Diphtheria in Thailand in the 1990s

Piyant Tharmaphornpilas,1 Pornsak Yoocharoan,1 Preecha Premgree,1 Surasak Younpairoj,1 Pisit Sriprasert,2 and Charles R. Vitek3

Diphtheria remains endemic in developing countries, but there are limited published data on the subject. Thailand’s diphtheria surveillance data are relatively complete and may give a fuller picture of the situation in similar countries. After routine immunization began in 1977, the incidence of reported diphtheria decreased by >98% to <0.1 case per 100,000 persons annually in the 1990s. Despite infant immunization coverage of >90%, diphtheria cases were reported throughout the 1990s, primarily among children <15 years old. Outbreaks were linked to both persistent endemic circulation and to importation of toxigenic Corynebacterium diphtheriae; suboptimal immunization coverage in minority and disadvantaged groups contributed. A serologic survey found 25% of adults 20–39 years old and 14% of adolescents 10–19 years old lacked immunity to diphtheria; these data indicate an accumulation of susceptible adolescents and adults. Diphtheria remains a threat in Thailand; improvements in diphtheria control will depend on improving childhood immunization coverage in Thailand and the surrounding region.

In the early 1970s, diphtheria remained highly endemic in Thailand and other developing countries, although routine immunization had reduced diphtheria to sporadic cases in highly industrialized countries [1]. In the late 1970s, the World Health Organization’s (WHO’s) Expanded Programme on Immunization (EPI) strengthened childhood immunization in developing countries and led to sharp decreases in diphtheria incidence. By 1990, diphtheria no longer appeared to be a major public health problem; eradication seemed to be a possibility [2]. A large-scale resurgence of diphtheria in the former Soviet Union in the 1990s [3] renewed interest in factors associated with persistent circulation of toxigenic Corynebacterium diphtheriae and in the potential for the reemergence of epidemics.

Routine surveillance data from developing countries are frequently inadequate to follow diphtheria trends. Thailand has a long-standing diphtheria surveillance system that has benefited from political stability and economic growth. In the 1990s, additional investigations were conducted by trainees from Thailand’s Ministry of Health’s Field Epidemiology Training Program (FETP). This report summarizes the epidemiology of diphtheria in Thailand, concentrating on the 1990s and using data from surveillance, outbreak investigations, and a serologic survey.

Thailand is a Southeast Asian country with a land area of 513,115 square kilometers—approximately the size of France. Thailand has 76 provinces that are grouped into 4 regions: north, northeast, central, and south (figure 1). The population is ~60 million, with ~80% living in a rural setting. About 15% of the population belong to minority groups, which include ethnic Chinese, Malays (southern region), and small mountain-dwelling tribes, such as the Hmong (northern region) [4]. Because of rapid economic growth, the per capita gross national product rose by >4% a year between 1979 and 1998 [5]. Although severely affected during the East Asian economic crisis in 1997–1998, the Thai economy began to recover in 1999.

Methods

Diphtheria surveillance system. Limited surveillance for diphtheria in Thailand began in 1963 and became nationwide by 1968 [6]. For surveillance purposes, a suspected diphtheria case patient is defined as a patient with low-grade fever and a nasopharyngeal membrane, with or without symptoms of pharyngitis [7]. Both public and private medical clinics exist in all provinces; each province has a provincial health office. By statute, all medical practitioners must report suspected diphtheria cases to the health office. In practice, sporadic cases and index cases in outbreaks are almost exclusively reported by hospitals. As they appear, suspected diphtheria cases are investigated urgently (almost always within 24 h of notification) by provincial epidemiologists. Specimens for culture are obtained from suspected case patients and close contacts of case patients. Chemoprophylaxis with erythromycin is offered to close contacts. Vaccination is offered to children and adults who are deficient in diphtheria immunization.
Figure 1. Map of Thailand

are not fully immunized, regardless of contact status. Case reports with basic demographic data are sent to the Division of Epidemiology (Ministry of Public Health) in Nonthaburi; complete reports of case investigations are not routinely sent.

In 1980, Thailand’s Ministry of Health initiated the FETP, a 2-year intensive training program in public health epidemiology. In the 1990s, FETP trainees investigated diphtheria outbreaks in Saraburi, Nan, and Burirum provinces and conducted a serology study of diphtheria immunity in Mukdahan Province.

Diphtheria immunization program. In 1977, Thailand implemented a routine infant immunization program, with 2 doses of diphtheria-tetanus toxoids–whole cell pertussis (DTP) vaccine recommended for all infants. In 1982, the recommendation was changed to 3 doses of DTP vaccine for infants. In 1992, the schedule was modified to 5 doses of DTP vaccine at ages 2, 4, 6, and 18 months and 4–6 years; a dose of tetanus and diphtheria toxoids (Td) was recommended at ages 12–16 years.

Childhood vaccination coverage. Thailand has conducted immunization surveys by WHO cluster survey methodology every year since 1980, except for 1997 and 1998. Since 1983, 11–27 provinces have been selected randomly each year, except in 1990, when all provinces were surveyed. Thirty clusters (60 clusters if the provincial population is >1 million) were surveyed in each province. The coverage reported here is higher than that reported by WHO for some years in the 1990s, because data were not complete by the WHO reporting deadline (Sirisak Warintharawat, Program Director, EPI, Thailand, personal communication).

Diphtheria serology study, Wanyai district, Mukdahan Province. A population-based serologic study of immunity to diphtheria was conducted in Wanyai district, a rural area with a population of 15,129, according to the 1996 census. By use of the computerized census list, the population was stratified into 6 age categories, and 70–80 individuals were chosen at random from each strata. Subjects were contacted, and serum samples were obtained between September 1996 and February 1997. Serum samples were tested for antibodies to diphtheria toxin at the Department of Medical Science (Ministry of Public Health, Nonthaburi) by use of a Vero cell toxin neutralization assay [8]. Individuals with diphtheria antitoxin antibody levels ≥0.01 IU/mL were considered to be immune.

Results

Diphtheria Epidemiology before 1990

In the prevaccine era, diphtheria was highly endemic among children in Thailand. In the early 1970s, the reported incidence was 4–6 cases per 100,000 persons, with ∼2000 cases and ∼120 deaths reported annually (figure 2). Before EPI, limited immunization was performed at some hospitals and private clinics; no coverage estimates are available.

After 1977, immunization coverage with diphtheria toxoid rapidly improved, exceeding 70% by 1986 and 80% by 1989. The incidence of diphtheria rapidly declined, falling to 2 cases per 100,000 persons by 1981 and 1 case per 100,000 persons by 1987. Overall, in the 1980s, 8129 cases and 548 deaths were reported (case-fatality rate [CFR], 6.7%). Diphtheria was seasonal, with 3804 cases (47%) reported during June through August. Preschool-aged children remained the primary group affected through the 1980s. The proportion of cases among children <5 years old fell slightly but progressively from 58% in 1981–1982 to 49% in 1988–1989.

Figure 2. Reported incidence of diphtheria cases and deaths and infant immunization coverage with diphtheria toxoid—Thailand, 1968–1999. Coverage estimates for 1980–1981 are based on 1–3 provinces only. Coverage surveys were not conducted in 1997–1998; data were not extrapolated between 96% (1996) and 97% (1999).
Diphtheria in the 1990s

In the 1990s, 425 cases of diphtheria were reported, with 83 deaths (CFR, 19.5%). Reported diphtheria incidence stabilized at ≈0.1 case per 100,000 persons annually. The age distribution of cases continued to shift toward older age groups, with only 38% of cases reported among children <5 years old (table 1). Diphtheria remained seasonal, with 52% of cases occurring in June–August.

Sporadic cases or outbreaks were reported from 63 of the 76 Thailand provinces. Estimated infant immunization coverage increased from 89% in 1990 to 97% in 1999. Southern provinces reported lower coverage estimates, a higher rate of diphtheria, and more years with diphtheria cases than other regions (table 2).

Limited data are available on laboratory investigation of cases. In 1993, C. diphtheriae was isolated from 15 of 28 reported cases; biotype and toxigenicity data are not available.

Diphtheria Outbreaks in the 1990s

**Saraburi Province, 1994.** Saraburi is located in central Thailand. Infant immunization coverage with 3 doses of DTP vaccine in Saraburi was 79% in 1988 and 91% in 1992; only 1 diphtheria case was reported in 1989–1993. In 1994, an outbreak with 18 cases was reported [9]. The index patient, a Hmong child, had recently migrated from northern Thailand. None of 6 patients with documented receipt of ≥3 doses of DTP vaccine died, as opposed to 3 (25%) of 12 patients with fewer doses or unknown vaccination histories. Twelve (67%) patients were 5–14 years old and, 3 (17%) were ≥15 years old.

**Nan Province, 1996.** Nan is located adjacent to Laos in northern Thailand. Infant immunization coverage with 3 doses of DTP vaccine in Nan was 93% in 1986 and 99% in 1994; no diphtheria cases were reported between 1987 and 1995. In June 1996, an outbreak was reported in neighboring districts in Laos; 7 Laotians with diphtheria were admitted to a hospital in Nan. Five laboratory-confirmed cases were reported among Nan residents; all patients had a history of contact with Laotians. All patients had received ≥3 doses of DTP vaccine and had mild illness. A community-wide campaign targeting children <15 years old with 1 dose of diphtheria toxoid was rapidly implemented, and the outbreak subsided in 2 weeks. During the outbreak, 3 other provinces in northeastern Thailand reported 1–2 cases of diphtheria without identified spread. One C. diphtheriae strain was analyzed at the Public Health Laboratory Service (PHLS); Central Public Health Laboratory, London; this strain was mitis biotype, D63 ribotype.

**Burirum Province, 1996.** Burirum is located adjacent to Cambodia in northeastern Thailand. Infant immunization coverage with 3 doses of DTP vaccine in Burirum increased from 78% in 1989 to 91% in 1995. Sporadic cases of diphtheria were reported from Burirum in 1990 and 1992–1994.

### Table 1. Distribution of reported diphtheria cases, by age group, 1980s versus 1990s, Thailand.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>No. (%) of cases, 1981–1989</th>
<th>No. (%) of cases, 1990–1999</th>
</tr>
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<tbody>
<tr>
<td>&lt;5</td>
<td>3042 (49.0)</td>
<td>161 (37.9)</td>
</tr>
<tr>
<td>5–9</td>
<td>2178 (35.1)</td>
<td>163 (38.4)</td>
</tr>
<tr>
<td>10–14</td>
<td>854 (13.7)</td>
<td>64 (15.1)</td>
</tr>
<tr>
<td>≥15</td>
<td>134 (2.2)</td>
<td>28 (6.6)</td>
</tr>
<tr>
<td>Unknown age</td>
<td>3 (&lt;0.1)</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Total</td>
<td>6211 (100)</td>
<td>425 (100)</td>
</tr>
</tbody>
</table>

* Age-specific data were not available for cases in 1980.

In 1996, 31 laboratory-confirmed or clinical cases of diphtheria were reported from May to August. Twenty-three (74%) case patients were 5–14 years old; 1 case patient was ≥15 years old. Treatment of initial case patients was delayed, because diphtheria antitoxin was no longer routinely stored at the provincial hospital because of the rarity of cases. Three case patients had myocarditis, and 3 had airway obstruction; no fatalities occurred. Ten patients, all with mild illness, had received ≥3 doses of DTP vaccine.

The index case was an unvaccinated 3-year-old child living in an urban slum; no contact with foreign travelers was identified. Outbreak control was difficult because of the transient housing conditions of slum residents; thus, the outbreak spread into the surrounding community. Since vaccination records were unobtainable for most children living in the slum area, revaccination was recommended for all children <12 years old. Twelve C. diphtheriae isolates were ribotyped at the PHLS laboratory. All strains were mitis biotype; ribotypes were D34 (8 isolates), D66 (2 isolates), D64 (1 isolate), and D67 (1 isolate).

**Chiangrai Province, 1999.** Chiangrai is located adjacent to Laos in northern Thailand. Infant immunization coverage with 3 doses of DTP vaccine in Chiangrai varied from 90% to 96% between 1988 and 1995. Sporadic diphtheria cases were reported in 1994 (3 cases) and in 1997 and 1998 (2 cases each year). In 1999, an outbreak was reported among mountain-dwelling minority communities, with 13 cases and 2 deaths; all cases were among children 3–14 years old. One case was laboratory confirmed. Seven case patients had received <3 doses of diphtheria toxoid or had no vaccination records. Because of the high proportion of villagers with inadequate vaccination or missing records, 2 doses of DTP or Td vaccine were recommended for all.

**Serologic Survey, Wanyai District, Mukdahan Province, September 1996 to February 1997**

Mukdahan is located in northeastern Thailand. No cases of diphtheria had been reported in Wanyai district since 1985; reported coverage with DTP vaccine exceeded 90% since 1990. Serum specimens were obtained from 446 individuals who were 2–91 years old; <2% of individuals contacted refused to participate. The lowest proportion of immune individuals (75%)
was found among adults 20–39 years old, followed by individuals 10–19 years old (86%; table 3).

**Discussion**

Thailand’s experience provides an opportunity to assess trends in a rapidly industrializing country that remains endemic for diphtheria. Before EPI, the rates of diphtheria in Thailand were among the highest reported in developing countries [10] but were >20-fold lower than US rates in the prevaccine era. Lower rates of diphtheria resulted from both incomplete surveillance and high rates of cutaneous infection with toxigenic *C. diphtheriae*. Cutaneous diphtheria is rarely diagnosed; it results in immunity to diphtheria toxin with relatively few complications [1].

The implementation of the EPI program led to dramatic increases in immunization in developing countries; infant coverage with 3 doses of diphtheria toxoid increased from <5% in 1974 to ~80% in the 1990s [1, 11]. Reported diphtheria cases from developing countries fell from >70,000 annually in the 1970s to 15,000–20,000 in the 1990s.

Despite the overall improvement, marked disparities remain in the reported incidence of diphtheria in developing countries. Some countries industrialized rapidly and now have high immunization coverage and living standards; these countries have achieved control of diphtheria comparable to that in highly industrialized countries. For example, Malaysia, Singapore, and South Korea have a combined population of >70 million, with an annual gross national product per capita of >$10,000; these countries reported only 40 diphtheria cases between 1990 and 1998 [12]. Many other developing countries, including Thailand, achieved marked reductions in diphtheria but continue to report sporadic cases and outbreaks. In the least developed countries, such as Afghanistan and Haiti, limited data suggest that diphtheria remains highly endemic but has decreased because of EPI.

In many developing countries with diphtheria, published data on the extent of disease and on factors contributing to persistence are limited. Although surveillance is facilitated by the specific clinical picture and high mortality of severe diphtheria, accurate surveillance requires networks of trained clinical and public health personnel; this infrastructure is lacking in many developing countries. Thailand’s network has been developed over 3 decades, and the higher incidence reported in Thailand in the early 1970s suggests more complete surveillance than in other developing countries. The reported CFR in Thailand in the 1970s and 1980s was similar to that in developed countries, suggesting that a fairly complete spectrum of disease was being reported.

The data show that Thailand has controlled diphtheria as a major public health problem, with a >98% drop in reported cases and a >90% drop in deaths since the 1970s. The decrease in the proportion of recent cases among preschool-aged children also supports the effectiveness of the infant immunization program. However, the persistence of cases without links to other countries indicates that endemic circulation of toxigenic *C. diphtheriae* continues; the multiple ribotypes found in the Buriram outbreak also support continued endemicity.

Several factors may explain persistent circulation despite high reported immunization rates. Cutaneous diphtheria is unlikely to be diagnosed, and no data on cutaneous diphtheria in Thailand are available. Surveys may overestimate actual coverage, and, even with high coverage, many children remain unvaccinated; these children are concentrated among economically disadvantaged and minority groups. In Australia [13], Canada [14], and the United States [15], persistent foci of toxigenic *C. diphtheriae* were found among disadvantaged minorities in the 1990s, although circulation was interrupted in the general population. The reasons for persistent circulation in some communities probably include increased opportunities for cutaneous infection, suboptimal nonhomogeneous immunization rates, and other factors linked to lower socioeconomic status.

Toxigenic strains of *C. diphtheriae* also enter Thailand from

| Table 2. Reported diphtheria cases and incidence rates and estimated infant coverage with 3 doses of diphtheria toxoid in Thailand, by region, 1990–1999 |
|---|---|---|---|---|---|---|
| Region | No. of cases, 1990–1999 | Average population | Annual incidence per 100,000 persons | Estimated infant immunization coverage (%), by year |
| | | | | 1991 | 1993 | 1995 | 1997 | 1999 |
| Central | 118 | 19,190,000 | 0.06 | 88–95 | 86–99 | 92–97 | NA | 95–99 |
| North | 56 | 11,765,000 | 0.05 | 82–93 | 88–97 | 91–98 | NA | 96–98 |
| Northeast | 142 | 20,572,000 | 0.07 | 87–99 | 90–95 | 93–100 | NA | 94–100 |
| South | 109 | 7,634,000 | 0.14 | 63–95 | 86–95 | 70–99 | NA | 93–97 |
| Total | 425 | 59,161,000 | 0.07 | 90 | 92 | 94 | NA | 97 |

* * Data represent ranges of survey results for regions and summary estimate for national data. NA, not available.

| Table 3. Diphtheria antibody levels among 446 subjects—Mukdahan Province, Thailand, 1996–1997 |
|---|---|---|---|
| Age group, years | No. of subjects | Subjects with antibody levels ≥0.01 IU/mL, % | Subjects with antibody levels ≥0.1 IU/mL, % |
| 2–4 | 75 | 92 | 80 |
| 5–9 | 69 | 94 | 73 |
| 10–19 | 69 | 86 | 75 |
| 20–39 | 85 | 75 | 53 |
| 40–59 | 75 | 92 | 55 |
| ≥60 | 75 | 97 | 63 |
| Total | 446 | 89 | 66 |
bordering countries that have lower immunization rates. Laos reported coverage of <60% throughout the 1990s and reported large outbreaks in both 1994 (193 cases) and 1996 (319 cases) [12]. Transborder population movements will reintroduce toxigenic strains into susceptible Thai populations until regional disease control is improved.

The lower rate of immunity to diphtheria among young adults in Wanyai is probably due to the reduction in circulation of toxigenic C. diphtheriae. With wide circulation, long-lasting immunity is produced by natural infection in childhood; immunity is reinforced by periodic natural boosting. In industrialized countries, circulation of toxigenic strains sharply declined once high levels of infant immunization were achieved. More adults in industrialized countries then became susceptible because of incomplete vaccination coverage and waning immunity among vaccinated persons in the absence of boosting; however diphtheria outbreaks involving susceptible adults have been rare as long as childhood immunity remains very high [3]. In Wanyai, the most susceptible cohort of adults (20–39 years old) would have been young children or adolescents when EPI began. Many of these individuals were missed by the early immunization program but escaped natural infection; others were immunized but have lost protective antibody levels.

A recent study in Taiwan also found a nadir of diphtheria immunity among young adults [16]. The susceptible adult cohorts in Thailand, Taiwan, and other countries where circulation of toxigenic C. diphtheriae is sharply reduced will be at risk throughout life. In contrast, recent studies from rural Kenya [17] and Delhi, India [18], found high levels of diphtheria immunity uniformly among adult age groups, despite incomplete infant immunization and no booster immunization, suggesting immunity from ongoing circulation of toxigenic strains.

The investigations in Thailand suggest that, despite increased susceptibility to diphtheria among older age groups, sporadic cases and outbreaks continue to primarily involve young children, presumably because of very high contact rates among children and suboptimal vaccination rates in certain groups. High immunization coverage in Thailand among all groups of children, especially among underprivileged and minority populations, is needed. Additional doses for older children and adults should be considered, depending on the age distribution of future diphtheria cases.

The higher CFR in the 1990s may reflect increased deaths and decreased reporting of milder cases and suggests that both treatment and surveillance of diphtheria may need improvement in Thailand. Rapid treatment with diphtheria antitoxin is necessary to limit mortality. Extra efforts are needed to maintain access to antitoxin and awareness among clinicians and health officers when incidence is low. Increased laboratory resources are needed to support surveillance and outbreak control in Thailand. Molecular typing can identify strains as epidemic or imported and can link cases [19]; international reference centers can provide this resource until local capacity is developed.

The improvement in diphtheria control has decreased but not eliminated the risk of exposure while traveling in Thailand. The risk is very low; despite >6 million tourist visits a year to Thailand, no cases among tourists have been reported. However, cases of diphtheria, including a fatal case, have been reported in visitors to African countries [20, 21] and the Indian subcontinent [22–24]. All travelers should ensure that they are current with respect to immunization for diphtheria, and travel medicine practitioners should be aware of high-incidence areas.

Thailand’s data may provide a clearer picture of the state of diphtheria control in similar rapidly developing countries. Routine immunization and economic development have greatly decreased but not eliminated diphtheria in Thailand. Residual disease is concentrated among economically disadvantaged groups, and importation from neighboring countries continues. The persistence of multiple foci creates a risk for the reemergence of epidemic diphtheria, although Thailand did not experience an increase in diphtheria during the recent economic crisis. Further improvements in diphtheria control will require increased commitment by national and international authorities. The recent initiation of the Global Alliance for Vaccines and Immunization to improve childhood immunization offers an important means to decrease disease burden in countries with limited resources.

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References


