

# A DIPHTHERIA OUTBREAK IN BURI RAM, THAILAND

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**Abstract.** In May 1996 there was an outbreak of diphtheria in Buri Ram, Thailand which infected 31 patients, 8 males and 23 females. The mean age of the patients was  $8 \pm 5$  years. Seventy-four percent had a history of childhood vaccinations. Common signs and symptoms included fever (100%) which was low grade in 61%, sore throat (90%), upper airway obstruction (3%), and hoarseness (10%). Pseudomembranes (seen in 100%) were located on the tonsils (71%), pharynx (22%), larynx (9.6%), and uvula (6%). The mean duration of symptoms prior to admission was 2 days with a range of 1 to 5 days. Complications included upper airway obstruction (10%) and cardiac complications (10%). There were no neurological complication or deaths. There were negative associations between cardiac complications, severity of disease and previous diphtheria vaccination. The ages varied from children to adults. Early recognition and prompt treatment decreased complications and mortality in this group of patients when compared with Chiang Mai and Queen Sirikit National Institute of Child Health (QSNICH) studies.

## INTRODUCTION

Infection caused by *Corynebacterium diphtheriae* is distributed worldwide and used to be a major life-threatening illness in many countries. The extended program of immunization (EPI) and the introduction of diphtheria toxoid in Thailand occurred in 1978. One thousand twenty-one cases of diphtheria were reported nationwide in Thailand in 1984 and 25 cases were reported in 1993. The incidence rates of diphtheria infection in Buri Ram Province for 1978 and 1995 were 0.06 and 0.63/100,000 population and the mortality rates were 0.07 and 0.14/100,000 population, respectively (Fig 1). On May 28, 1996 a cluster of cases of diphtheria was reported in Buri Ram Province. A number of small outbreaks of diphtheria have been reported over the years. In Chiang Mai Province in 1980 there

were 129 cases reported. In Saraburi Province, 18 cases were reported in 1994. In Lampang Province, 6 cases were reported in 1996. In Si Sa Ket Province and Ubon Ratchathani Province, 1 case each were reported. (Sirisanthana and Sirisanthana, 1980; Nakornnoi, 1994; Pitaksiripens *et al*, 2000; Saipan *et al*, 2000). Re-emergence of this disease is possible as evidenced by the recent resurgence of diphtheria in the countries of the former Soviet Union (Hardy *et al*, 1996). Lack of recognition of the disease and delay in the diagnosis and treatment may increase the mortality of diphtheria patients (Viriyautsahakul *et al*, 1994). We review here an outbreak of diphtheria from a decade ago, including the clinical manifestations, laboratory tests, complications, treatment, contact cases, outcomes, and preventive measures of the outbreak.

## MATERIALS AND METHODS

A retrospective review of the data of patients diagnosed with diphtheria infection at the Buri Ram Hospital from May 28, to August 10, 1996 was carried out. The data col-

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lected included age, sex, clinical presentation, site of the pseudomembranous lesions, laboratory tests, complications, treatment, contact case management, outcomes and preventive measures. The incidence of diphtheria infection treated at Buri Ram Medical Center from 1987-1995, vaccinations and demographic data were also reviewed. The diagnosis of diphtheria infection was based on clinical manifestation with or without bacteriological confirmation. The definition of probable diphtheria infection was when the signs and symptoms of respiratory infection included pseudomembranous lesions. The definition of confirmed diphtheria infection included the same as probable diphtheria and were divided in two groups: 1) a probable case of diphtheria with complications, such as upper airway obstruction, myocarditis or neuritis without positive *C. diphtheriae* cultures; 2) laboratory confirmed diphtheria was a probable case with a positive culture for toxigenic *C. diphtheriae*. A vaccination history was obtained from review of the vaccination book for each child. Case contacts were proved with cultures. The carriage rate was calculated from reports from the Buri Ram Office of Public Health. The throat was cultured for *C. diphtheriae*, and plated on Tellurite medium; toxigenic (ELEK'S) tests were also performed. All specimens were sent to the Division of Clinical Pathology, Department of Medical Science, Ministry of Public Health to confirm the diagnosis. Case contacts were classmates, family or close contacts of the patients. Descriptive statistics were carried out for frequency, percent, mean, median and standard deviation. An analytical statistic chi-square test and Fisher's exact test were also carried out.

### RESULTS

Baseline data of 31 diphtheria cases are presented in Table 1. The first case of diphtheria was a 4-year old Thai girl admitted to Buri Ram Hospital on May 28, 1996 with

fever, sore throat and bleeding of pseudomembranous lesions of both tonsils. She had no previous vaccinations. Thirty-one cases were reported from May 28 to August 10, 1996. Twenty-five patients were from Mueang District, 2 from Krasung District, 2 from Khu

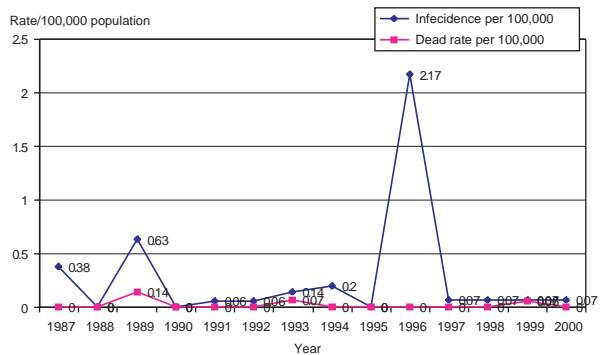


Fig 1—Annual reports of diphtheria cases and death due to diphtheria cases in Buri Ram Province, 1987-1999.

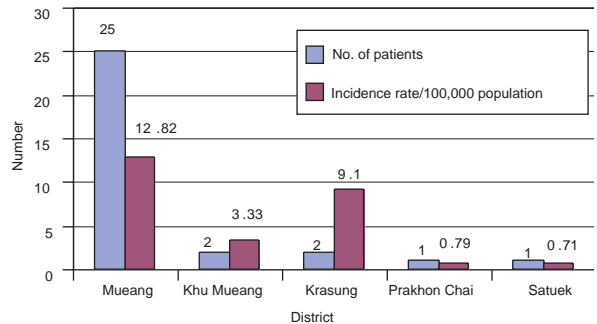


Fig 2—Incidence of diphtheria per 100,000 population in Buri Ram Province by district.

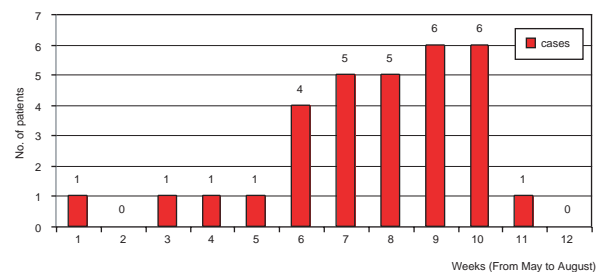


Fig 3—Cases of diphtheria in Buri Ram Province, 1996.

Table 1  
Baseline data of diphtheria cases in Buri Ram Province.

Case No.	Age/Sex (Yr)	Vaccine Number of doses/ total series	Days prior to Rx	Fever	Stridor	Sore throat	Pseudo mem-brane	Toxigenic diphtheria	AST	Albumin-uria	Cortico-steroid use	Carditis	Upper airway obstruction
1	3/F	0/4	1	L	+	+	PTL	-	-	-	+	- b	+
2	12/F	0/5	2	L	-	-	TP	-	-	-	-	-	-
3	11/F	1/5	1	L	-	+	TP	-	-	-	+	-	-
4	10/F	3/5	2	H	-	+	TP	+	-	-	-	-	-
5	4/F	2/5	4	L	+	+	PTLU	+	123	+	+	+ a,b	+
6	4/F	4/5	2	L	-	+	T	+	-	+	+	-	-
7	6/F	?	1	L	-	+	T	+	-	-	-	-	-
8	9/F	2/5	2	L	-	+	TU	+	+	-	-	-	-
9	14/F	1/5	3	L	-	+	TL	+	-	-	+	-	-
10	11/F	5/5	2	L	-	+	T	+	+	+	+	-	-
11	11/M	5/6	1	L	-	+	T	+	-	-	-	-	-
12	5/F	4/5	2	H	-	+	T	+	-	+	+	-	-
13	8/F	5/6	2	L	-	+	T	-	33	-	-	-	-
14	10/M	4/5	1	H	-	+	T	+	-	-	-	-	-
15	4/F	4/5	5	L	+	+	T	+	-	-	+	-	-
16	30/F	?	2	L	-	+	T	+	-	-	-	-	-
17	9/F	4/5	1	H	-	+	T	+	-	-	-	-	-
18	4/F	4/5	5	H	-	+	T	-	-	-	+	-	-
19	10/F	5/6	1	H	-	+	TP	+	-	-	-	-	-
20	10/M	5/6	2	L	-	+	L	+	-	-	-	-	+
21	9/F	6/6	2	L	-	+	T	-	23	+	+	-	-
22	9/F	5/5	1	L	-	+	T	-	-	-	-	-	-
23	4/M	3/5	5	H	-	+	T	-	21	-	+	+	-
24	5/F	3/5	3	L	-	+	TP	+	28	+	+	-	-
25	2/F	3/4	2	H	-	+	T	+	+	-	+	-	-
26	3/M	4/4	2	L	-	+	T	-	+	-	+	-	-
27	5/M	5/5	1	L	-	+	T	+	-	+	-	-	-
28	6/F	1/5	2	H	-	+	T	-	30	-	-	-	-
29	3/M	4/4	3	L	-	+	T	+c	30	-	+	+	-
30	12/F	5/5	3	H	-	+	T	+c	-	-	-	-	-
31	7/M	5/5	2	L	-	+	T	+c	-	-	-	-	-

L = Fever < 38°, H = Fever > 38°, P = Pharynx, T = Tonsils, L = Larynx, U = Uvula  
a = tracheostomy, b = Referred, c = *S. pyogenes*

Mueang District, 1 from Satuek District and 1 from Prakhon Chai District (Figs 2 and 3). Of the 31 cases, 8 were males and 23 were females with a male to female ratio of 1: 3. The mean age of the patients was  $8 \pm 5.2$  years (range 2-30) years. Twenty-nine percent of patients were < 5 years old, 52% were 5-10 years old, 19% were 11-15 years old and 3%

were older than 15 years old. Females were infected more often in all age groups.

#### Vaccinations

A history of previous vaccination against diphtheria was obtained. Seventy-four percent of patients had received a diphtheria vaccine; 10% had completed the vaccination series;

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Table 2  
 Characteristics of diphtheria cases in Buri Ram Province diagnosed from May to August 1996 compared to other studies.

	Buri Ram 1996	QSNICH 1976-1985	Chiang Mai 1980
No. of cases	31	381	129
Female : male ratio	3:1	1:1	1:1
Percent in age range			
≤ 5 years old	26	0	16
5-10	52	50	39
>10-15	19	33	33
> 15	3	17	12
Mean	8 ± 5	4 ± 2.7	13
Range	2 - 30	0.4 - 13.4	2 - 31
<b>Vaccination status (%)</b>			
Completed vaccinations	9.6	74.7	5.4
Partial vaccinations	64.5	-	-
No vaccinations	16	17.1	56.6
Unknown	9.6	8.2	38
<b>Days prior to admission</b>			
Mean/(Range)	2.005 (1/0-5)	3.3 (2.1/0-11)	2 (1-3)
Peak	2	3	3
<b>Symptoms and signs (%)</b>			
Fever	100	90	92.4
Sore throat	90	88	91.6
Headache	-	28	-
Dysphagia	3	27	-
Vomiting	-	-	-
Hoarseness	10	-	36.7
Edema of the neck	-	16	11.3
<b>Location of pseudomembrane</b>			
Tonsils	7	61.9	98.4
Pharynx	16	55.9	-
Pharynx and larynx	6	-	-
Others uvula, larynx	16	24.4	1
<b>Tracheostomy (cases)</b>	1	4	-
<b>Complications (%)</b>			
Paralysis of the palate	-	4.7	6
Carditis	10	10	29
Upper airway obstruction	10	42.3	1
<b>Laboratory data (mean)</b>			
Hematocrit (%)	38.7	37.8	-
WBC/mm <sup>3</sup>	13,428	16,280	17,375
Neutrophils (%)	68	66.8	60
Proteinuria (%)	38.7	52.7	41
Pyuria (%)	-	2.7	33
Throat culture			
Toxigenic <i>C. diphtheriae</i> (%)	67	63	60
<i>Streptococcus pyogenes</i> (%)	10	8.9	5
Mean AST/ IU/l (range)	41 (21-123)	66 (20-661)	-
AST > 100 IU/l (%)	4	11.8	-
<b>Treatment with corticosteroids in children &lt;5 years old (%)</b>	100	-	100
<b>Mortality rate (%)</b>	0	8.8	3.9

64% received only part of the series, 16% had no previous vaccinations and 10% had an uncertain history. Of the 3 cases with carditis, 2 received only part of the vaccine series (2/5, 3/5) and 1 completed the series.

Common clinical manifestations included fever (100%) which was low grade in 69%, and pseudomembranous lesions (100%). Three cases (10%) had carditis, one case had both upper airway obstruction and myocarditis. Ten percent had difficulty breathing and 10% had hoarseness. The mean duration of fever prior to admission was 2 days (range 1-5 days). Pseudomembranous lesions were located on the tonsils in 71%, tonsils and pharynx in 16%, tonsils pharynx, larynx and uvula in 3%, tonsils, pharynx and larynx in 3%, tonsils and uvula in 3% and only larynx in 3%. One case of laryngeal diphtheria needed emergency tracheostomy. Six percent had both pharyngeal and laryngeal diphtheria. No nasal or cutaneous diphtheria were seen in this series. The cases of myocarditis presented with cardiac arrhythmias, second degree heart block, bundle branch block and non-specific S-T segment or T-wave changes. All the myocarditis patients recovered within two weeks. One case was referred to Queen Sirikit National Institute of Child Health (QSNICH). There were no neurological complications.

Laboratory investigations included a mean hematocrit level of 38.7% (range 32-43%), a white blood cell count (WBC) of 13,428/cm<sup>3</sup> and a mean neutrophil percent of 68%. Analysis of protein in the urine showed proteinuria in 38.7%; trace protein in 20%, 1+ protein in 8% and 2+ in 16%. The mean serum aspartate transaminase (AST) was 41.4 IU/l (range 21-123). The AST level was >100 IU/l in one case (4%) with myocarditis. Throat cultures of the cases revealed 67.7% were positive for toxigenic *C. diphtheriae*, whereas only 0.52% were positive in the case contacts. The *C. diphtheriae*

was sensitive to penicillin, tetracycline, erythromycin, Cotrimoxazole, chloramphenicol, cephalothin, kanamycin and gentamicin.

#### Treatment

Prompt treatment with antibiotics and antitoxin was initiated as soon as the clinical diagnosis was made. Diphtheria antitoxin was given at a dosage which varied based on the extent of the diphtheria lesions and the duration of illness. Diphtheria antitoxin 20,000 - 80,000 units was used for pharyngeal diphtheria and 20,000-40,000 units for laryngeal diphtheria after skin test. Penicillin (at 100,000 units/kg/day) was given for 10 days. Erythromycin (at 50 mg/kg/day) was the alternative antimicrobial drug in patients with a history of hypersensitivity to penicillin. All patients under five years of age, patients with carditis and those with delayed treatment were given oral prednisolone at a dosage of 2 mg/kg/day for one week with a tapering dosage during the second week and also received diphtheria vaccine before being discharged followed by a second shot after two months. For children under 6 years of age a booster was given at one year. Patients who had myocarditis or laryngeal diphtheria were treated according to symptoms. Electrocardiographic tracings were obtained daily during hospitalization. Those with an abnormal EKG had a repeat EKG at one week, and one month. A complete blood count, urine analysis and serum AST were also performed.

Contact cases received diphtheria vaccine and penicillin or erythromycin and were advised to return if they had fever or sore throat. Contacts who had fever or sore throat received diphtheria antitoxin 5,000 units intramuscularly or intravenously and erythromycin orally. Thereafter, they were given a diphtheria vaccine.

There were no deaths in this epidemic. One case was referred due to a short supply of antitoxin and one case developed myocarditis with heart block.

It took 11 weeks to control the epidemic during which almost 100,000 doses of diphtheria vaccine were given to children (under five years of age 29,066 doses, over age five 63,440 doses). Active intervention was carried out for carriers; 52.6% were school contacts, 31.6% were community contacts, 10.5% were household contacts and 5.3% were unknown contacts.

## DISCUSSION

In our study, there were 31 cases of diphtheria, 21 cases were laboratory confirmed, 3 cases were clinically confirmed while the rest were probable cases. In the first three cases there was no Tellurite medium but later cultures were confirmed to be toxigenic at the Department of Medical Science. This incident in Mueang District correlates with lower vaccination coverage than the other districts in Buri Ram Province (Nipa Sutipan, personal communication). The epidemic began in an urban area, then spread to a rural area (Fig 2), however a previous epidemic in Chiang Mai Province began in a rural area then spread to an urban area (Sirisantana *et al*, 1980). The mean age and age range ( $8 \pm 5$  years and 2-30 years) in this study were older than the Queen Sirikit National Institute of Child Health (QSNICH) study from 1976-1985 ( $4 \pm 2.7$  years and 0.4-13.4 years) (Pancharoen *et al*, 2001) but were younger than the Chiang Mai study (13 and 2-31 years) (Sirisantana *et al*, 1980). There were more infections in the 5-10 year old age group in Buri Ram (52%) and in the QSNICH study (50%) than in the Chiang Mai study (39%). Adults were also infected in these epidemics (Sirisantana *et al*, 1980; Pancharoen *et al*, 2001). Adolescents and adults were more likely to be affected during outbreaks of diphtheria in the states of the former Soviet Union (Hardy *et al*, 1996). No cases in our study were under one year old. Only 1 case (3%) needed tracheostomy which

was the same as in the Chiang Mai study but in the QSNICH study there were four cases needing tracheostomy. Females were three times more likely to be infected than males in the Buri Ram study, however in the Chiang Mai and QSNICH studies the sex ratios were equal. This may be caused by older children playing with the same sex.

The Buri Ram and QSNICH reports found 74.1% and 74.7%, respectively, were vaccinated against diphtheria, while the Chiang Mai study found only 5% were vaccinated (57% were not vaccinated and 38% had an uncertain history). The symptoms were less severe because immunity destroyed the toxin. The vaccine coverage rates for Buri Ram patients under one year of age in 1989, 1992 and 1995 were 77.6, 88.1 and 90.5%, respectively, which is high, therefore, there were no cases under one year of age. Vaccinated patients may become infected and act as carriers for diphtheria, spreading it to nonvaccinated patients (Zalma *et al*, 1970). The index patient had not been vaccinated and transmitted infection to the group who had not received the full vaccine series.

The mean duration from onset of fever to receiving diphtheria antitoxin was shorter than previous reports (Buri Ram  $2 \pm 1$  days, 0-5 days; QSNICH  $3 \pm 2$ , 0-11 days); Chiang Mai 3 days, 2-3 days. The mean duration of illness in the carditis cases before being treated was 4 days but the non-carditis cases was 2 days, the difference was not statistically significant.

The manifestations of the illness were not different from previous reports and included fever in 100% and sore throat in 90% and a pseudomembrane in 100%. There was no edema of the neck in the Buri Ram study but in the QSNICH and Chiang Mai reports edema was seen in 16 and 11.3%, respectively. Cardiac complications occurred in 10% in our study, the same as in the QSNICH study, but

the Chiang Mai study found a higher occurrence of complications (29%). One of the three cases with myocarditis had multiple sites of pseudomembranes, on the tonsils, pharynx, larynx and uvula. She had received partial vaccination, (2/5 doses) and had an AST > 120 IU/l but recovered by two weeks.

The results of the complete blood counts, PMN percents, and albuminuria were not significantly different among the three studies. This may be due to the effect of antitoxin since urinalyses were obtained after treatment. Throat cultures revealed *Streptococcus pyogenes* in 10% of patients, which is the same as in the QSNICH study; it was 5% in the Chiang Mai study. Sixty-seven percent of the diphtheriae were toxigenic in the Buri Ram study, 63% in the QSNICH study and 60% in the Chiang Mai study. This is only a moderate yield since special culture media are needed, which are routinely prepared. The sensitivity tests were the same as the other two studies, mainly sensitive to penicillin and erythromycin.

Corticosteroids were used in the patients under five years old and in those who had carditis. No mortalities occurred in this study, but the mortality rates were 8.8% in the QSNICH study, 3.9% in the Chiang Mai, 17% in Saraburi, (Nakornnoi *et al*, 1994), 16.7% in Lampang (Pitaksiripens *et al*, 2000) and 57% in Ubon Ratchathani (Saipan *et al*, 2000).

In this epidemic the majority were females in each age group. Susceptible persons were infected due to incomplete vaccination coverage, suboptimal vaccine efficiency and waning immunity among vaccinated people in the absence of periodic booster doses. The accumulation of susceptible people over time may be sufficient to sustain epidemic diphtheria transmission. Vaccinated people may become infected or become carriers but have

less morbidity and mortality. A longer delay prior to treatment resulted in more complications. Diphtheria may re-emerge in Thailand in the future especially in children and in young adults (Nakornnoi *et al*, 1994; Pitaksiripens *et al*, 2000; Saipan *et al*, 2000). Early recognition and prompt diagnosis and treatment may reduce complications and mortality.

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