



Research article

Seroprevalence of antibodies against diphtheria, tetanus, and pertussis across various age groups during the post-COVID-19 pandemic period in Chonburi Province, Thailand

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ABSTRACT

Background: Limited data exists regarding population immunity against diphtheria, tetanus, and pertussis in Thailand during the post-COVID-19 pandemic period. This study aimed to evaluate the age-specific seroprevalence of anti-diphtheria toxoid (anti-DT) IgG, anti-tetanus toxoid (anti-TT) IgG, and anti-pertussis toxin (anti-PT) IgG in individuals across diverse age groups in Chonburi province, Thailand following the COVID-19 pandemic.

Methods: Between October 2022 and January 2023, a total of 657 participants from Chonburi Province, Thailand, were included in this study. The participants were categorized into 9 age groups: <5, 5–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61–70, and >70 years. Analysis of anti-DT, anti-TT, and anti-PT IgG levels was conducted using commercial ELISA kits (EUROIMMUN, Lübeck, Germany).

Results: Overall, 65.4 % of the population had seroprotection against diphtheria (antibody level ≥ 0.1 IU/mL), while 95.1 % had seroprotection against tetanus (antibody level ≥ 0.1 IU/mL). The 31–40 years age group exhibited the lowest seroprotection for diphtheria (48.9 %), and the >70 years age group had the lowest seroprotection for tetanus (73.3 %). The <5 years age group showed the highest seropositive rate and highest geometric mean titers for anti-PT IgG. On the

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contrary, the majority of individuals over 11 years of age displayed anti-PT IgG levels below 40 IU/mL.

Conclusions: To prevent diphtheria and pertussis outbreaks in Chonburi province, implementing catch-up vaccination is necessary. Targeted interventions should be deployed to enhance vaccination coverage among the susceptible population.

1. Introduction

Diphtheria, an acute infectious disease that primarily targets the upper respiratory system, is caused by the toxin-producing *Corynebacterium diphtheriae* (*C. diphtheriae*). In the past, diphtheria posed a significant public health threat. With the introduction of the diphtheria toxoid vaccine, commonly included in combination vaccines such as DTwP (diphtheria, tetanus, and whole-cell pertussis) and DTaP (diphtheria, tetanus, and acellular pertussis) for children, the incidence of diphtheria has significantly decreased in numerous countries with robust vaccination programs [1]. Nevertheless, diphtheria outbreaks continue to be reported globally. Diphtheria cases predominantly involve individuals who are either unvaccinated or incompletely vaccinated, and occasionally including adults with waning vaccine immunity [2,3].

Tetanus is a bacterial infection caused by *Clostridium tetani* (*C. tetani*) [4]. According to The Global Burden of Disease (GBD) database by the Institute for Health Metrics and Evaluation, an estimated 21,326 individuals died from tetanus in 2021 [5]. The majority of new cases are concentrated in South Asia and Sub-Saharan Africa [6]. Upon completing the three-dose primary immunization, it is advisable to administer tetanus-containing vaccine booster doses at the ages of 12–23 months, 4–7 years, and 9–15 years [4]. Since 1995, Thailand has consistently achieved a coverage rate exceeding 95 % for the third dose of DTwP, reaching as high as 97 % by the year 2022 [7,8]. However, the coverage of fourth and fifth doses has gradually increased in recent years, reaching 97.8 % and 90.3 % in 2013, respectively [9].

Pertussis, commonly known as "whooping cough", is an infectious bacterial disease that targets the respiratory system. Pertussis primarily spreads through inhaling droplets from infected individuals. Despite the long-standing use of pertussis vaccines, pertussis continues to persist worldwide [10–12]. One contributing factor to the resurgence of pertussis is the waning of vaccine-induced immunity [13]. In a study by Klein et al., in 2011, it was found that the effectiveness of DTaP vaccine wanes substantially after the fifth dose at ages 4–6 years [14]. In contrast to diphtheria and tetanus, the levels of antibodies against *Bordetella pertussis* (*B. pertussis*) antigens are not definitively correlated with clinical protection. Previous seroepidemiological surveys of antibodies to pertussis toxin (PT) primarily provide estimates of *B. pertussis* circulation in the community and offer essential data to refine immunization programs [15].

In 1977, Thailand initiated a routine infant immunization program with two doses of DTwP. This regimen was later modified to three doses in 1982 and increased to four doses administered at 2, 4, 6, and 18 months in 1987 [9]. Since 1992, the vaccination schedules have incorporated a second booster dose administered at the age of 4–6 years. A booster dose of tetanus toxoid (TT), which has since been replaced by diphtheria-tetanus vaccine (dT) in 2012, is also recommended during adolescence and every 10 years thereafter. In our seroprevalence study conducted in 2014 to assess immunity against diphtheria in the Thai population, it was found that the 30–39-year-old age group exhibited the lowest seroprotection rate (87.7 %) [16]. This cohort was born during the years when the EPI began, indicating a potential period of reduced coverage. Furthermore, our seroprevalence survey conducted in 2017 among Thai elderly individuals (aged ≥ 60 years) revealed that 51.4 % and 56.6 % of the elderly had antibody levels ≥ 0.1 IU/mL (the threshold for seroprotection) against diphtheria and tetanus, respectively. This suggests the need for administering a booster dose to maintain antibody levels above the threshold [17]. In the case of pertussis, our serosurvey in 2014 indicated that 2.6 % and 6.8 % had anti-PT IgG levels exceeding 100 IU/mL and ranging from 40 to 100 IU/mL, respectively, indicating recent exposure to *B. pertussis* in the community.

During the COVID-19 pandemic, there was a significant decrease in well-child visit rates, immunization administrations among children, and routine adult vaccinations [18,19]. This could lead to gaps in immunity within the population and the possibility of outbreaks of vaccine-preventable diseases. Therefore, we conducted this seroprevalence study during the post-pandemic period (between October 2022 and January 2023) in individuals residing in Chonburi province, Thailand. The study aimed to assess the age-specific seroprevalence of anti-DT IgG, anti-TT IgG, and anti-PT IgG and to assist policymakers in defining vaccination campaigns and implementing preventive strategies against these three diseases.

2. Methods

2.1. Study design and participants

The serosurvey was conducted in 11 districts in Chonburi province, Thailand between October 2022 and January 2023. This study served as a sub-study within the larger research project aimed at determining the overall prevalence of SARS-CoV-2 infection in Thailand [20]. Chonburi province, located in the eastern Gulf of Thailand approximately 90 km from Bangkok, was chosen as the representative city of Thailand according to the reasons previously described [20]. The large research project was a population-based, age-stratified, random sampling study that included a total of 1459 individuals [20]. A subset of the population ($n = 657$) was chosen to evaluate the seroprevalence of anti-DT IgG, anti-TT IgG, and anti-PT IgG. The sample size was calculated using a formula with a

significance level of 0.05 and the anti-DT seropositivity rate of 0.9 [16]. This study required 650 participants to achieve a margin of error of 2.5%. The inclusion criteria comprised individuals between 1 month and 80 years with no immunosuppressed status, malignancy, or severe hematologic disorders. The research protocol underwent review and approval by the Institutional Review Board of the Faculty of Medicine at Chulalongkorn University (IRB number 0706/65) and the Chonburi Provincial Public Health Office Institutional Review Board (IRB number 0024–2565). This study was conducted in compliance with the Declaration of Helsinki and the principles of good clinical practice. Participants or their parents were provided with information about the study's objectives, and written informed consent was obtained from all participants or their parents prior to enrollment.

2.2. Sample collection

Blood samples (3–5 mL) were collected at the study site in Chonburi province. The blood samples underwent centrifugation to obtain serum samples, which were then aliquoted and stored at -20°C until laboratory testing. Subsequently, the samples were transported to the virology laboratory at the Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University in Bangkok for serological testing.

2.3. Serological assays

Anti-DT, anti-TT and anti-PT IgG levels were analysed using commercial ELISA kits (EUROIMMUN, Lübeck, Germany) according to the manufacturer's instructions. The lot number for anti-DT IgG was E230117BL, for anti-TT IgG were E230816DS and E221202AF, and for anti-PT IgG was E230117BM. Results were expressed in international units per millilitre (IU/mL). Sera were initially diluted 1:100 as written in the manufacturer's protocol. Samples with levels above the upper limit of detection were further diluted until they were within ranges of detection. Samples with values below the lower limit of quantification (LLOQ; 0.01 IU/mL for anti-DT and anti-TT IgG and 5 IU/mL for anti-PT IgG) were calculated as half of the LLOQ.

Anti-DT IgG levels were divided into the following four categories: ≤ 0.01 IU/mL (susceptible), >0.01 – <0.1 IU/mL (partial protection), 0.1 – <1.0 IU/mL (full protection), and ≥ 1.0 IU/mL (long-term protection) [21]. Anti-TT IgG levels were divided into the following four categories: ≤ 0.01 IU/mL (susceptible), >0.01 – <0.1 IU/mL (partial protection), 0.1 – <1.0 IU/mL (full protection), and ≥ 1.0 IU/mL (long-term protection) [21]. Seroprotection rate against diphtheria and tetanus was defined as antibody level ≥ 0.1 IU/mL. For pertussis, level >100 IU/mL indicated acute *B. pertussis* infection or recent vaccination, while 40–100 IU/mL were interpreted as probable past exposure to *B. pertussis*. Level of 5–40 IU/mL was interpreted as no evidence of recent acute infection and <5 IU/mL indicated seronegativity [9].

2.4. Statistical analysis

Data on the seroprevalence of anti-DT IgG, anti-TT IgG and anti-PT IgG are presented as numbers and percentages. The Geometric mean titers (GMT) with their 95 % confidence intervals were calculated by taking the arithmetic mean of the log-transformed values of the antibody levels and then converting it to the real value (GMT) using a table of antilogarithms. One-way analysis of variance (ANOVA) was used to evaluate statistically significant differences in the GMT between different age groups. This analysis was conducted on the log-transformed data, which were found to be normally distributed. All statistical analyses were performed with SPSS v23.0 (IBM Corp., Chicago, IL). Figures were generated using GraphPad Prism v9.4.1 (GraphPad Software, San Diego, CA). A p -value <0.05 was considered statistically significant.

Table 1
Demographic data of the participants in this study.

Age group, years	Sample size		
	Total	Male (%)	Female (%)
< 5	49	22 (44.9)	27 (55.1)
5–10	63	31 (49.2)	32 (50.8)
11–20	117	63 (53.8)	54 (46.2)
21–30	94	43 (45.7)	51 (54.3)
31–40	92	49 (53.3)	43 (46.7)
41–50	93	43 (46.2)	50 (53.8)
51–60	91	39 (42.9)	52 (57.1)
61–70	43	22 (51.2)	21 (48.8)
> 70	15	8 (53.3)	7 (46.7)
Total	657	320 (48.7)	337 (51.3)

3. Results

3.1. Study participants

The demographic data of participants in this study are presented in Table 1. The participants' ages ranged from 1 year to 79 years. This study included 320 men (48.7 %) and 337 women (51.3 %).

3.2. Seroprotection against diphtheria and anti-DT IgG GMT

Overall, 65.4 % of participants exhibited anti-DT IgG levels of ≥ 0.1 IU/mL, indicating a seroprotection level (Table 2). The 31–40-year-old age group had the lowest seroprotection rate at 48.9 %, followed by the 51–60-year-old age group at 50.6 %, and the 41–50-year-old age group at 57.0 %. This implies that adults are at a higher risk of diphtheria. The highest seroprotection rate was observed in the <5-year-old age group (95.9 %), aligning with recent vaccination. Interestingly, the elderly (>70 years of age) exhibited a high seroprotection rate of 80.0 %.

A similar pattern was observed in the anti-DT IgG GMT as shown in Fig. 1A. The lowest anti-DT IgG levels were identified in adults aged 31–40 years (GMT 0.11 IU/mL), followed by adults aged 41–50 years (GMT 0.13 IU/mL). Additionally, the <5-year-old age group exhibited significantly higher anti-DT IgG levels compared to adults between 21 and 70 years ($p < 0.001$) (see Supplementary Table 1).

3.3. Seroprotection against tetanus and anti-TT IgG GMT

In total, 95.1 % of participants achieved seroprotection against tetanus (anti-TT IgG >0.1 IU/mL) with a GMT of 1.6 IU/mL (95 % CI: 1.4–1.8 IU/mL) (Table 2 and Supplementary Table 2). Within the group of individuals who achieved seroprotection, 69.7 % exhibited high levels of anti-TT IgG (>1.0 IU/mL) as shown in Fig. 1B. Children and adults below 50 years of age demonstrated >97 % of seroprotective status for tetanus. The percentages of individuals with low levels of anti-TT IgG increased with age. In the 61–70-year-old age group and the >70-year-old age group, only 76.7 % and 73.3 %, respectively, had protective levels of antibodies against tetanus.

In contrast to the anti-DT IgG GMT, the anti-TT IgG GMTs of adults over 50 years of age were lower than those of other groups ($p < 0.001$) (Supplementary Table 2). This finding aligns with the decline in seroprotection rates with age.

3.4. Anti-PT IgG seropositivity rate and GMT

In this study, 57.4 % exhibited seropositivity (anti-PT IgG >5 IU/mL) for pertussis, with a GMT of 7.4 IU/mL (95 % CI: 6.8–8.1) (Fig. 1C and Supplementary Table 3). Notably, 2.3 % of subjects displayed an anti-PT IgG titer ≥ 100 IU/mL, and 7.0 % had a titer between 40 and 100 IU/mL, indicating acute or recent exposure to *B. pertussis* or recent vaccination. Among individuals with an anti-PT IgG titer ≥ 40 IU/mL ($n = 61$), 65.6 % belonged to age groups of <5 and 5–10 years as shown in Supplementary Table 4. In the elderly population aged over 60 years, 6.9 % (4/58) displayed anti-PT IgG levels surpassing 40 IU/mL, potentially indicating recent infection with *B. pertussis*. The highest anti-PT GMTs were identified in the < 5-year-old age group, with a GMT of 44.3 IU/mL (95 % CI 33.5–58.5 IU/mL) ($p < 0.001$).

4. Discussion

In this study, the serological status of anti-DT IgG, anti-TT IgG, and anti-PT IgG was evaluated in a population residing in Chonburi Province, Thailand, during the post-COVID-19 pandemic era. The seroprotection rate for diphtheria observed in the present study was lower than that reported in a previous seroepidemiological survey conducted between 2011 and 2013. The earlier survey involved 890

Table 2

The percentage of individuals with seroprotective concentrations of anti-DT IgG and anti-TT IgG (antibody ≥ 0.1 IU/mL) among different age groups.

Age group, years	Total	Seroprotection rate (antibody ≥ 0.1 IU/mL)					
		Diphtheria			Tetanus		
		N	%	95 % CI	N	%	95 % CI
< 5	49	47	95.92	90.0–100.0	48	97.96	93.0–100.0
5–10	63	53	84.13	75.0–93.0	62	98.41	95.0–100.0
11–20	117	84	71.79	63.0–80.0	115	98.29	95.0–100.0
21–30	94	65	69.15	60.0–78.0	94	100.00	100.0–100.0
31–40	92	45	48.91	39.0–59.0	91	98.91	97.0–100.0
41–50	93	53	56.99	47.0–67.0	92	98.92	96.0–100.0
51–60	91	46	50.55	40.0–61.0	79	86.81	79.0–93.0
61–70	43	25	58.14	43.0–72.0	33	76.74	64.0–89.0
> 70	15	12	80.00	58.0–100.0	11	73.30	50.0–100.0
Total	657	430	65.40	62.0–69.0	625	95.10	93.0–97.0

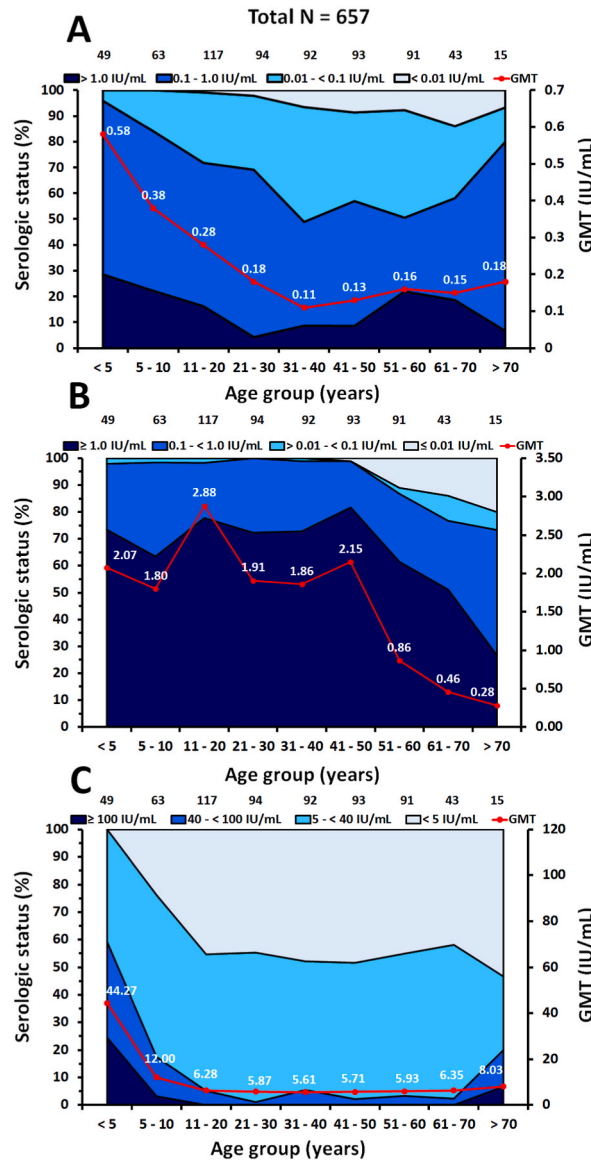


Fig. 1. Serologic status and geometric mean titer (GMT) of anti-DT IgG (A.), anti-TT IgG (B.) and anti-PT IgG (C.) across different age groups of individuals residing in Chonburi Province, Thailand (2022–2023). The left y-axis represents the percentage of individuals with a given antibody titer; the right y-axis represents the GMT with means indicated as red dots. The numbers above red dots indicated GMT (IU/mL).

Thai adults across four age groups (20–29, 30–39, 40–49, and 50–59 years) in seven different geographical areas of Thailand (Chiang Mai, Ratchaburi, Chon Buri, Nakhon Si Thammarat, Phitsanulok, Khon Kaen, and Songkhla). The seroprotection rates in that study ranged from 83 % to 99 %, with the lowest rate observed in the 30-39 year-old age group (87.7 %) [16]. The lower percentage of seroprotected individuals in the present study could likely be attributed to: 1) potentially suboptimal seroconversion among those who received DTWp during infancy, 2) the absence of booster doses during adulthood, and 3) a decrease in natural exposure to circulating *C. diphtheriae*. Furthermore, a recent study conducted in 2017 among the elderly population (>60 years of age) in Khon Kaen, Thailand, also revealed that approximately 50–60 % of individuals had seroprotective levels of anti-DT IgG [17].

The seroprotection rates for diphtheria among children under 5 years of age from Chonburi province in this study were higher than those observed in Nha Trang, Vietnam (96 % vs 68 %) [22]. The lower rate in Nha Trang could be attributed to factors such as low DTP3 coverage and suboptimal seroconversion rates after DTP vaccination, possibly influenced by malnutrition or external factors like suboptimum cold chains. Thailand has sustained a high coverage of the three-dose DTWp during infancy, leading to high levels of anti-DT IgG and a seroprotective rate in children under 5 years. According to records from the Bureau of Epidemiology, Ministry of Public Health, Thailand, there were 8 and 6 reported cases of diphtheria in the years 2021 and 2023 (0.01/100,000), respectively [23]. The age group of reported diphtheria cases varies ranging from children to adults, likely due to incomplete vaccination or waning

immunity in adulthood. The immunity gap observed in Thai adult and elderly population in the present study prompted the initiation of a catch-up dT vaccination campaign and the promotion of five-dose DTwP coverage in children. These measures could prevent outbreaks of diphtheria within the community.

Our study revealed that over 95 % of the participants were seroprotected against tetanus, with the seroprotection rate declining with age. This corresponds to the reported cases of tetanus in older Thai adults aged above 30 years from 2021 to 2022, during which there were 28 and 29 cases per year (0.04/100,000), respectively [24]. No cases of tetanus were reported in individuals under 30 years. The administration of five doses of tetanus-containing vaccine could have contributed to the establishment of long-lasting immunity among Thai children and young adults. The findings of the present study on immunity against tetanus were consistent with a previous survey conducted in 2004, which identified a decrease in the seroprotective rate of anti-TT IgG in Thai individuals with advancing age [25]. Another study conducted in the Thai elderly population also reported that less than 70 % of the elderly achieved seroprotection against tetanus [17]. It is possible that the elderly population may not have been immunized at all or received partial immunization with tetanus-containing vaccines during their earlier years. To address this immunity gap, it is recommended that older adults and the elderly should receive decennial boosters with dT to maintain protection against tetanus [26]. According to the findings of the present study, the target population for tetanus booster vaccinations should be Thai individuals aged above 51 years.

In 2023, individuals aged <4 years accounted for 65 % of all reported pertussis cases in Thailand. Among children 0–4 years old with pertussis, infants <1 year of age, who were too young to be fully vaccinated, were the most affected age group. Three deaths due to pertussis were reported in infants <1 year in 2023 [27]. Although to a lesser extent, older children and adults also contracted pertussis in 2023, suggesting the circulation of *B. pertussis* in the community. The present study demonstrated a significant decline in the GMT of anti-PT IgG during adolescence, which persisted at a low level through adulthood. This decline could be attributed to the waning of vaccine-induced immunity. Notably, the present study showed that 3.8 % (21/545) of individuals aged over 11 years had anti-PT IgG levels >40 IU/mL, indicating acute or recent pertussis. This aligns with our previous seroprevalence survey of anti-PT IgG in 2014, indicating that 6.3 % of individuals aged >11 years had serological evidence of exposure to *B. pertussis* [9]. Similarly, a previous study in Italy reported that in the age group ≥65 years, the prevalence of subjects with anti-PT IgG levels between 40 and 100 IU/mL was 6.7 %, which was higher than in other age groups [15]. This emphasizes the potential role of adults and the elderly population in the transmission of *B. pertussis* [15]. The prevalence of anti-PT IgG seropositivity (>5 IU/mL) in children <5 years in our study was 100 %, of which 59.2 % had anti-PT IgG levels >40 IU/mL. Without vaccination records, it is challenging to confirm whether this is attributable to vaccination or infection. However, considering the reported pertussis incidence of 0.03–0.39 per 100,000 population in Thailand between 2022 and 2023, it is likely that the high seropositivity rate in children <5 years was a result of recent vaccination [27]. A previous study in China found that anti-PT IgG in children peaked at post-primary series vaccination (6 months of age) and post-first booster vaccination (18–23 months), and then continuously declined thereafter to its nadir at 6 years-old in the absence of pre-school booster [28]. To prevent outbreaks of pertussis across all age groups, several measures should be considered, including maternal immunization during pregnancy, increased vaccine coverage in children residing in remote areas, and the administration of a booster dose of Tdap for individuals aged ≥11 years.

This study has some limitations. Firstly, the population was recruited from a single province, and therefore, the results may not be fully representative of the entire country. Secondly, the relatively small number of individuals in the older age group may restrict our ability to make comparisons in seroprevalence rates and GMTs with other groups. Lastly, the absence of vaccination records hinders our ability to correlate them with the serologic findings.

The findings of this present study suggest that dT booster vaccination should be implemented for the Thai adult and elderly population to sustain seroprotection and diminish susceptibility to diphtheria and tetanus. Additionally, considering the incorporation of pertussis vaccination into the Thai universal coverage scheme for pregnant women in July 2023 [29], extending pertussis-containing vaccines to Thai adolescents and adults should be considered and integrated into the Thai EPI to enhance immunity against pertussis.

CRediT authorship contribution statement

Nasamon Wanlapakorn: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Nungruthai Suntronwong:** Formal analysis. **Sithichai Kanokudom:** Formal analysis. **Suvichada Assawakosri:** Formal analysis. **Preeyaporn Vichaiwattana:** Investigation. **Sirapa Klinfueng:** Investigation. **Lakana Wongsrisang:** Investigation. **Thanunrat Thongmee:** Investigation. **Ratchadawan Aeemjinda:** Investigation. **Nongkanok Khanarat:** Investigation. **Donchida Srimuan:** Project administration, Data curation. **Thaksaporn Thatsanathorn:** Project administration, Data curation. **Ritthideach Yorsaeng:** Data curation. **Apirat Katanyutanon:** Data curation, Conceptualization. **Wichai Thanasopon:** Data curation, Conceptualization. **Wichan Bhunyakitikorn:** Data curation, Conceptualization. **Chaninan Sonthichai:** Data curation. **Piyada Angsuwatharakorn:** Data curation, Conceptualization. **Withak Withaksabut:** Data curation. **Jira Chansaenroj:** Investigation, Formal analysis, Data curation. **Natthinee Sudhinaraset:** Project administration. **Yong Poovorawan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Informed consent statement

Informed consent was obtained before participant enrollment. The study was conducted according to the Declaration of Helsinki and the Good Clinical Practice Guidelines (ICH-GCP) principles.

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University (IRB number 0706/65) and the Chonburi Provincial Public Health Office Institutional Review Board (IRB number 0024–2565).

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nasamon Wanlapakorn reports financial support was provided by the Health Systems Research Institute (HSRI). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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