostics, Luxembourg, Belgium) for detection of dengue virus, chikungunya virus, West Nile virus, *Plasmodium* spp., *Rickettsia* spp., *Leptospira* spp., *Salmonella* spp. and FTD Tropical fever Asia (Fast Track Diagnostics, Luxembourg, Belgium) for detection of Japanese encephalitis virus, Hantaan virus/Seoul virus, *Burkholderia mallei/pseudomallei* and *Leishmania* spp.

2.3. Statistical analysis

All data were entered into Microsoft Access version 2007. Data

management and all analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were applied to describe distributions of enrolled cases by demographics, syndromes, and etiologies.

3. Results

There were 463 patients enrolled into the study. The median age of the enrolled patients was 50.5 years old (interquartile range 33–65 years of age) and 53.0% were female. Among the study subjects reporting occupation, farmers and laborers were the most common, 32.9% and 32.3% respectively, followed by officers (15.6%), students (11.0%) and housewives (8.3%).

The most common syndromes reported from enrolled patients included 187 cases (41.5%) of fever with unidentified source, respiratory symptoms 150 cases (33.3%), gastrointestinal symptoms 51 cases (11.3%), hemorrhagic symptoms 39 cases (8.6%), jaundice 15 cases (3.3%) and neurological symptoms 9 cases (2.0%). The median period between date of onset and date of seeking medical care was 3.5 days (interquartile range 1–5 days). Of enrolled patients, 24.6% (114 cases) were identified for etiological agents. Regarding the laboratory testing from the sites at the hospitals, they were performed for agents believed to be endemic to the region in addition to a variety of emerging pathogens as shown in Table 1. The specimens collected in 2013–2014 were negative either for viral family PCR assays or 16S rRNA (data not shown). The negative results from multiplex real-time PCR assays were not shown in Table 1.

Overall, zoonotic and vector borne agents were confirmed in 59 (12.7%) of 463 study patients. There were 53 cases detecting vector borne diseases including dengue virus (34 cases), scrub typhus (15 cases), comorbidities of scrub typhus and dengue fever (2 cases), Japanese B encephalitis (1 case) and malaria (1 case). The other six cases of zoonotic diseases included leptospirosis (3 cases), melioidosis (2 cases), and *Streptococcus suis* (1 case).

Among the six study patients who had zoonoses, three had fever with an unidentified source, two had fever with jaundice, and one had fever with respiratory symptoms. Fever with an unidentified source and fever with respiratory symptoms were mostly found in vector borne disease. The results were similar to a group of non-zoonotic and vector borne disease (Table 2).

General hygiene practices such as washing hands before eating food and after defecation were in good standards in both groups of patients with zoonotic/vector borne agents and patients without zoonotic/vector borne agents. However, the majority of patients with zoonotic/vector borne agents noticed rats in or near the household area and had contact with animal feces, greater than in those patients without zoonotic/vector borne agents [82.9% *vs.* 71.0%, 95% confidence interval (*CI*) 0.84–4.67 and 20.0% *vs.* 10.3%, 95% *CI* 0.80–5.42] as shown in Table 3. The prevalence ratio of regularly drinking alcoholic beverages among patients with zoonotic/vector borne agents was 13.5 (95% *CI* 2.35–77.21) when compared to the patients without zoonotic/vector borne agents (Table 3).

Table 1
Distribution of pathogens identified among enrolled patients.

Pathogens	Tested cases	Positive (*n*)	Positive (%)
Melioidosis titer	13	2	15.4
CSF culture	3	2	66.7
Streptococcus pneumoniae		1	
Japanese B encephalitis virus		1	
PCR technique	463	30	6.5
Dengue fever[1]	189	20	10.6
Plasmodium spp	189	1	0.5
Influenza A[2]	45	2	4.5
Influenza B[2]	45	1	2.3
Adenovirus[2]	45	1	2.3
Metapneumovirus[2]	45	1	2.3
Rhinovirus[2]	45	1	2.3
Parainfluenza[2]	45	1	2.3
Influenza H1N1[3]	7	1	14.3
Herpes virus	2	1	50.0
Dengue screening test	158	19	12.0
Influenza screening test	45	1	2.2
Salmonella screening test	97	0	0.0
Typhoid screening test	59	0	0.0
Scrub typhus screening test	184	17	9.2
Leptospirosis screening test	138	3	2.2
Malaria screening test	24	1	4.2
Hemoculture	70	12	17.1
Streptococcus species		1	
Streptococcus suis		1	
Streptococcus group A		1	
Streptococcus viridans		2	
Gram negative bacilli		4	
Gram positive cocci		1	
Klebsiella pneumonia		1	
Tuberculosis		1	
Urine culture	15	7	46.7
Pseudomonas aeruginosa		1	
Acinetobacter baumannii		2	
Escherichia coli		3	
Enterococcus sp.		1	
Stool culture	6	2	33.3
Fungi		1	
Yeast		1	
Sputum culture	8	3	37.5
Acinetobacter baumannii		1	
Tuberculosis		1	
Candida albicans		1	

[1]: FTD Tropical fever core assay; [2]: FTD Respiratory Pathogens 21 assay; [3]: Anyplex™ FluA/B Typing.

Enrolled study subjects who raised animals accounted for 316 subjects (69.6%). Contact with dogs (74.8%) was the most common reported animal exposure followed by chickens (65.0%), cats (58.9%), cattle (1.9%), pigs (1.0%), and goats (0.5%). All participants exposed to those animals showed a low proportion of regular use of personal protective equipment as following using boots (13.5%), using gloves (8.1%), using masks (5.2%), and using aprons (3.3%).

Table 2

Etiologic agents categorized by syndrome among study participants at the sites.

Pathogens	Syndrome (*n*)					
	Fever with respiratory symptoms	Fever with neurological symptoms	Fever with gastrointestinal symptoms	Fever with jaundice	Fever with haemorrhagic symptoms	Fever with unidentified source
Zoonotic disease	1	0	0	2	0	3
Vector borne disease	11	0	7	0	6	29
Non-zoonotic and vector borne disease	9	1	1	0	1	17

Table 3

Health factors of enrolled patients.

Health factors		Patient without zoonotic/vector borne agents [*n* (%)]	Patient with zoonotic/vector borne agents [*n* (%)]	Prevalence ratio	95% *CI*
Underlying diseases		107 (42.3)	14 (34.1)	0.71	0.35–1.41
Frequency of alcoholic beverage	Never	175 (69.2)	27 (63.4)	1.00	
	Sometimes	76 (30.0)	12 (26.8)	0.90	0.46–2.07
	Always	2 (0.8)	5 (9.8)	13.50	2.35–77.21
Frequency of consumption of uncooked food	Never	141 (56.6)	21 (55.3)	1.00	
	Sometimes	108 (43.4)	17 (44.7)	1.06	0.53–2.10
Wash hands before eating food		201 (79.8)	35 (85.4)	1.48	0.59–3.71
Wash hands after defecation		229 (92.7)	36 (90.0)	0.71	0.24–2.56
Having contact with any sick person over past one month before getting sick		33 (13.1)	6 (14.6)	1.13	0.44–2.90
Having injection over past one month before getting sick		46 (18.3)	9 (22.0)	1.26	0.56–2.82
Noticed rats in or near the household area		179 (71.0)	34 (82.9)	1.98	0.84–4.67
Having contact with animal feces		23 (10.3)	7 (20.0)	2.17	0.80–5.42

4. Discussion

The overall incidence of zoonotic and vector borne agents in adult patients diagnosed with FUO was 12.7% (59/463). Our data are similar to data published in a study from the Republic of Armenia[5], but with lower incidence than other studies[6,7]. Prasad *et al.*[6] systemically reviewed etiology of severe febrile illness in low- and middle-income countries and found 3.8% having bacterial zoonosis and 28.5% having malaria while Perez-Avraham *et al.*[7] conducted a study among febrile Bedouin patients in Southern Israel and found 27% of study population diagnosed with one or more zoonoses. A reason of the different results may be from a difference of study populations and surrounding environment including geographical areas and animal populations, which influence high or low risk areas for zoonotic and vector borne diseases. Our study was conducted in one regional hospital and six community hospitals in three provinces. Although the majority of study sites were located in communities of agriculture areas, the majority of the study population was mixed between farmers and laborers, who might not work in the field areas and have rare exposures with animal reservoir or arthropod vectors. The characteristics of our study population could have diluted the effect of risks from zoonotic and vector borne disease.

From Table 1, dengue fever and scrub typhus were the major causes of patient hospitalized FUO. The results were similar to other studies that found dengue was responsible for febrile illnesses in sub-Saharan Africa and other countries[8-10]. A study in Rajasthan, India[11] presented 49.1% of patients with FUO that were confirmed by scrub typhus immunoglobulin M antibodies by ELISA and had a similar result to another prospective study among patients with FUO in Chennai City, South India[12], presenting 23% of patients positive for immunoglobulin M antibodies against *Orientia tsutsugamushi*. FUO is one of the diseases notified by law under the National Communicable Disease Surveillance System in Thailand. In the National Epidemiological Record, FUO rates had been steady at approximately 500–700 cases per 100 000 population or 300 000–500 000 cases per year. A peak of FUO was reported to mostly occur in the rainy season of Thailand[4]. The seasonal occurrence of scrub typhus is more frequent during the rainy season[13] and a study of distribution, seasonal variation, and dengue transmission in Sisaket, Thailand[14] showed more *Aedes aegypti* larvae per household in the rainy season. There are multiple causes of FUO but dengue and scrub typhus were the most common causes in Thailand that were associated with reporting syndromes of fever with an unidentified source as shown in Table 2. Scrub typhus is known to occur all over India. These data might underestimate dengue and scrub typhus in the National Epidemiological Record because of their nonspecific clinical manifestations. The incidences of dengue and scrub typhus were probably reported under an item of FUO. Supporting the screening test for early diagnosis of dengue fever and scrub typhus should be highlighted as the significance of early reporting and ruling out scrub typhus in FUO cases, especially in the community hospitals.

Zoonotic diseases found in our study included leptospirosis, melioidosis, and *Streptococcus suis* infection. Seasonal variation of leptospirosis and melioidosis were observed, with the highest incidence during rainy season from July to October[4,15]. This seasonal variation showed a similar pattern with the report of FUO as discussed above. A higher proportion of observing rats in the household of patients with zoonotic/vector borne agents when compared to those without zoonotic/vector borne agents could be associated with rodent-borne disease, especially for leptospirosis. Temperature in the rainy season is also a major factor influencing potential reproduction of rodents, which tends to increase during this season[16]. Another rodent-borne disease, in particular, hantavirus infections, can be detected in patients who initially present with pulmonary syndromes and hemorrhagic fever with renal syndromes[17]. There were 21 patients hospitalized due to fever with respiratory symptoms and 7 patients hospitalized due to fever with hemorrhagic symptoms in our study. However, a testing of hantavirus did not include laboratory methodology. The high proportion of

observing rats in the household among the populations in Thailand, according to 71% in patients without zoonotic/vector borne agents and 82.9% in patients with zoonotic/vector borne agents emphasizes the need to strengthen surveillance and find etiological agents of rodent-borne diseases in Thailand.

From the study population in this study, only 10% of participants exposed to those animals reported wearing boots regularly at work, and less than 10% reported wearing masks, aprons, and gloves. The use of good hygiene and work practices, and wearing personal protective clothing and equipment (PPE) can protect farm workers from other infectious diseases including zoonotic diseases[18]. Effective enforcement and measuring the use of PPE, and training courses to provide perceptions of health threats and benefits gained by wearing PPE should be implemented at the farms or in the people who are risk to zoonoses.

There are many pathogens such as trypanosomiasis, schistosomiasis, monkeypox, West Nile virus, Japanese encephalitis, brucellosis, *Bartonella* species, anthrax, *etc*. causing zoonotic fever and vector borne disease of patients with FUO. Unfortunately, many pathogens were not selected to be in the test panel of laboratory tests in this study. It is suggested that patients with fever of an unidentified source of infection should be considered for further laboratory investigation to identify commonly found pathogens among those patients.

We found 13% of patients hospitalized due to FUO in Thailand showed evidence of zoonotic and vector borne agents. Dengue virus and scrub typhus were most frequently detected in the study populations. The number of cases of FUO, from dengue fever, scrub typhus and other zoonotic diseases including leptospirosis and melioidosis detected in our study were highest in the rainy season from July to October. Clinicians should be aware of those diseases when patients are admitted to the hospital with fever of an unidentified etiology, especially during the rainy season, to give a proper clinical management before the disease progresses.

Conflict of interest statement

We declare that we have no conflict of interest.

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