

# DIPHThERIA OUTBREAK IN THAILAND, 2012; SEROPREVALENCE OF DIPHTHERIA ANTIBODIES AMONG THAI ADULTS AND ITS IMPLICATIONS FOR IMMUNIZATION PROGRAMS

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**Abstract.** An age distribution shift in diphtheria cases during a 2012 outbreak in northeastern of Thailand suggests adults are increasingly at risk for infection in Thailand. Data regarding immunity against diphtheria among the adult Thai population is limited. We review a 2012 diphtheria outbreak in Thailand and conducted a nationwide seroepidemiological survey to determine the prevalence of diphtheria antibodies among Thai adults in order to inform immunization programs. A total of 41 confirmed cases, 6 probable cases and 101 carriers of diphtheria were reported from northeastern and upper southern Thailand. The diphtheria outbreak in northeastern Thailand occurred among adults aged  $\geq 15$  years; sporadic cases occurred among children from upper southern Thailand. We conducted a seroepidemiological survey of 890 Thai adults from 4 age groups (20-29, 30-39, 40-49 and 50-59 years) in 7 different geographical areas of Thailand (Chiang Mai, Ratchaburi, Chon Buri, Nakhon Si Thammarat, Phitsanulok, Khon Kaen and Songkhla). Diphtheria toxin antibody levels were measured with a commercially available ELISA test. The seroprotection rate ranged from 83% to 99%, with the highest in eastern Thailand (Chon Buri, 99%) and the lowest in northern Thailand (Chiang Mai, 83%). Diphtheria antibodies declined with increasing age. We recommend one dose of diphtheria-tetanus toxoid (dT) vaccine once after 20 years of age in order to boost the antibody and revaccinations every 10 years to prevent future outbreaks.

**Keywords:** diphtheria, outbreak, seroprevalence, immunization, adult

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## INTRODUCTION

Diphtheria is an infection characterized by sore throat, low-grade fever and an adherent membrane on the tonsils, pharynx, and/or nasal cavity. Diphtheria

toxin produced by *C. diphtheriae* can cause myocarditis and polyneuritis (Atkinson *et al*, 2012). Diphtheria is spread by direct contact or by inhalation of aerosolized secretions from infected individuals. Before the wide-spread use of the diphtheria-tetanus toxoid and whole cell pertussis (DTP) vaccines, the case-fatality rates from respiratory tract diphtheria ranged from 2% to 20%, with an average of 10% for patients who received attentive medical care (Brenzel *et al*, 2006).

While once common, diphtheria is now rare because of the wide-spread use of the DTP vaccine. The percentage of infants receiving 3 doses of the DTP vaccine increased from 20% in 1980 to 78% in 2005 in developing countries, with substantial variation by district and country (Scheifele and Ochnio, 2009). Thailand began a routine infant immunization program with 2 doses of the DTP vaccine for all infants in 1977 (Tharmaphornplas *et al*, 2001), and with 3 doses beginning in 1982. After wide-spread use of the vaccine in Thailand, rates of diphtheria among Thais declined substantially from 1,600-2,400 cases per year during 1971-1977 to 19 cases per year in 2002 (Tiparat and Kooharat, 2002). By 2000, DTP vaccine coverage in Thailand was estimated to be 97% among infants below one year of age and since then has continually increased (WHO, 2013). However, diphtheria remains a problem in spite of efforts to achieve vaccination coverage, especially in southern Thailand, where vaccination coverage estimates for infants aged  $\leq 12$  months were lower compared to other regions (69% in Pattani Province, 74% in Yala Province and 85% in Narathiwat Province) (Tonghong, 2010). Sporadic cases of diphtheria have also been reported in many provinces in recent years. In 1994, a total of 18 cases of diphtheria were identified

in an outbreak in Saraburi Province (CDC, 1996). In 1996, a diphtheria outbreak was reported in Buri Ram Province (Pantukosit *et al*, 2008) with a total number of 31 cases. The annual rate of diphtheria infection in Thailand has gradually increased, amounting to 77 cases per year in 2010 (Tonghong, 2010), the majority of which (71 out of 77) were from southern Thailand. The ages of infected individuals ranged from 7 years to 50 years. The majority were children aged  $\leq 15$  years; however, 10% (8 of 77 cases) were among adults. This suggests some age groups are more vulnerable to infection, most likely due to lower vaccine coverage or waning antibody levels in adulthood.

The duration of protective immunity after primary immunization has become a subject of interest. Diphtheria antibody levels among adults aged  $\geq 20$  years show a significant age-related decrease in antibody levels with increasing age, reaching a minimum in the 30-39 year old age group, with fewer than half of subjects having protective antibody levels (Pachón *et al*, 2002; Kurugöl *et al*, 2011). The concept of herd immunity (National Network for Immunization Information, 2014) states that outbreaks of diphtheria among adults are possible when less than 85% of the population has protective antibody levels. In Thailand, a seroepidemiological survey of diphtheria immunity was conducted among 364 people aged 2-86 years in Nakhon Ratchasima Province (Chasangbong *et al*, 2004). Although the antibody titers of all 364 people exceeded protective levels ( $>0.1$  IU/ml), the study found that immunity to diphtheria declined with age. Another seroepidemiological survey of diphtheria immunity in Khon Kaen Province, Thailand in 2011 found adults aged 20-50 years were at the highest risk for diphtheria infection (Bansiddhi *et al*, 2012).

Table 1  
Diphtheria cases by age group and province during an outbreak in Thailand  
(June 2012 - January 2013).

Provinces	Confirmed cases	Probable cases	Carriers	Median age (range) (in years)
<b>Northeastern region</b>				
Loei	26	1	68	26 (2-72)
Phetchabun	5	0	13	33 (20-37)
Nong Bua Lam Phu	3	1	7	12.5 (9-48)
Nakhon Ratchasima	3	2	0	33.5 (33-43)
Udon Thani	1	0	3	32
Maha Sarakham	0	1	2	9
<b>Upper southern region</b>				
Surat Thani	1	1	0	9 (8-10)
Nakhon Si Thammarat	2	0	8	1.5 (1-2)
Total	41	6	101	26 (2-72)

Declining seroprotection rate among adults suggests the potential for future outbreaks of diphtheria. Several studies recommend a booster dose of dT for adults to maintain diphtheria immunity (Ilna, 2000; Kurugöl *et al*, 2011; Bansiddhi *et al*, 2012). In Thailand, compliance with the recommendation to have a booster dose of dT among adults has been relatively low. Additional data regarding immunity against diphtheria among Thais of various ages can help guide dT booster vaccine programs among adults. We evaluate a 2012 diphtheria outbreak in Thailand and report a nationwide seroepidemiological study we conducted to determine the prevalence of diphtheria susceptibility among Thai adults.

## MATERIALS AND METHODS

Data regarding diphtheria outbreaks in Thailand were retrieved from the Department of Disease Control, Ministry of Public Health. The records of diphtheria

cases were reviewed to determine disease patterns and determine the epidemiology. The following case definitions were used by the Committee of the Department of Disease Control: a confirmed case was defined as a case presenting with fever, throat exudate and throat swab culture positive for *Corynebacterium diphtheriae*; a probable case was defined as a person presenting with clinical symptoms of diphtheria or a close contact of a confirmed case; a carrier was defined as someone without clinical symptoms who had a throat culture positive for *Corynebacterium diphtheriae*.

### The 2012 outbreak of diphtheria in Thailand

A total of 38 confirmed cases, 5 probable cases and 93 carriers of diphtheria were reported from northeastern Thailand between June 2012 and January 2013. There were also sporadic confirmed cases of diphtheria in the upper south of Thailand during the same period of time as shown in Table 1.

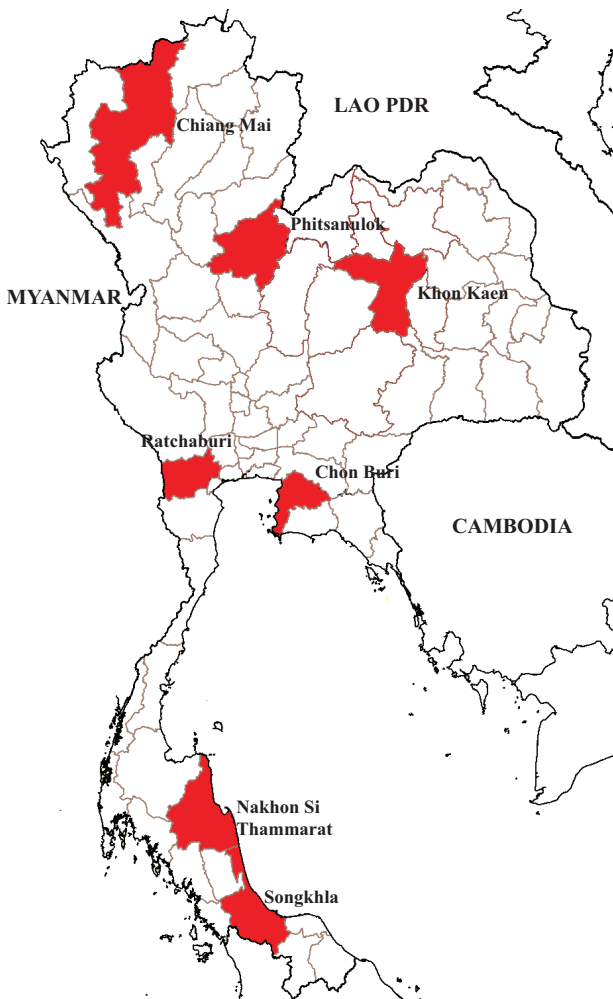


Fig 1—Seroepidemiological survey areas conducted in February 2013 in six regions and in June 2011 in Khon Kaen Province Thailand (Bansiddhi *et al*, 2012).

### Seroprevalence of antibody against diphtheria toxin

A cross sectional study was conducted on 890 randomly selected Thai adults. These were divided into two groups: the first group was comprised of healthy Thai blood donors aged 20-59 years randomly chosen from provincial blood bank centers in each region (299 males and 300 females) in February 2013. The second group was comprised of 291

from individuals aged 20-59 years from Khon Kaen Province, Thailand in June 2011. This second group consisted of individuals presenting for a routine health check-up and acutely ill patients seeking medical care at Chum Phae Hospital, Khon Kaen Province, Thailand. These data were extracted from a previous seroepidemiological survey of diphtheria immunity in Khon Kaen Province (Bansiddhi *et al*, 2012) using the same ELISA methods. The sample size was chosen based on an assumption of a 90% prevalence of diphtheria antibodies and a significance level of  $p < 0.05$ . These 890 samples were divided into four age groups (20-29, 30-39, 40-49 and 50-59 years) residing in 7 different geographical areas of Thailand (Chiang Mai, Ratchaburi, Chon Buri, Nakhon Si Thammarat, Phitsanulok, Khon Kaen and Songkhla) (Fig 1). All the specimens in this study were kept at the Center of Excellence in Clinical Virology, Chulalongkorn University and Hospital. All personal identifiers, except age and gender, were removed from the data set and specimens. The research protocol was approved by an institutional review board (IRB) at the Faculty of Medicine, Chulalongkorn University (IRB number 042/56) and conducted in accordance with the Helsinki Declaration II. The IRB waived the need for consent because the samples were anonymous.

### Laboratory methods

Diphtheria antibody levels were measured with a solid-phase IgG-specific ELISA (IBL International, Hamburg, Germany) according to a published protocol (Bansiddhi *et al*, 2012). The data were then classified according to the levels of antitoxin: 0.01-0.099 IU/ml susceptible; 0.1-0.99 IU/ml showed a satisfactory, protective level; 1-1.499 IU/ml showed a high level of immunity; 1.5-2 IU/ml showed a

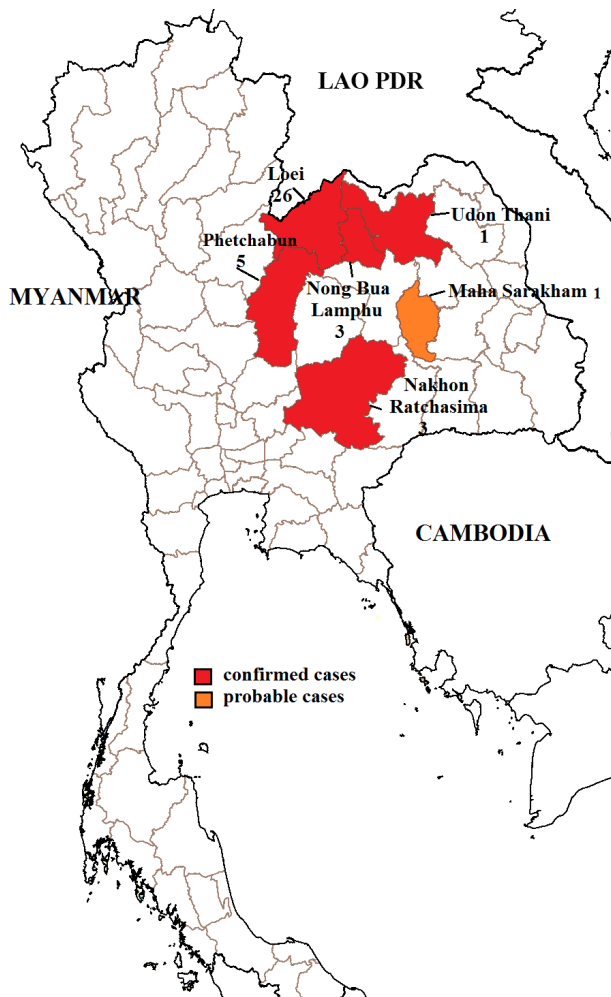


Fig 2—Areas where confirmed and probable diphtheria cases were reported during a diphtheria outbreak during June 2012 - January 2013, Thailand.

very high level of immunity and  $\geq 2$  IU/ml showed long-lasting immune protection.

#### Statistical analysis

Geometric mean titers (GMTs) were calculated using the log transformation of serological titers and from taking the antilog mean of the transformed values. Seroprotection rates (SPRs) for each age group were defined as the fraction of the population with a diphtheria antibody

level  $\geq 0.1$  IU/ml. The antibody levels and personal data were entered into SPSS version 15 (SPSS, IBM, Armonk, NY) by age group and gender.

## RESULTS

### The 2012 diphtheria outbreak in Thailand

The 2012 diphtheria outbreak in Thailand was first identified in Dan Sai District, Loei Province in June 2012. The first case was a 40-year-old immunocompromised alcoholic male, who subsequently died of acute myocarditis. The second case was a 25-year-old male from a nearby village; subsequent cases were reported in a village close to where the second case lived and then spread to neighboring provinces (Fig 2). In October, diphtheria cases were also reported in upper southern Thailand (Surat Thani and Nakhon Si Thammarat). A total of 6 fatalities from acute myocarditis were reported.

The Ministry of Public Health (Rangseewong and Siriarayaporn, 2013) stated that between June 2012 and January 2013, a total of 38 confirmed cases, 5 probable cases, and 93 carriers of diphtheria were reported from northeastern Thailand (Fig 2). There were also sporadic confirmed cases reported from upper southern Thailand. The majority of confirmed cases in the northeastern outbreak were reported among adults. However, in upper southern Thailand, all the cases occurred among children aged  $<15$  years (Table 1).

### Seroprevalence of antibodies against diphtheria toxin

The highest GMT was found among subjects aged 50-59 years (GMT 0.49 IU/ml). Followed by those aged 20-29 and 40-49 years (0.43 IU/ml and 0.38 IU/ml, respectively). The lowest GMT was found among those aged 30-39 years (GMT 0.34

Table 2  
Percentage population susceptible to diphtheria by age group and province.

Age group (years)	Seroprotection rates against diphtheria by age group										Total subjects	Average seroprotection rate <sup>a</sup> % (n)
	Chiang Mai % (n)	Phitsanulok % (n)	Chon Buri % (n)	Ratchaburi % (n)	Nakhon Si Thammarat % (n)	Songkhla % (n)	Khon Kaen % (n)	20-29	30-39	40-49		
Total subjects	100	100	100	100	100	99	291	890	-	-	-	-
20-29	96 (24)	96 (24)	100 (25)	88 (22)	88 (22)	87 (21)	91 (74)	230	92.2 (212)	92.2 (212)	92.2 (212)	92.2 (212)
30-39	80 (20)	76 (19)	100 (25)	100 (25)	88 (22)	76 (19)	90 (70)	228	87.7 (200)	87.7 (200)	87.7 (200)	87.7 (200)
40-49	80 (20)	84 (21)	96 (24)	96 (24)	100 (25)	88 (22)	92 (66)	222	91 (202)	91 (202)	91 (202)	91 (202)
50-59	76 (19)	80 (20)	100 (25)	88 (22)	100 (25)	96 (24)	100 (60)	210	92.9 (195)	92.9 (195)	92.9 (195)	92.9 (195)
Overall	83 (83)	84 (84)	99 (99)	93 (93)	94 (94)	87 (86)	92.8 (270)	-	90.9 (809)	90.9 (809)	90.9 (809)	90.9 (809)

<sup>a</sup>Seroprotection rate was defined as the fraction of the population with a diphtheria antibody level  $\geq 0.1$  IU/ml.

IU/ml). The overall GMT was 0.40 IU/ml.

The overall seroprotection rate among Thai adults was 90.9%; however, middle-aged adults aged 30-39 years had the lowest seroprotection rate (87.7%) (Table 2). The seroprotection rates in different regions ranged from 83% to 99%, with the highest rate being in Chon Buri (99%) and lowest in Chiang Mai (83%). The group with the lowest seroprotection in 4 provinces was the 30-39 year age group (76% in Phitsanulok, 88% in Nakhon Si Thammarat, 76% in Songkhla, and 90% in Khon Kaen (Bansiddhi *et al*, 2012).

Serological profiles varied by geographical areas but some common themes were noted. In Phitsanulok, Ratchaburi, Chon Buri and Songkhla Provinces, the lowest GMT values were seen in the 30-39 year old age group (0.24 IU/ml, 0.28 IU/ml, 0.37 IU/ml and 0.21 IU/ml, respectively). In Nakhon Si Thammarat the lowest GMT was found in the 20-29 year old age group (0.56 IU/ml); in Khon Kaen, the lowest GMT was found in the 40-49 year old age group (0.36 IU/ml) and in Chiang Mai the lowest GMT was found in the 50-59 year old age group (0.19 IU/ml) (Fig 3). The majority of the studied subjects (632 out of 890, 71%) had diphtheria immunity levels of 0.1-0.99 IU/ml; only 6.6% (59 out of 890) had a long-lasting immunity level (> 2 IU/ml).

## DISCUSSION

We examined a 2012 diphtheria outbreak and the prevalence of diphtheria immunity in a Thai population. During the 2012 outbreak of diphtheria in the northeast of Thailand, most of the affected individuals were between 15-44 years. This was most likely due to waning vaccine-induced immunity and decreased opportunity to acquire natural immunity.

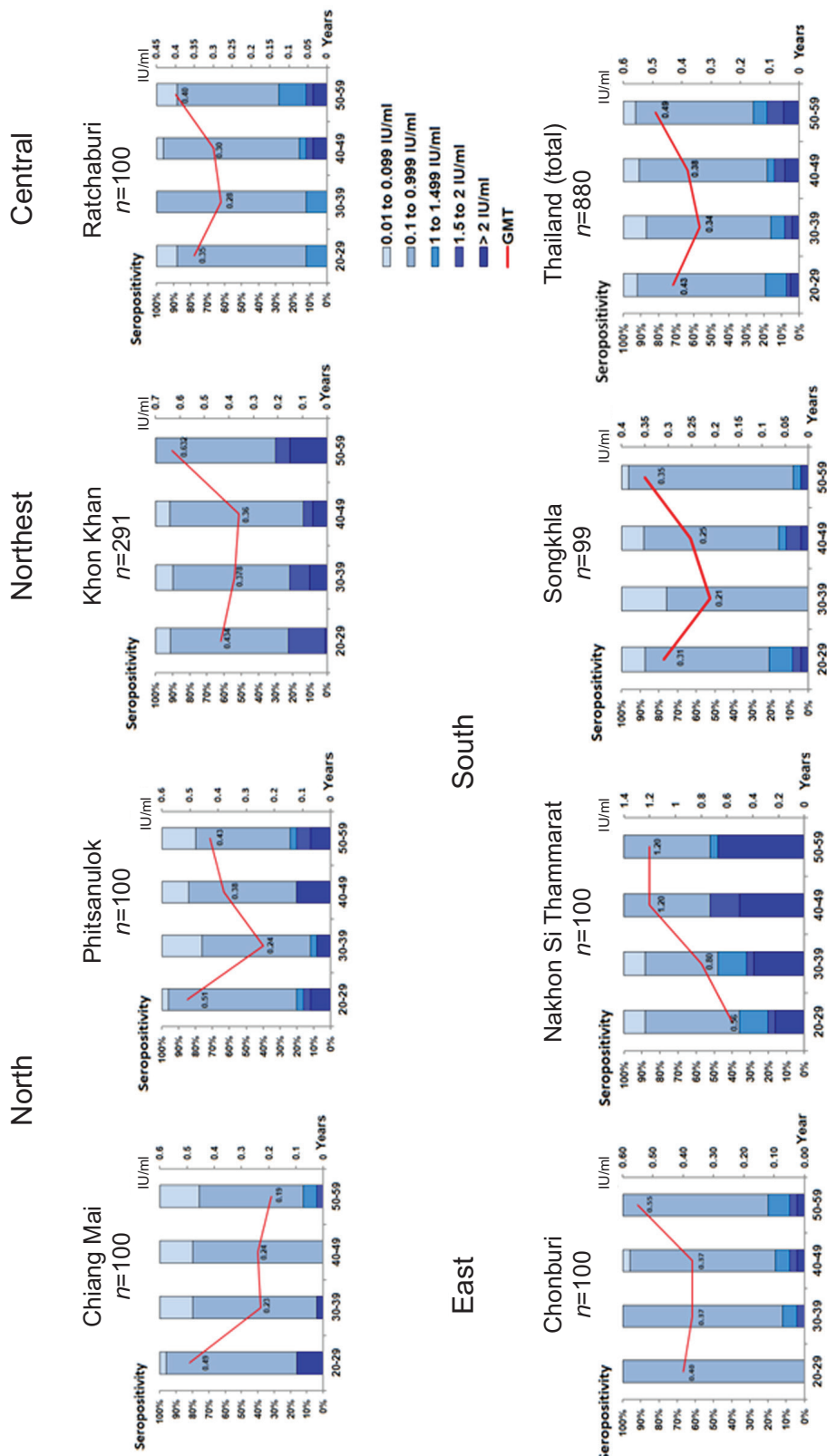


Fig 3—Percentages of seropositivity and diphtheria antitoxin levels by age group for various provinces during February 2013 in six regions and in June 2011 in Khon Kaen Province, Thailand (Bansiddhi *et al*, 2012).

The sporadic diphtheria cases in southern Thailand were mostly among those aged  $\leq 15$  years. Tonghong (2010) found vaccination rates among children aged  $< 12$  months in southern Thailand were lower than other areas of Thailand. This finding underscores the need for continued vaccination efforts, especially among economically disadvantaged populations, such as tribal children and children from families living in distant rural areas in southern Thailand.

Since diphtheria among humans is caused by a toxin, carriers may transmit the pathogen to those not yet immunized. Maintaining herd immunity to prevent outbreaks requires complete childhood vaccination and booster dT vaccination in adults (Scheifele and Ochnio, 2009).

In the second part of this study we conducted a nationwide seroepidemiological survey of immunity to diphtheria among Thai adults. Among the studied population, 90.9% had protective immunity to diphtheria; however, the results of our serological study suggested a higher percentage of diphtheria susceptibility among adults aged 30-39 years. The lower percentage of those seroprotected in this age group was probably due to: 1) suboptimal seroconversion among those who received two doses of DTP in infancy during 1977-1982, 2) lack of booster doses during adulthood, and 3) reduction in exposure to circulating *C. diphtheriae*. The second lowest seroprotection rate was found among adults aged 40-49 years (91%). This group did not receive the DTP vaccine during infancy.

The seroprotection rates in the Thai population was in our study are higher than in studies from some other countries: a study from Germany in 1993 found 76% of people had protective antibody levels

(Klouche *et al*, 1995), a study from Turkey in 2003 found 30.6% of subjects aged 40-49 years had protective antibody levels (Alp Cavus *et al*, 2007). No diphtheria outbreaks have been reported in Germany or Turkey as opposed to Thailand; this may be because Thailand's neighboring countries such as Lao PDR, Cambodia and Myanmar, have a higher incidence of *C. diphtheria*, which can spread cross border to Thailand (WHO, 2014).

Several studies have found protective antibody levels decrease with increasing age (Souliou *et al*, 1997; Di Giovine *et al*, 2013), except for some elderly populations over 60 years old, where seroprotection rates for diphtheria were higher than in younger age groups. In our study, the percentages of individuals with protective immunity varied by geographical area.

Based on herd immunity (Fine, 1993) ( $1-1/R_0$ ) with a basic reproductive number ( $R_0$ ) for diphtheria of 7, diphtheria immunity in at least 85% of the population is required to prevent a diphtheria outbreak. The seroprotection rates in some age groups in our study were lower than this threshold, especially among those aged 30-59 years. Antibodies levels were lower suggesting risk of future outbreaks.

The 2012 diphtheria outbreak in Thailand raises questions about vaccination policy, including the timing a number of booster dT doses required to protect adults. Since 2008, the national vaccine policy for Thailand recommends a DTP-HB (Diphtheria-Tetanus Toxoids-whole cell Pertussis and Hepatitis B) vaccine for infants aged 2, 4 and 6 months, a DTP for children aged 18 months and 4 years, and a booster dT vaccine at the age of 12 years before leaving primary school. This explains the high GMT values found among those aged 20-29 years. However, the



immunity declines over time. The World Health Organization (WHO) recommends people living in low endemic and non-endemic areas need a booster every 10 years to maintain life-long protection (Scheifele and Ochnio, 2009). A study from the Russian Federation (Brennan *et al*, 2000) reported adults with an unknown vaccination history or who are likely to be immunologically naive to toxigenic strains of diphtheria should receive at least 3 doses of dT for protection. In Thailand, the current guidelines recommend a booster dose of dT for those who have been vaccinated during childhood once at age 20 years and then every 10 years. This study further provides evidence for the importance of adhering to the current recommendations.

Inadequate immunity to diphtheria is likely in the near future due to waning immunity among adults. Adults should receive dT booster vaccine to maintain adequate seroprotection levels following recommendations. For adults with an unknown history of vaccination, 3 doses of dT vaccine are recommended. The dT vaccine may be given during clinic visits for other reasons, such as for injuries or during antenatal care in order to prevent future outbreaks of diphtheria in Thailand.

#### ACKNOWLEDGEMENTS

This work was supported by The Bureau of General Communicable Diseases, Department of Disease Control (DDC), Ministry of Public Health; the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission (HR 1155A-55, WCU-001-HR57, WCU-007-HR57); the Thailand Research Fund (DPG5480002); the Center of Excellence in Clinical Virology, Chulalongkorn

University; the Integrated Innovation Academic Center (IIAC), Chulalongkorn University; the Centenary Academic Development Project (CU56-HR01); the Ratchadaphisek Somphot Endowment Fund of Chulalongkorn University (RES560530093), King Chulalongkorn Memorial Hospital; the National Blood Center, the Thai Red Cross. We would like to thank the staff at Chum Phae Hospital, Khon Kaen for providing us the blood samples. We also thank Mr Brian Muchmore, Ms Petra Hirsch and Dr Sompong Vongpunsawad for reviewing the manuscript. Finally, we would like to thank MK Restaurant Company Limited, The Siam Cement Pcl and the Masu company for their support.

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