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Field Epidemiology Training Program, Bureau of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625901734-5, Fax: +6625918581, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Epidemiological and Serological Study of Re-emerging Diphtheria in Dansai District, Loei Province, Thailand, June to October 2012

Pailin Phupat[1,*], Sittisak S[2], Pimrat K[3], Junti K[4], Jivapaisarnpong T[5], Paveenkittiporn W[5], Pittayawonganon C[1]

1 Field Epidemiology Training Program, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand
2 Dansai District Health Office, Loei Province, Thailand
3 Dansai Hospital, Loei Province, Thailand
4 Office of Disease Prevention and Control for Region 6, Khon Kaen Province, Department of Disease Control, Ministry of Public Health, Thailand
5 Department of Medical Sciences, Ministry of Public Health, Thailand

* Corresponding author, email address: vinctvis@yahoo.com

Abstract

In July 2012, two fatal cases of diphtheria were reported from Dansai District of Loei Province, where had been free from diphtheria for a decade. An investigation was conducted to confirm the etiology, identify source of the outbreak and measure the prevalence of antibody to diphtheria toxin among the population. Medical records were reviewed. Active case finding and throat swab screening were done in all villages. Throat swab samples were sent for culture. *Corynebacterium diphtheriae* isolates were sent for toxin testing and a subset for multi-locus sequence typing (MLST). A serological survey of diphtheria antibody was done in 132 respondents in two villages. A total of 37 cases and 26 carriers were found. Total 18 (48.6%) cases were children. Two fatal cases (5.4%) were adults. All 16 (61.5%) children carriers had received the recommended doses of DTP or dT from the EPI program in the past. In the serological survey, 39.4% (52/132) had protective antibody, including 68.8% (11/16) of children and 35.3% (41/116) of adults. About 79% of people who had protective level received at least one dose of diphtheria toxoid. With MLST, three new subtypes were identified, including ST243, ST244 and ST245. Dansai outbreak was confirmed with the emergence of new pathogenic strains. A low proportion of sera (39.4%) had protective antibody level. A booster dose of diphtheria and tetanus toxoid should be considered.

Keywords: diphtheria, outbreak, serological survey, Loei, Thailand, *C. diphtheriae*

Introduction

Diphtheria is a disease of upper respiratory tract caused by *Corynebacterium diphtheriae*. Toxins of the organism cause systemic effects and may lead to death. With an overall case fatality rate of 5-10% in the pre-vaccine era,[1] this disease is a major cause of illness and death among children worldwide.[1,2]

In the early 1970s, diphtheria was highly endemic in Thailand, resulting in child deaths.[2] After introduction of diphtheria vaccine into the expanded program for immunization (EPI) in Thailand during 1977, number of diphtheria cases declined.[2,3] The EPI program schedules five doses of diphtheria-tetanus-pertussis (DTP) vaccine at ages of 2, 4, 6 and 18 months, and 4-5 years.[3] Booster doses of diphtheria and tetanus toxoids (dT) are given to 6th grade students aged around 12 years.[3,4] In 2006, Thailand Ministry of Public Health (MOPH) began providing dT instead of tetanus toxoid (TT) to pregnant women in antenatal clinics and health promoting hospitals (HPH) so as to protect newborns from diphtheria as well as tetanus.[5]

In nationwide cross-sectional surveys conducted during 1999, 2003 and 2008, coverage for three doses of DTP vaccine (DTP3) was reported to be 97%, 98% and 99%, and for four doses (DTP4) was 90%, 93% and 97% respectively.[3,4] Coverage for five doses of DTP vaccine (DTP5) was 54% in 2003 and 79% in 2008 while coverage of dT vaccine among 6th grade students was 94% in 2008.[4]

With increasing vaccine coverage, Thailand aimed for diphtheria elimination.[2] Despite that, in 2010, an increase in locally acquired cases was reported in the far southern provinces of Thailand.[6] In addition, during July 2012, provincial health office in Loei, a northeastern province, notified Bureau of Epidemiology (BOE) of two laboratory-confirmed fatal diphtheria cases in Dansai District[7] although Loei

Province had been free of diphtheria for the past decade (Figure 1).[6] Thus, from July to October 2012, BOE, Office of Disease Prevention and Control for Region 6 and local surveillance and rapid response team (SRRT) conducted a joint investigation. Objectives were to confirm the diagnosis, identify source of the outbreak, measure the prevalence of antibody to diphtheria toxin among the population as an indicator for coverage of the vaccination program, and recommend prevention and control measures.

Method

This investigation involved case finding, active surveillance, serological survey for diphtheria antibody, and laboratory assays for toxin production and genetic analysis.

Case and Carrier Finding

We reviewed medical records of hospitalized patients with diagnosis of exudative tonsillitis or oral candidiasis, as lesions of these diseases are similar to respiratory diphtheria, between April to August 2012 at Dansai Hospital. We also collected medical records of persons who visited Dansai Hospital or one of 15 HPH of Dansai District with symptom of white membrane in the upper respiratory tract, or was diagnosed as diphtheria or suspected diphtheria by a physician from August to October 2012. Case investigation reports and laboratory results from Dansai Hospital and provincial hospital were reviewed.

Active Surveillance for Diphtheria

In collaboration with health volunteers, active surveillance for diphtheria was done in all 97 villages of Dansai District through a weekly door-to-door survey which was done using a newly developed case screening protocol. A person who had sore throat, white membrane in the upper airway or history of direct contact with a known case or carrier was examined and a throat swab was collected by trained health care officers for culture.

Case Definitions

A suspected case of diphtheria in this investigation was defined as a person who lived in Dansai District and had fever, sore throat or white membrane in the upper respiratory airway between June to October 2012. A confirmed case was a suspected case tested positive for *C. diptheriae* by culture.

A carrier was a person who did not have any sign or symptom of diphtheria, but was positive for *C. diptheriae* and diphtheria toxin. However, in presence of a confirmed case or carrier in the same sub-district, a person tested positive only by culture was also regarded as a carrier, despite results of toxin testing.

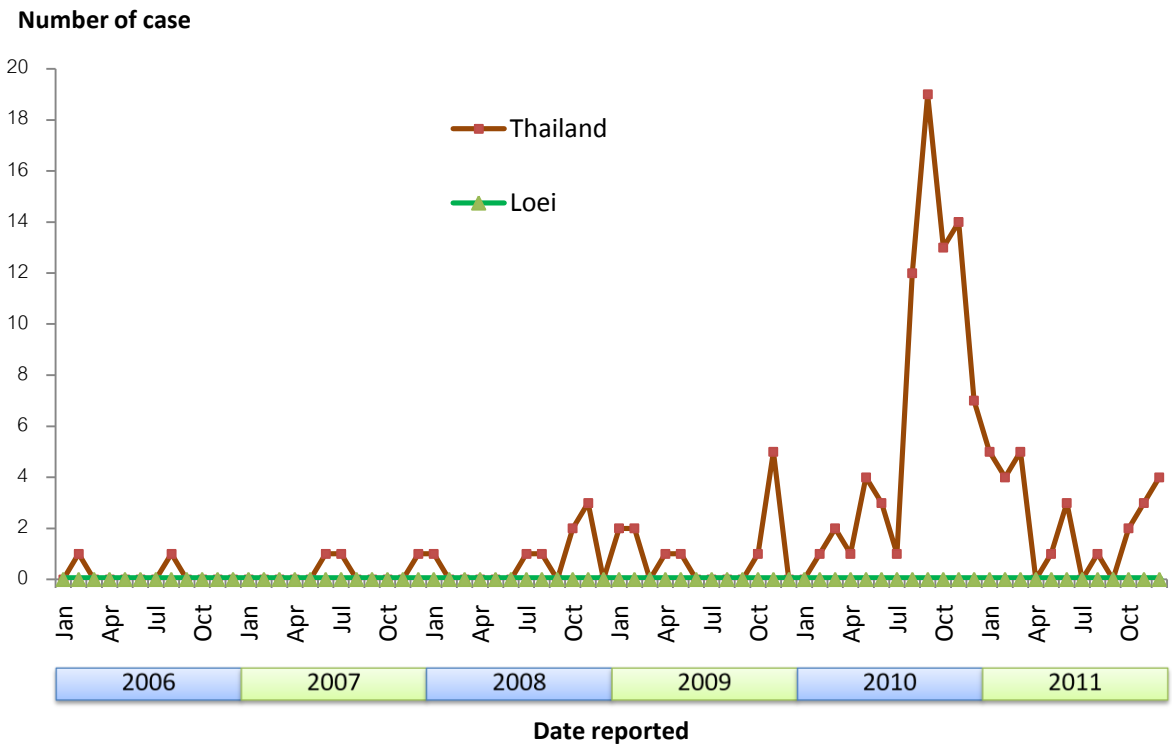

Figure 1. Number of diphtheria cases reported in the national passive surveillance in Dansai District, Loei Province and Thailand, 2006-2011[6]

A close contact was a person who had direct contact via sharing food, drinking glass or living in the same house with a suspected or confirmed case within 14 days before the case's onset of symptoms until recovery or death, or had direct contact with a carrier within 14 days before throat swab collection until last day of chemoprophylaxis of the carrier.

Laboratory Testing

Throat swab samples of villagers from 97 villages were sent for *C. diphtheriae* culture at the Dansai Hospital, Loei Provincial Hospital and National Institutes of Health. *C. diphtheriae* colonies growths from all positive swab samples were sent for toxin test by Elek method[7] which is used to detect in vitro toxin-producing organisms, including *C. diphtheriae*. Some of specimens with toxigenic *C. diphtheriae* were sent for identification using multi-locus sequence typing (MLST) and compared with known *C. diphtheriae* genetic sequences on the MLST website database.[8]

Serological Survey

A cross-sectional serological survey was done in two villages: Pakpong Village in Pakman Sub-district and Dandoo Village in Pong Sub-district, which were selected purposively because in Dandoo Village, there was one case with recent date of onset and thus, had not yet provided mass vaccination while in Pakpong Village, mass vaccination was administrated only a few days earlier, which was too soon to generate the antibodies. Mass vaccination was completed in the other villages more than two weeks before our serological survey and there was no confirmed case or carrier identified in there.

The target sample size of 145 persons was calculated based on 20% estimated prevalence on protective level of serum diphtheria antibody using 95% confidence interval (CI). Volunteers were selected by random sampling using a name list ordered by age. Excluded people were children less than five years old, disabled persons, pregnant women, people who did not stay in the villages during two weeks before the onset of confirmed case in that village, and those who were unwilling to participate. Finally, there were 132 total respondents, including 62 persons from Pakpong (total population 282 persons) and 70 persons from Dandoo (total population 129 persons).

A face-to-face interview was conducted using a structured questionnaire. The variables collected were demographic data, health status, immunization history, signs, symptoms and complications of diphtheria (fever, sore throat, cough, white membrane in throat, anorexia, swelling of neck, chest tightness, dyspnea and muscle weakness), and risk factors such as contact and travel history. Throat swabs and 5mL of blood samples were collected from all respondents.

Antibody Testing

Total 132 blood samples were sent to the Institute of Biological Products in MOPH to test for anti-toxin level by micro-cell culture technique.[9] Level less than 0.1 IU/mL indicated non-protection while level 0.1 IU/mL or more was considered as protective.

Ethical Clearance

As a rapid public health response to this outbreak, an ethical clearance for human research was not required.

Results

Study Site

Dansai District in Loei Province is located in the northeastern region of Thailand bordering Lao PDR. About 85% of the area is mountainous. According to records in Dansai Hospital, estimated population in this district during 2012 was 40,120. Approximately 2% were Hmong hill tribe and most people worked in agriculture.[10]

Case and Carrier Finding

Total 37 confirmed cases of diphtheria, with onset from 24 Jun to 17 Oct 2012, were found (Figure 2) in nine out of 10 sub-districts of Dansai District (Figure 3). Overall case incidence between June to October 2012 was 92 per 100,000 population. Among all confirmed cases, 18 cases were children less than 15 years while 19 cases were adults. Age ranged from 5-72 years (mean 22.1 years). Majority was in the age group of 5-14 years (45.9%), followed by 20-44 years (40.5%) and the lowest was those older than 44 years (13.5%). No cases were found among children less than five years and those aged 15-19 years. There were 15 males (40.5%) and 22 female (59.5%). Seven cases (18.9%) were fully vaccinated, according to the EPI program, while all were children (Table 1).

Most confirmed cases had mild symptoms although 24% needed hospitalization. Two adults died from cardiac complications (case-fatality proportion 5.4%). Both cases were never vaccinated and had history of heavy alcohol drinking. The first case, aged 40, was infected with human immunodeficiency virus (HIV) and the second case, aged 25, was a methamphetamine addict from the Hmong hill tribe.

Clinical manifestations of all cases were sore throat (94.6%), fever (89.2%), white membrane in throat (51.4%), cough (37.8%), poor appetite (35.1%) and

neck swelling (16.2%). A toxigenic strain of *C. diphtheriae* was found in 78.4% of confirmed cases (Table 1).

During the investigation, 26 carriers of *C. diphtheriae* were found in Dansai District (64 per 100,000 population). Among them, 16 (61.5%) were children less than 15 years old and 10 were adults, with mean age of 13.5 years (range 4-41 years). As with the cases, most carriers aged between 5-14 years (57.7%), followed by 20-40 years (23.1%), 15-19 years (15.4%) and 4 years or less (3.8%). There were 15 males (57.7%) and 11 females (42.3%). All 16 child

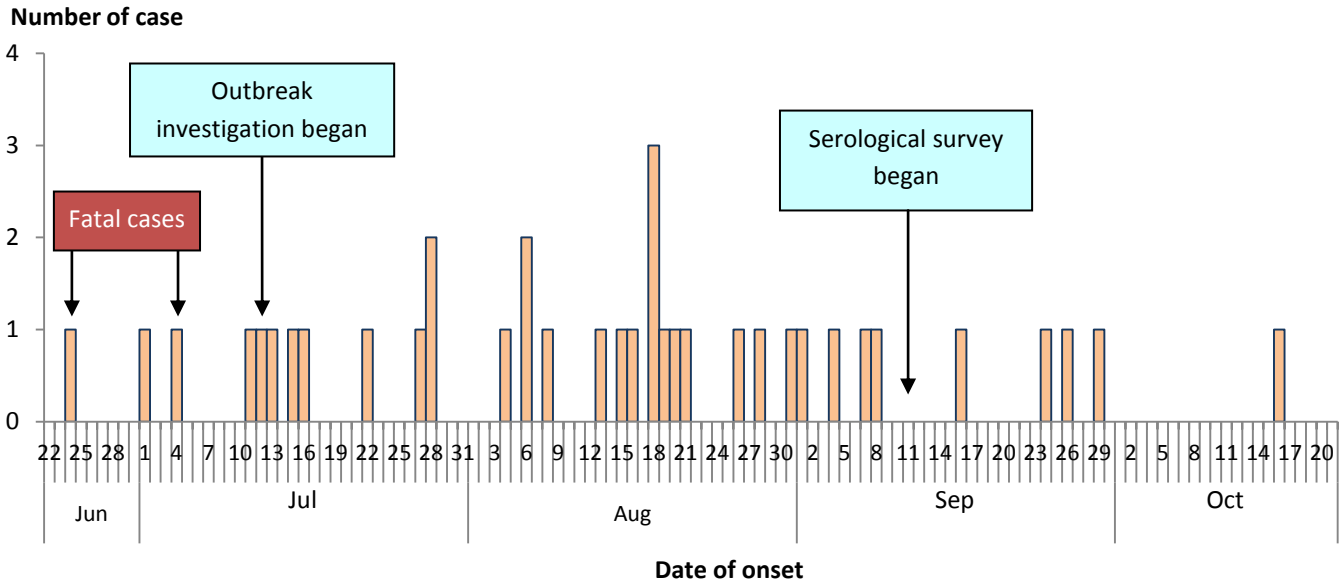

Figure 2. Confirmed diphtheria cases by date of onset in Dansai District, Loei Province, June to October 2012 (n=37)

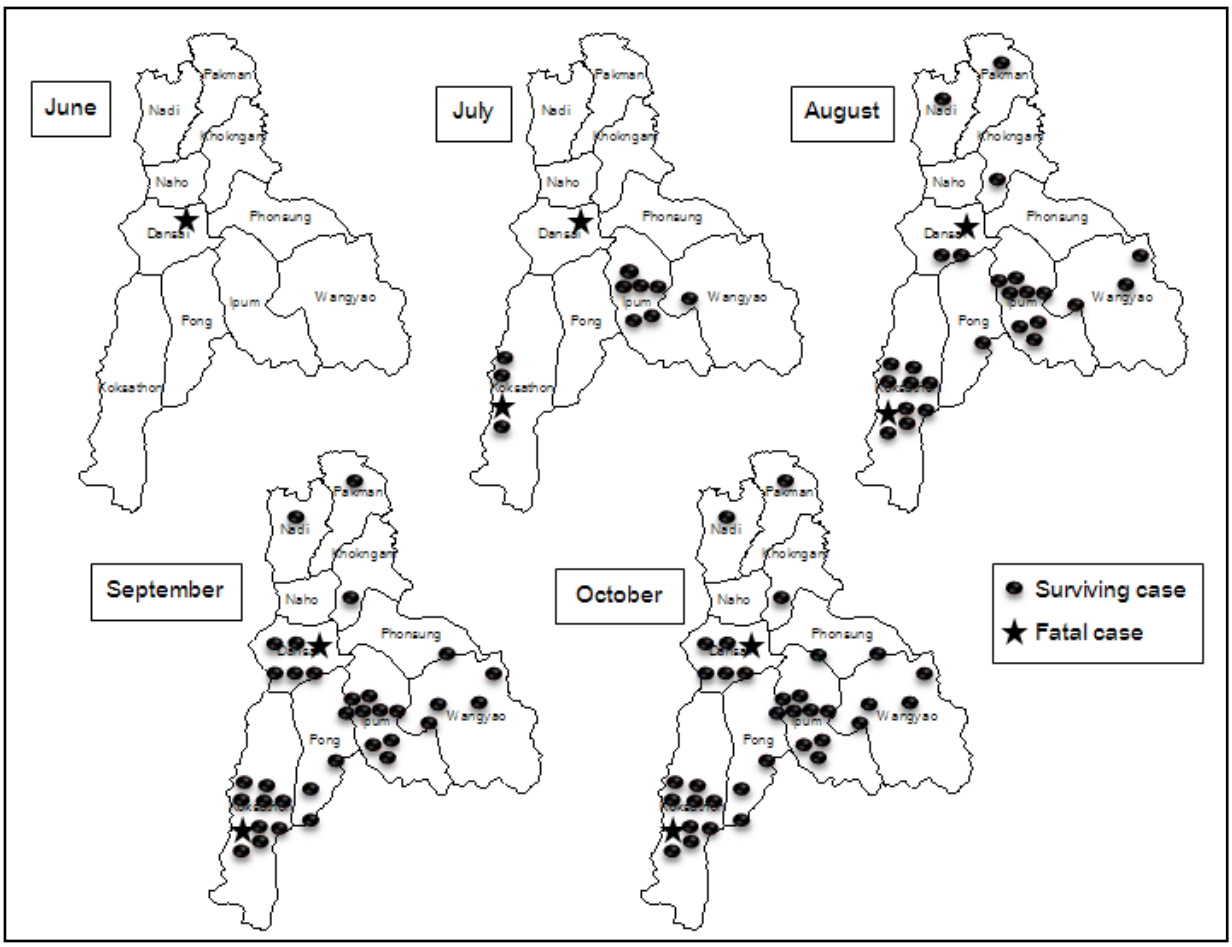

Figure 3. Distribution of confirmed diphtheria cases by month of onset and sub-district, and by case outcome, Dansai District, Loei Province, June to October 2012 (n=37)

Table 1. Characteristics of confirmed cases and carriers of diphtheria in Dansai District, Loei Province, June to October 2012

Variable	Case (n=37)		Carrier (n=26)	
	Number	Percent	Number	Percent
Gender				
Male	15	40.5	15	57.7
Female	22	59.5	11	42.3
Age (year)				
0-4	0	0	1	3.8
5-14	17	45.9	15	57.7
15-19	0	0	4	15.4
20-44	15	40.5	6	23.1
≥45	5	13.5	0	0
History of complete diphtheria vaccination				
0-14 years	7	18.9	16	61.5
≥ 15 years	0	0	4	15.4
Overall	7	18.9	20	76.9
Hospitalization				
Yes	9	24.3	0	0
No	28	75.7	0	0
Laboratory testing				
Positive to *C. diphtheriae*	37	100	26	100
Elek test				
Positive	29	78.4	17	65.4
Negative	5	13.5	8	30.8
Not done	3	8.1	1	3.8

carriers had received the recommended doses of DTP or dT from the EPI program and four (15.4%) adult carriers had completed immunization in the past. The Elek test showed that 65.4% of carriers were tested positive for toxin of *C. diphtheriae* strain while 30.8% were negative (Table 1).

Among 22 toxigenic *C. diphtheriae* specimens sent for MLST, three new clonal patterns of diphtheria genetic sequences were detected: ST243 (13 cases, two carriers), ST244 (one case, three carriers) and ST245 (one case, two carriers) (Figure 4,5). The first clonal emerged Dansai was ST243. All three clonal pattern were found at the center of Dansai, Ipum Sub-district.

Diphtheria Anti-toxin Serological Survey

Among a total of 132 persons included in the serological survey, 16 were children, including one confirmed diphtheria case, and 116 were adults. For gender, 54 persons were male and 78 were female.

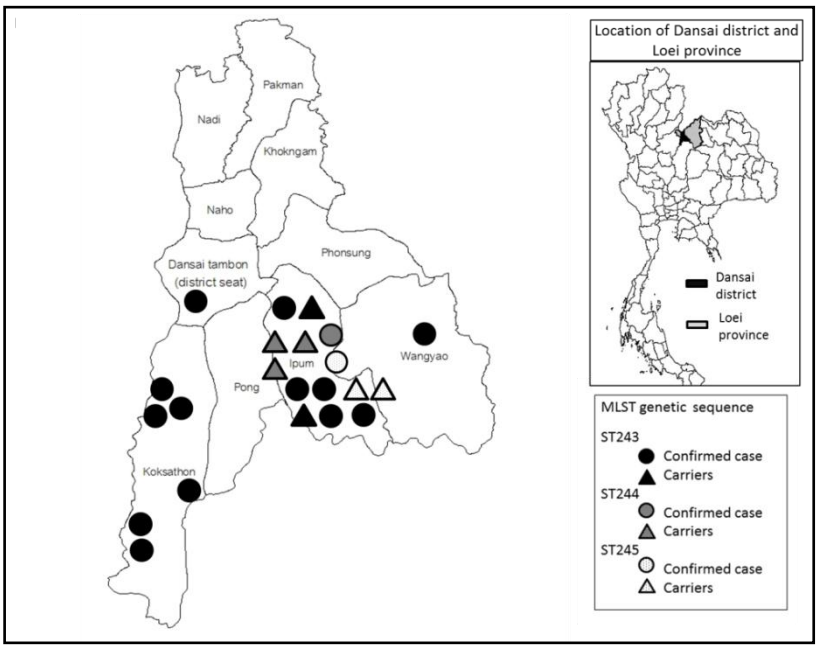

Figure 4. Distribution MLST of *C. diphtheriae* isolation from confirmed cases and carriers by sub-districts, Dansai District, Loei Province, June to October 2012 (n=22)

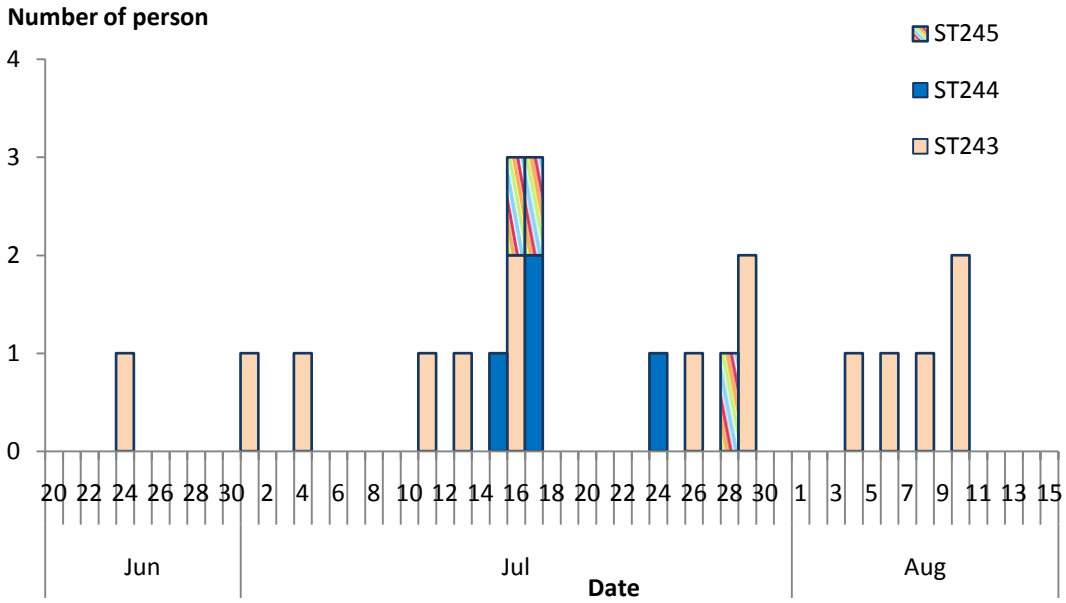

Figure 5. Confirmed diphtheria cases and carriers by MLST sequences by date of onset for cases or date of throat swab collection for carriers, Dansai District, Loei Province, June to October 2012 (n=22)

Mean age was 45.5 years (range 7-87 years) (Table 2). About 24% of the participants reported a sign or symptom of diphtheria in the questionnaire.

Protective level of diphtheria antibody were found in 52 out of 132 (39.4%), Of these, 68.8% (11/16) were children and 35.3% (41/116) were adults. Based on vaccination history, 78.8% (41/52) with a protective level received at least one dose of diphtheria toxoid while 50.0% (40/80) of volunteers with non-protective antibody level did not receive immunization or remember their vaccination history (Table 2).

Table 2. Immune status of respondents from serological survey in Dandoo and Pakpong Villages, Dansai District, Loei Province, September 2012

Variable	Total number (n=132)	Protective level (n=52)		Non-protective level (n=80)	
		Number	Percent	Number	Percent
Gender					
Male	54	23	42.6	31	57.4
Female	78	29	37.2	49	62.8
Age (year)					
≤ 15	16	11	68.8	5	31.2
> 15	116	41	35.3	75	64.7
Interval prior diphtheria toxoid vaccination					
Within 2 weeks	18	12	66.7	6	33.3
2 week - 1 month	6	4	66. 7	2	33.3
>1 month - 6 months	6	1	16. 7	5	83.3
>6 month - 10 years	34	20	58.8	14	41.2
>10 years	17	4	23.5	13	76.5
None or N/A	51	11	21.6	40	78.4
Culture and toxin assay					
Toxigenic *C. diphtheriae*	1	1	100	0	0
Non-toxigenic *C. diphtheriae*	2	0	0	2	100
Negative for *C. diphtheriae*	129	51	39.5	78	60.5
Case definition					
Suspected case	32	18	56.3	14	43.7
Confirmed case	1	1	100	0	0
Carrier	2	0	0	2	100
Not meeting any case definition	97	33	34.1	64	65.9

Out of 132 throat swabs collected for culture, the one sample collected from the confirmed case at Dansai Hospital found to have toxigenic *C. diphtheriae*.

Among 131 samples collected in Dandoo and Pakpong Communities, 2 carriers with non-toxigenic *C. diphtheriae* were found. The confirmed hospital case had a protective level against diphtheria toxin while the two carriers had none (Table 2). Nine adults (four males and five females) were found to have high levels of serum anti-toxin (>2.56 IU/mL). Although one of them had contacted with a confirmed case, that person did not meet our definition of a close-contact. All of them already had dT immunization and three of them (33.3%) had the most recent dose less than two weeks ago, followed by four (44.4%) at 2 weeks to 6 months and two (22.2%) at 6 months to 10 years. Throat swab results from all of them were negative for *C. diphtheriae*.

Discussion

This Dansai outbreak followed a pattern similar to re-emergence of diphtheria in the former Soviet Union in the 1990s. The epidemic was first recognized with reports of fatal adult cases. Then, additional child cases and carriers were detected.[12] The second similarity was a shift in age of diphtheria cases.[13,14] During diphtheria epidemics in Thailand around 1980s and 1990s, 98% and 91% of cases were children respectively.[2] However, in this outbreak, the adult cases nearly equaled the child cases. This situation might occur from lack of natural "wild" infection to boost immunity in adults. Another similarity was that adults tended to have more severe complications than children[13,15] while the last was a large number of carriers among well-vaccinated children.[13,16]

The diphtheria outbreak in Dansai District was widespread, with many cases and carriers detected. Considering the difficult geography and transportation, *C. diphtheriae* might silently circulate in remote sub-districts among clinical cases and carriers for a long period before a fatal case prompted the notification. This hypothesis was supported by the MLST results, which identified three genetic sequences in those areas. The variation of genetic sequences suggested bacterial reproduction of many generations.[8] The first likely genetic sequence was ST243 which was found in the first generation of Dansai cases and carriers. This subtype remained to be the major sequence found throughout the epidemic in Dansai. With the incubation period of diphtheria around 2-5 days,[1] the epidemic curve probably reflected many generations of spread of *C. diphtheria* (Figure 2). Despite that, it was not clear how ST243 entered Dansai as it did not match any genetic sequence found from previous outbreaks in the southern region of Thailand.[11]

In this investigation, vaccinated cases were likely to have milder symptoms and fewer complications than unvaccinated ones. Similar findings were reported from diphtheria outbreaks in the former Soviet Union, Finland and Sweden.[12,13,19,20] From the previous epidemics, a decreased in diphtheria cases was caused by a mass vaccination.[12,13] In order to rapidly control a diphtheria epidemic, emergency vaccination campaigns should target persons at high risk for severe complication or death such as immunocompromised hosts, those younger than five, those older than 40 years and people abusing drugs.[1,12,17,18,21]

Cardiac complications from diphtheria were causes of the two deaths. Contributing factors associated with mortality were non-vaccination, heavy alcohol drinking, severe underlying disease and delayed specific treatment for diphtheria. These findings were also found in the 1990s epidemics in the former Soviet Union[14] and the 2012 outbreaks in the southern provinces of Thailand.[17,18]

From a serological survey result, unlike a previous hospital-based seroprevalence study in Khon Kaen Province, a commerce center of northeastern region, which found 94.8% of the study population had protective antibody level,[21] we found only 39.4% had protective level in Dansai District. This difference was found in both children and adults, and was likely to cause by a variation in population since Dansai was a rural area.[21] Nearly half of the confirmed cases in children had received recommended vaccines from the EPI program. However, in our serological survey, 50% of people who claimed to have been vaccinated for diphtheria had low level of immunity. Thus, even for patients with a history of vaccination, the diphtheria diagnosis should not be ruled out. Misdiagnosis of diphtheria could lead to severe complications and even death,[17] as well as further spread of the disease in communities.[14,15] Our serological survey identified that most adults had non-protective level of antibody to diphtheria toxin, including those with a history of vaccination as children. This finding might have been caused by lack of natural "boosters" from circulating *C. diphtheria*.

Limitations

A major limitation of this investigation was inability to identify the primary source of the outbreak as the investigation was started late. Other limitations included incomplete medical records for vaccination history, especially in adults. In addition, many

patients and respondents could not remember their contact and risk history.

Conclusion

The Dansai outbreak was possibly the first sign of a re-emergence of diphtheria in Thailand. A likely long period of occult propagation was suggested by the discovery of three new diphtheria genetic sequences. Nevertheless, mechanism of diphtheria spread in Dansai was still unknown. While most cases were found among children, incidence in adults also rose, with more severe complications. Vaccinated children tended to be carriers. Overall immunity levels remained low, especially in adults.

Recommendations

Better surveillance systems and control measures should be instituted, including an emergency vaccination campaign in the epidemic area. According to a poor immunity found in results of a study, we suggested scheduling dT booster vaccination to implement every 10 years in adults in this area. To prevent future epidemics, further studies on diphtheria serology and vaccine effectiveness were required. National vaccine strategy should also improved by increasing vaccine coverage of children and adding adult dT to the EPI.

Acknowledgement

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Suggested Citation

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