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Editorial

It is Time for the Elimination of Preventable Communicable Diseases

Wiwat Rojanapithayakorn, Senior Editor

In the fields of communicable disease prevention and control, there are four levels of achievements that can be expected, namely (1) control, (2) reduction, (3) elimination, and (4) eradication. They are listed here from easy to difficult to achieve. Some experts may group the first two together, and some may add extinction as one more category after the eradication. Generally, disease control means to implement the health program in a way that limit spreading of the disease in order to ensure no more new cases. For disease reduction, the main objective is to reduce the magnitude of cases, which will lead to the limitation of health and socio-economic consequences. The distinction between control and reduction can be observed by looking at the nine global noncommunicable disease targets for 2025 set by the World Health Organization which specifies 25% reduction of hypertension (reduction category) and 0% increase of diabetes and obesity (control category). The reduction achievement can be considered as success, although it may or may not reach the level of elimination or eradication which are the ultimate goals of disease control.

Elimination of disease means the reduction of incidence of a specified disease to zero in a defined geographic area whereas eradication means permanent reduction to zero of infection caused by a specific pathogen. In the long history of human public health, only one disease has been eradicated: smallpox. Continued intervention measures for smallpox control are no longer necessary. Attempts have been made to eradication poliomyelitis, yaws, malaria and a few more. Global efforts to eradicate polio began in 1988 are still unsuccessful. Much more efforts are needed to eradicate polio and other diseases in the pipeline, particularly in the world of increased social and political conflicts. The more possible targets are to aim for disease elimination.

The meaning of the term “elimination” has been compromised widely. The following terms are common examples:

- Elimination: reduction of incidence of a specified disease in an area to zero.
- Elimination as a public health problem: acceptable level of reduction as long as the incidence or prevalence does not exceed a certain level.
- Zero local transmission: acceptable level as long as all new cases are patients from outside the area.
- Zero disease: no disease reported. However, for HIV disease, the three zeros concept allows certain levels of incidents for new cases, new deaths and discrimination.
- Ending the disease: aiming to gradually reduce the disease incidence to zero (such as “ending AIDS”).

The acceptance of the compromised terms reflects the lowering degree of expectation for disease control interventions. Stronger advocacy and more efforts are required to shape the control achievement to the real elimination.

Naturally, all communicable diseases are preventable. The modes of disease transmission are mostly well-known (by personal contact, vector borne, air borne, food and water consumption, etc.). However, human daily living lifestyles cannot ensure zero transmission of all diseases. Nevertheless, some infections can be prevented by increasing body immunity to pathogens, particularly by immunization, the very mean leading to the eradication of smallpox. The 2-dose measles, mumps and rubella initiated

in Finland since 1982 had resulted in 25 years measles elimination since 1996, and mumps and rubella from 1997. Such 2-dose immunization approach has become a prototype for global measle elimination program.

In this issue of OSIR, reports on vaccine preventable diseases are the majority (pertussis, chickenpox and COVID-19). History tells us that availability of vaccines alone is not the answer to disease elimination. Effective and efficient strategies are needed to ensure reception of vaccination by the target populations. Public health personnel should put more efforts to gain and ensure community participation in the immunization program. Until then, elimination of vaccine preventable disease will become reality. It is already too late for the elimination of many immunizable communicable diseases of which their vaccines have been made available for over 30 years.

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Predicting Factors for Malaria Reintroduction and A Multi-factorial Approach to Prevent Malaria Outbreaks in the Malaria-free Areas

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Abstract

Thailand's National Malaria Elimination Strategy, 2017–2026, aims to reach zero indigenous transmission by 2024. During 2016–2021, Thailand had successfully reduced its malaria burden by more than 80%. However, a resurgence of malaria in 2022 saw an increase in the incidence in 33 provinces. To identify the predictors of malaria epidemic re-occurring in malaria-free areas, secondary data of malaria-reintroduced villages in 2022 were obtained from the Malaria Information System. A descriptive cross-sectional study was conducted to compare characteristics, prevention, and response measures between villages with and without sustained local transmission after malaria reintroduction. A retrospective cohort study was conducted to determine the associations between sustained local transmission and potential predictors. Among the transmission foci in 2022, 336 villages had previously been malaria-free, of which 73 (21.7%) reported sustained local transmission. A multi-level logistic regression model, considering villages clustered within provinces, found that villages located in a district which contained active foci (adjusted odds ratio (AOR) 1.03, 95% confidence interval (CI) 1.01–1.05) and having a higher proportion of non-Thai cases (AOR 12.3, 95% CI 5.69–26.6) were significantly associated with sustained local transmission whereas coverage of malaria control within 7 days was protective (AOR 0.20, 95% CI 0.09–0.44). Areas with high migrant populations were associated with a higher risk of malaria reintroduction. Proactive case search should target these populations to quickly detect reintroduced cases and conduct timely control to prevent further local transmission.

Keywords: malaria, reintroduction, sustained local transmission, elimination, Thailand

Introduction

Malaria is one of the world's deadliest infectious diseases. The estimated number of malaria deaths globally in 2021 was 619,000.[1] To reduce morbidity and mortality related to malaria, the World Health Organization advocated member states to jointly eliminate the disease by 2030 and the global technical strategy for malaria 2016–2030 was adopted by the World Health Assembly in May 2015.[2] To comply with this global mission, Thailand introduced the malaria elimination program in 2016 and established the National Malaria Elimination Strategy (NMES) 2017–2026 which was approved by the Thai cabinet. The goal of NMES is to reach zero indigenous malaria cases throughout the country by 2024 and eliminate malaria by 2026. The strategy includes four steps: 1) Scaling up malaria elimination in Thailand, 2) Developing technologies, innovations, measures, and models that are appropriate for malaria elimination, 3) Developing partnerships among stakeholders at the national and international levels to enable malaria elimination, and 4) Promoting and empowering communities to protect themselves from malaria.[3]

During the first-half of NMES, Thailand successfully reduced the burden of malaria by more than 80% with the number of cases declining from 19,080 in 2016 to 3,266 in 2021. Additionally, malaria transmission foci (villages) have been contained from 1,084 to 495 foci and are concentrated in the border areas with Myanmar, Cambodia, and Malaysia resulting in an increase of malaria free areas from 42 provinces in 2016 to 48 provinces in 2021.[4] However, a resurgence of malaria in 2022, particularly along Thai-Myanmar border, increased the annual incidence to 10,155 cases

across 675 transmission foci in 33 provinces.[4] This increasing number of malaria cases has raised concerns and awareness among Thailand's Department of Disease Control (DDC), Ministry of Public Health and its stakeholders. Therefore, several efforts have been implemented such as strengthening surveillance with active case detection in malaria-affected communities, building up the capacity of case investigation, laboratory testing, and case management, accelerating transmission foci investigations, close monitoring and evaluation of vector control measures, and engaging stakeholders at all levels to integrate malaria elimination into the public health system and local administrations.[5,6] With these efforts, most of the malaria-reintroduced villages reported no further malaria local transmissions within four weeks after the first introduced case was detected. However, some villages continued to report additional indigenous cases and became epidemic areas again.[4]

To describe the malaria situation and identify predictors of malaria in previously malaria-free areas, we identified malaria-reintroduced villages in 2022 and compared epidemiological characteristics, prevention measures, and malaria response activities between villages with and without sustained local transmission for more than four weeks after malaria reintroduction. It is hoped that the findings of this study can help in the prevention of re-establishment of local malaria transmission, particularly in malaria-free areas, and provide recommendations to revise the operational plans of NMES in 2024–2026.

Methods

A descriptive cross-sectional study was conducted to describe the malaria situation in Thailand between 2016–2022 using malaria case report data obtained from the Malaria Information System (MIS). In 2022, malaria-reintroduced villages were identified. Epidemiological characteristics, prevention measures, and malaria response activities including case management were compared between villages with and without local transmission after malaria was reintroduced to their areas.

A retrospective cohort study was conducted to determine predictors for sustained local transmission. Malaria-reintroduced villages in 2022 were the cohort of interest.

Data Sources and Data Collection

Secondary data were obtained from the MIS, a web-based program for reporting malaria cases under the Division of Vector-borne Diseases, Department of Disease Control. The descriptive study included malaria cases between 2016–2022. For malaria resurgence in 2022, 336 malaria-reintroduced villages were identified. We used data of those villages including malaria prevention activities prior to the reintroduction, characteristics of cases, case investigation, and control measures.

Study Population and Definitions

Malaria cases reported to the MIS during 2016–2022; the reporting case definition was defined as any person with or without symptoms of malaria who had the malaria parasite in their blood smear, either thick or thin blood film, or had a positive result of malaria rapid diagnostic test.

Malaria areas according to Thailand NMES were classified as follows; A1—active foci, a village with reported indigenous cases in the current year, A2—residual foci, a village without local malaria transmission within the current year but not yet malaria-free for three consecutive years, B1—high and moderate receptivity, a village in which malaria transmission was not reported within the last three years, but vectors present, and B2—low and no receptivity, a village in which transmission was not reported within the last three years and vectors absent.

Malaria-reintroduced villages identified in 2022 were defined as those being malaria-free for at least one year (malaria area A2, B1, or B2) but found a new malaria case regardless of the source of infection.

Proactive case detection referred to malaria active case search with blood testing in high-risk areas for malaria reintroduction before a malaria case was detected.

A 1-3-7 approach referred to malaria response activities including case notification to the MIS within one day, case investigation to identify the source of infection within three days, and malaria control in the affected area within seven days after malaria diagnosis.[7]

Complete case follow-up, according to the NMES, referred to all malaria cases being followed up at least four times after treatment to ensure clinical and parasitological cure.

Data Analyses and Statistics

Descriptive study

The annual malaria incidence from 2016–2022 was calculated per 100,000 population. Each year, the number of Thai and non-Thai cases were determined. Malaria reintroduction and further sustained local transmission were calculated in 2021 and 2022 to demonstrate the resurgence of malaria in Thailand. Of the 336 malaria-reintroduced villages in 2022, epidemiological characteristics, prevention and control

measures were described as a proportion, mean, or median. Characteristics were described among villages with and without sustained local transmission using a t-test or Mann-Whitney test for continuous variables and Chi-square or Fisher's exact test for categorical variables.

Analytical study

Dependent variable: A dichotomous outcome of interest was considered from 336 malaria-reintroduced villages in 2022. The outcome was divided into two groups, 1) malaria was controlled within four weeks with no further local transmission, and 2) sustained local transmission for more than four weeks after a reintroduced case was reported.

Independent variables: Data of epidemiological characteristics, coverage of malaria preventive measures, and malaria response activities were aggregated to correspond with the unit of analysis (a village) as shown in Table 1.

Data analyses

A multi-level logistic regression model was used to measure the associations between sustained local transmission and potential predictors. This model incorporates a random intercept with the province as a higher-level variable, considering the hierarchical structure of the data (i.e., villages clustered within the province). Potential predictors were identified from the independent variables that had a *p*-value <0.10 from the descriptive study. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were reported. Epi-info™ version 7, Centers for Disease Control and Prevention, Atlanta, USA and R were the data analytic tools.[8,9]

Table 1. Management of independent variables for data analysis

Independent variables	Variable types		
	From MIS	For descriptive study	For analytical study
Classified malaria area (NMES)	Categorical (A2, B1, B2)	Categorical (A2, B1, B2)	Categorical (A2, B1, B2)
Located in districts with A1 area	Yes / No	Yes / No	Yes / No
Nationality	Categorical (Thai / non-Thai)	Proportion of non-Thai cases in each village	Categorical (≤10%, >10%)
Age (years)	Ordinal	Proportion of cases aged under 15 years in each village	Categorical (≤25%, >25%–50%, >50%)
Insecticidal net provided ≥1 net per 2 persons in last 3 years	Number of nets and population in each village	Yes / No (ratio of nets per population in each village >1:2)	NA
Proactive case detection	Yes / No	Yes / No	Yes / No
Proportion of cases notified within 1 day	Continuous (Proportion (%))	Mean proportion of the villages	NA
Proportion of cases investigated within 3 days	Continuous (Proportion (%))	Mean proportion of the villages	NA
Proportion of cases controlled within 7 days	Continuous (Proportion (%))	Mean proportion of the villages	Categorical (≤50%, >50%–80%, >80%)
4-time follow up of *P. vivax*	Continuous (Proportion (%))	Median proportion of the villages	NA
Complete follow up of *P. falciparum* or *P. knowlesi*	Continuous (Proportion (%))	Median proportion of the villages	NA
Insecticide-treated net or spraying	Yes / No	Yes / No	Yes / No

MIS: malaria information system. NMES: National Malaria Elimination Strategy. NA: not applicable.

Results

During 2016–2021, the annual malaria incidence declined from 11,595 cases (8.3 per 100,000 population) to 3,266 cases (2.0 per 100,000 population). However, in 2022, the incidence increased to 10,155 cases (8.7 per 100,000 population) and both Thai and non-Thai populations were affected. Additionally, as shown in Figure 1, most cases in 2022 were non-Thai, in contrast to the previous periods where Thais predominated.

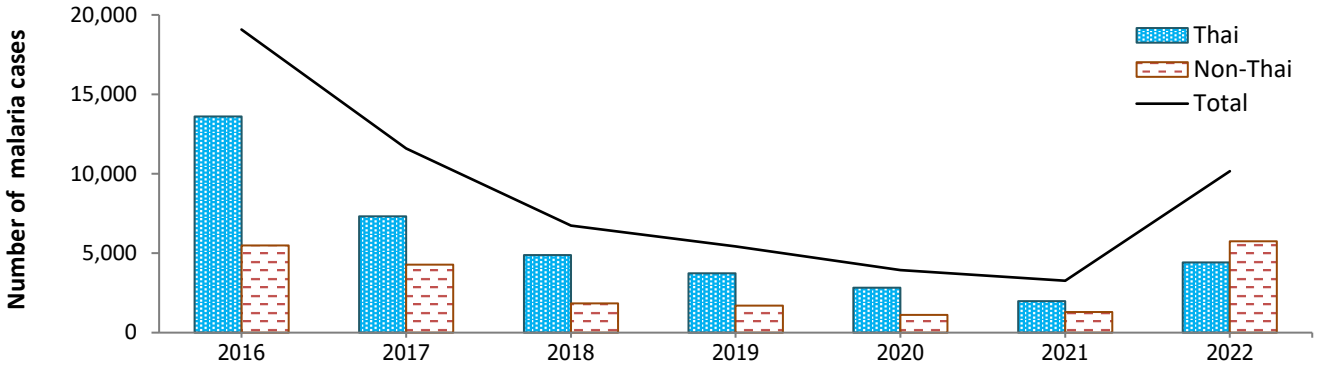

Figure 1. Annual malaria cases (black line) stratified by nationality (vertical bars), Thailand, 2016–2022

The distribution of transmission foci by district in 2021 compared to 2022 is shown in Figure 2. Malaria transmission foci reduced from 1,084 villages in 120 districts (35 provinces) in 2016 to 495 villages in 76 districts (29 provinces) in 2021. However, the number of transmission foci increased in 2022 to 675 villages in 90 districts (33 provinces).

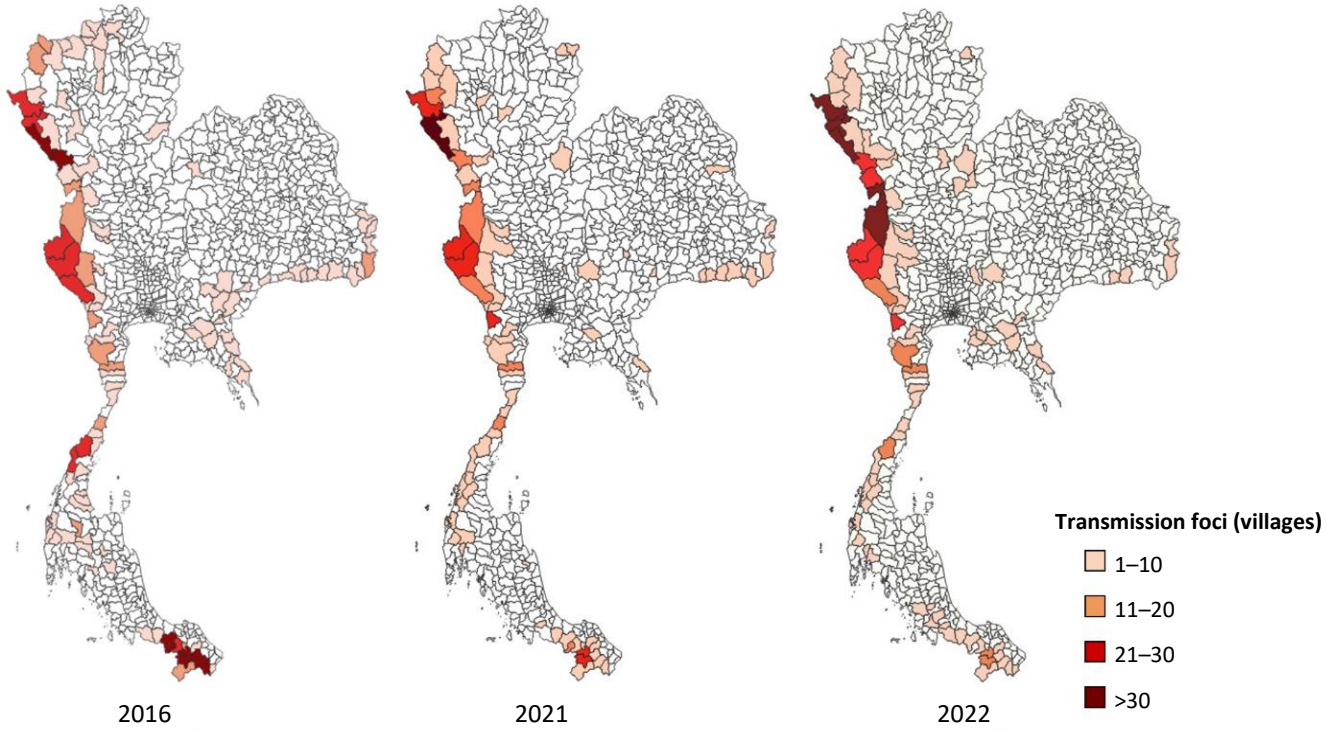

Figure 2. Distribution of malaria transmission foci by district, Thailand, 2016, 2021 and 2022

According to the NMES, the Division of Vector-Borne Diseases, DDC annually classified all villages in Thailand to be A1, A2, B1, or B2 areas to prescribe malaria prevention and elimination measures. Malaria elimination resources and commodities were also mobilized specifically to each area. At the beginning of 2021 and 2022, there were 92,222 and 92,368 malaria-free villages, respectively. In 2021, 132 malaria-free villages reported reintroduction of malaria cases. Of those, 11 (8.3%) could not control the transmission. In 2022, 336 malaria-free villages reported reintroduction, which resulted in 73 (21.7%) having sustained local transmission, as shown in Table 2.

Table 2. Number of malaria-free and malaria reintroduced areas in Thailand, 2021–2022

Year	Number of villages		
	Malaria-free at beginning of the year (A2, B1, and B2 areas)	Malaria reintroduced during the year (%)	Sustained local transmission (%)*
2021	92,222	132 (0.14)	11 (8.3)
2022	92,368	336 (0.36)	73 (21.7)

**Sustained local transmission was defined as villages continuously reporting indigenous cases for more than 4 weeks after a malaria case was reported.*

Considering that the number of malaria-reintroduced villages in 2022 was 2.6 times higher than in 2021, and the proportion of villages with sustained local transmission after the reintroduction in 2022 increased to 21.7%, the risk of a malaria epidemic reoccurring among those reintroduced areas should be determined. Therefore, we compared characteristics of malaria-reintroduced villages in 2022 between the villages with and without sustained local transmission after the reintroduction. NMES classified areas, the proportion of non-Thai cases, proportion of child cases, prevention measures, malaria responses, and control activities are compared between villages with and without sustained local transmission in Table 3. Of the 336 villages compared, 263 (78.3%) could control malaria and stop transmission within four weeks whereas 73 (21.7%) had sustained local transmission. NMES classified areas, Proactive case detection as a malaria preventive measure, and the coverage of insecticide-treated bed nets or spraying when a malaria case was detected had significantly different proportions between the two types of villages. Additionally, villages with sustained local transmission had higher proportions of non-Thai and child cases than villages without sustained local transmission. For 1-3-7 activities, only malaria control within seven days showed a significant lower coverage in the villages with sustained local transmission. Complete follow up of *P. vivax* cases was also lower in villages with sustained local transmission.

Table 3. Characteristics of malaria-reintroduced villages in 2022 compared to villages with and without sustained local transmission after the reintroduction

Characteristics	Malaria reintroduced villages in 2022 n (%)			*P*-value‡
	Total (336 villages)	Without sustained local transmission* (263 villages)	With sustained local transmission† (73 villages)	
Characteristics of malaria-reintroduced villages				
NMES classified area				0.04
A2	132 (39.3)	94 (35.7)	38 (52.1)	
B1	168 (50.0)	140 (53.3)	28 (38.4)	
B2	36 10.7)	29 (11.0)	7 (9.6)	
Located in A1 districts	262 (78.0)	194 (73.8)	68 (93.2)	<0.005
Proportion of non-Thai cases§	55.5%	35.7%	61.6%	<0.005
Proportion of cases <15 years old§	26.8%	24.0%	27.6%	0.06
Coverage of malaria preventive measures				
Insecticidal net provided ≥1 net per 2 persons in last 3 years	63 (18.8)	48 (18.3)	15 (20.6)	0.73
Proactive case detection	75 (22.3)	64 (24.3)	11 (15.1)	0.06
Coverage of malaria response and control activities				
Case notification within 1 day¶	71.5% (38.2)	71.4% (39.2)	71.6% (34.8)	0.97
Case investigation within 3 days¶	76.8% (34.8)	77.0% (35.8)	75.8% (31.3)	0.79
Malaria control within 7 days¶	56.0% (42.4)	58.9% (43.8)	45.7% (35.2)	0.02
Complete follow up of *P. vivax*#	100% (66.7–100)	100% (66.7–100)	90.3% (75.0–100)	0.03
Complete follow up of *P. falciparum* or *P. knowlesi*#	100% (100–100)	100% (100–100)	100% (75.0–100)	0.51
Insecticide-treated net or spraying	128 (38.1)	109 (41.4)	19 (26.0)	0.02

**Malaria was controlled within 4 weeks and no further local transmission. †Having sustained local transmission for more than 4 weeks after reintroduced case was reported. ‡Chi-square or fisher's exact test for categorical variables. T-test or Mann-Whitney test for mean or median respectively. §Calculated from a total number of malaria cases in each group (664 cases in the village without sustained local transmission and 2,179 cases in the village with sustained local transmission). ¶Mean (standard deviation) coverage of cases. #Median (interquartile range) coverage of cases. NMES: National Malaria Elimination Strategy.*

Table 4 presents the results of the multi-level logistic regression model to measure the associations between sustained local transmission and potential predictors identified from descriptive study. Considering villages clustering within provinces, villages located in an A1 district were more likely to have sustained local transmission after malaria reintroduction (AOR 1.03, 95% CI 1.01–1.05) compared to other villages. Villages having a higher proportion of non-Thai cases was strongly associated with sustained local transmission (AOR 12.3, 95% CI 5.69–26.6) and having a coverage of malaria control within seven days higher than 80% of cases was significantly associated with a reduced risk (AOR 0.20, 95% CI 0.09–0.44).

Table 4. Associations of sustained local transmission with characteristics of malaria-reintroduced villages, malaria preventive measures, and malaria response and control activities from the random effect model considering villages clustered within province*

Predicting factors†	Adjusted odds ratio	95% confidence interval
NMES classified as an A2 area	1.66	0.82–3.36
Locating in districts with A1 area	1.03	1.01–1.05
Proportion of non-Thai >10% of cases	12.3	5.69–26.6
Proportion of child cases (%)		
>25–50	0.94	0.38–2.31
>50	0.40	0.13–1.24
Proactive case detection	1.06	0.42–2.65
Insecticide-treated net or spraying	0.54	0.26–1.13
Coverage of malaria control within 7 days (%)		
>50–80 of cases	0.70	0.29–1.68
>80 of cases	0.20	0.09–0.44

**ICC (Intraclass correlation coefficient) = 5 x 10^{-34}. †Independent variables that have a p-value <0.10 from the descriptive analyses were included in the model. NMES: National Malaria Elimination Strategy.*

Discussion

Despite the nationwide implementation of the malaria elimination strategy and efforts, Thailand was not able to achieve the goal of its NMES to stop local transmission by 2024. Our study findings indicate that disease incidence and transmission foci were increasing, particularly in villages located near the Myanmar border. Additionally, the change of epidemiology shows that most malaria cases in Thailand shifted from Thai to non-Thai. After a political crisis broke out in Myanmar in 2021, it was estimated that 4–5 million migrants were living in Thailand.[10,11] Therefore, managing the influx of migrant populations is critical and a serious obstacle to the elimination of malaria.

Among transmission foci in 2022, 336 villages were malaria-free for at least one year, of which 204 were malaria-free for at least three years. Moreover, 73 (21.7%) of these villages could not control the transmission, leading to sustained local transmission. Villages classified as either A2 or located in a district having a village classified as A1 had a higher proportion of sustained local transmission. A1- and A2-classified areas reflect an ecological environment in which Anopheles mosquitoes exist and transmit malaria to humans.[12] We also found that non-Thai cases play a significant role in sustaining transmission and present challenges for the prevention of malaria reintroduction.[13–15] For malaria prevention and response measures, coverage of insecticidal bed net according to NMES (at least one net/two persons/household) was not a significant predictor. This finding is supported by the results of Thailand's malaria survey in 2017 in which only 37% of those surveyed used an insecticidal bed net while sleeping. Therefore, higher coverage of bed net use may not help prevent malaria transmission because the proportion of residents using this protective measure is low. However, malaria response, i.e., malaria control within seven days after index case detection and complete follow-up, particularly for *P. vivax* cases, is important for halting malaria transmission. Similar to another study, imported *P. vivax* infection is a sustained risk for secondary infections among local populations so that timely malaria response, including radical elimination of parasites, is essential.[16]

We found a significant positive association between sustained local transmission of malaria in reintroduced villages and those located in districts classified as A1. The implication is that these areas are receptive and vulnerable for malaria re-establishment.[17,18] Therefore, prevention of malaria reintroduction and effective malaria control should still be in place and targeted to all villages, including those reporting no malaria cases for more than three years. We also found that villages with at least 80% coverage of malaria control within seven days was protective for sustained local transmission. This NMES indicator should be closely monitored and emphasized to all reintroduced cases. Another interesting finding from our analysis is the small intra-class correlation coefficient, which suggests that while the risk of sustained local transmission was associated with several village-level factors, the impact of provincial characteristics on the baseline risk of sustained local transmission was not evident in this study.

Limitations

Similar to other studies that use secondary data, some information of cases and response activities were missing from the MIS, such as complete follow up of

cases and could not be included in the analytical model. Other factors that might affect malaria transmission, e.g., vector profiles in the villages and anti-malaria drug compliance of malaria cases were also not available in the MIS. Their omission could therefore introduce omitted variable bias.

Conclusion and Recommendations

This study demonstrates multiple factors associated with sustained local transmission after malaria reintroduction. Although most villages in Thailand are free from malaria, the increasing influx of migrant populations throughout the country increases the risk of malaria reintroduction. Since resources for malaria control are limited, and requires well-trained vector control staff to handle disease outbreaks, reintroduced cases must be detected as early as possible and preventative measures of local transmission should be strictly implemented. To proactively detect an imported case, all malaria-free areas in Thailand should be assessed for their receptivity and vulnerability for malaria reintroduction. Villages which have ecological environments that support vector breeding should be considered as receptive areas whereas villages with migrant populations should be considered as vulnerable areas. Malaria screening among migrants should be integrated through an existing public health program, e.g. migrant workers health checkup when applying for a work permit. Coverage of proactive case searches among migrant populations should be an additional indicator of the malaria operational plan. Radical cure with complete follow up of *P. vivax* is usually difficult among migrant population and causes *P. vivax* carriers to remain in the population. The DDC should consider alternative or innovative treatment such as short-course of primaquine or long-acting single dose aminoquinoline providing them with an on-site glucose-6-phosphate dehydrogenase (G6PD) testing to ensure G6PD normal status.[19–22] Indicators of complete anti-malaria treatment and radical cure with complete follow up should also be separately evaluated among non-Thais to clearly understand the situation and can be targeted to areas with low completeness. Finally, a multisectoral approach targeting migrant populations in receptive and vulnerable areas needs good collaboration between public health and other sectors to reach the target populations. An action plan for the prevention of malaria re-establishment at local levels should be developed by all stakeholders.

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Conflict of Interest

The author declares that there are no conflicts of interest regarding the publication of this article.

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Addressing Pertussis Outbreaks in the Deep South of Thailand, 2024: a Comparative Cost-effectiveness Study of Various Vaccination Coverage Strategies

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Abstract

Pertussis outbreaks continue to challenge public health efforts in the Deep South of Thailand. Low vaccination coverage is among many key contributory factors. The objective of this study is to explore policy alternatives aiming to expand vaccination coverage in Thailand's Deep South. We applied a compartmental model alongside rapid cost-effectiveness analysis to examine how different vaccination strategies impact pertussis cases and associated costs. Four vaccination scenarios with varying coverage levels (ranging from 62% to 91% within a 120-day timeframe) were compared against a scenario with the baseline vaccine coverage (61%). With a reproduction number (R_0) of five, the model predicted a remarkable decrease in pertussis cases and fatalities as the vaccination coverage increases. All scenarios yielded cost-saving outcomes, with the scenario of an increase of 10% coverage being the most cost-effective relative to the status quo. However, in high epidemic states (R_0=6), the scenario of an increase of 30% coverage was the most optimal for cost-saving in deaths prevention. These results highlight the need for expedite vaccine roll-out and the integration of non-pharmaceutical interventions for pertussis control. Further studies that explore various aspects of the model while incorporating more intricate parameters are recommended.

Keywords: pertussis, vaccine coverage, vaccine-effectiveness, cost-effectiveness

Introduction

Pertussis is a highly contagious respiratory disease caused by *Bordetella pertussis* (*B. pertussis*).[1,2] It usually begins with common-cold-like symptoms, but the coughing can last for weeks or months and symptoms may include typical symptoms such as paroxysmal cough, inspiratory whooping, post-pertussis vomiting, or apnea in children aged less than one year.[3] Its common transmission route is by person-to-person direct contact through respiratory droplets or contact with airborne droplets.[4] People of all ages can be infected but children less than one year are the most vulnerable and are prone to complications.[3–5]

Pertussis is a vaccine-preventable disease. In Thailand, the Expanded Program on Immunization schedules five doses of diphtheria and tetanus toxoids, whole-cell pertussis (DTwP) vaccine at 2, 4, 6, 18 months, and 4–6 years of age, and Tetanus toxoid and lower dose of diphtheria and acellular pertussis vaccines (Tdap) is recommended for children aged over seven years and adults and pregnant women with 27–36 weeks gestational age.[6–8] Vaccine effectiveness (VE) after five doses ranged from 98% in the first 12 months to 71% by five years.[9] The VE of three doses of diphtheria-tetanus-pertussis vaccines (DTP) was 83.5% (95% confidence interval (CI) 79.1–87.8%) between 6–11 months following the last dose of immunization.[10] Immunity against pertussis will last about 5–7 years.[6] Children who have a history of vaccination will get milder symptoms when infected.[6]

In the latter half of 2023, the incidence of pertussis cases in Thailand continued to rise and exceeded the 5-year median. The majority of cases (307/323) were found in the Deep South of Thailand (three southernmost provinces, namely, Narathiwat, Pattani,

and Yala).[11] Many outbreak clusters occurred in these provinces in late 2023. For example, two clusters of pertussis occurred in Pattani with over 30 cases involved in both clusters combined.[12–14] The age range of the cases varied from 18 days to 53 years. Both clusters occurred among household and community contacts. The age-appropriate DTP vaccine coverage in the outbreak villages ranged from 43.0% to 70.5%.

The low DTP vaccine coverage remains a major problem of pertussis outbreaks in the Deep South of Thailand. This region has experienced pertussis outbreaks and continues to exhibit low rates of pertussis vaccine adoption. Data from the Health Data Center, Ministry of Public Health (MOPH), Thailand showed that the vaccine coverage of first dose, third dose, and fifth dose DTP in these provinces in 2023 ranged between 70–81%, 37–66%, and 34–70%, respectively. These figures were lower than the national target vaccine coverage (90%).[15]

The Division of Epidemiology and the Division of Communicable Diseases of the Department of Disease Control (DDC) of the MOPH are the main responsible authorities for halting the increasing trend of pertussis. One of the key action points is to expedite the vaccination rate for people in Thailand's Deep South region. Thus, it is imperative to assess the outcomes of vaccine programs in different coverage scenarios through both the public health and economic lens. Therefore, the objective of this study is to assess a scenario-based prediction of the number of cases and deaths by pertussis and cost-effectiveness in different vaccine coverage scenarios.

Methods

Study Design

We used the susceptible-infectious-recovered model combined with cost-effectiveness analysis.[16] Our study encompassed around two million residents of all ages in the provinces of Thailand's Deep South, as mentioned above. At the time of our investigation, the overall coverage for primary vaccination (3-dose DTP) across all ages in this region was 61%, with an average vaccination rate of about 50 individuals per day. Under the status quo, the projected vaccine coverage over the next 120 days would increase by merely one percent.

Our focus on the 3-dose primary vaccination stemmed from the necessity for infants to receive three doses of the DTP vaccine to establish robust pertussis immunity. Thus, we aimed to complete the 3-dose primary vaccination to enhance immunity, with effectiveness typically ranging between 80–99% after completion.[17] However, the vaccine campaign in this study targeted all age groups, assuming that anyone with an incomplete DTP vaccination regimen could be vaccinated. Our target vaccination period spanned 120 days, aligning with the recommended interval for completing primary vaccinations, as per the Expanded Program on Immunization schedule administered.[8]

To assess vaccine coverage policy options, we categorized policies into four scenarios: Scenario 1—maintaining the current vaccination rate, leading to 62% coverage in 120 days, Scenario 2—raising coverage to 70% (a 10% increase) in the same period, Scenario 3—reaching 80% coverage (a 20% increase) within 120 days, and Scenario 4—achieving 90% coverage (a 30% increase) within the timeframe. Notably, the baseline complete 3-dose vaccine coverage at the start of the analysis was 61%. Table 1 summarizes these scenarios.

Figure 1 shows epidemic dynamics using a stock and flow diagram, with transitions between stocks governed by differential equations. Populations in each stock were determined by integrating functions over the flows. The transition from susceptible to infectious primarily depended on the basic reproductive number (R_0). Susceptible individuals were divided into those with incomplete and complete 3-dose vaccinations. Incomplete vaccination individuals either completed their vaccinations or stayed in the incomplete group. The rate of transition to the vaccination strand was governed by the frequency at which individuals were scheduled for immunization, reflecting the average vaccination rate in the population and the target vaccination period of 120 days. For model simplicity, the complete vaccinated population also incorporated those who already received booster doses.

Table 1. Summary of policy scenarios for primary vaccination for the Deep South of Thailand (all ages)

Scenario	Percentage increase of vaccination coverage by day 120	Vaccination rate (shots per day)	Overall complete vaccination coverage by day 120 (all ages)
1	0.7%	50	62% (61+0.7%)
2	10%	682	71% (61+10%)
3	20%	1,365	81% (61+20%)
4	30%	2,047	91% (61+30%)

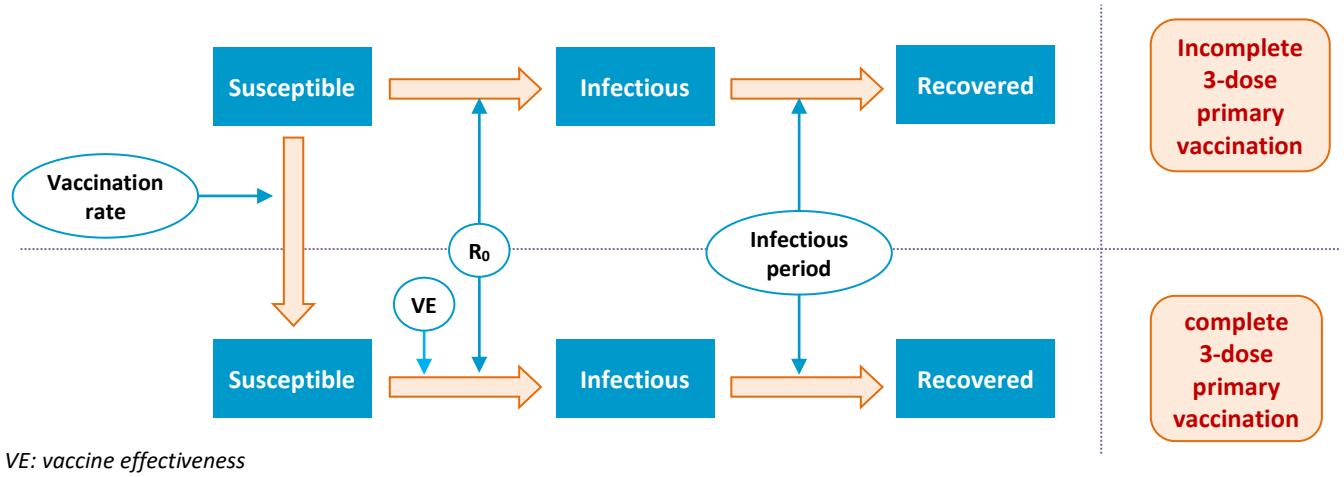

Figure 1. Model framework

Model Parameters and Assumptions

We used Vensim® software to execute the model, with the following assumptions serving as the basis for our calculations.[18]

First, we assumed homogeneous mixing within each vaccination group; all susceptible individuals had an equal chance of contact with infectees.

Second, we assumed a 50% cross-contact rate between infectious individuals, regardless of vaccination status, meaning susceptible persons had an equal chance of contact with both completely and incompletely vaccinated individuals.

Third, we set the start date of the model as 1 Feb 2024, and iterated over a one-year period (365 days) where the vaccination rate across model scenarios varied within the first 120 days. This notion was based on the hypothesis that the epidemic force, as determined by the R_0, continued throughout the year.

Fourth, due to difficulties in determining the active infectious population at the outbreak's onset, we estimated the initial pool as four times the new confirmed cases over three weeks in January 2024.[11] This was based on a 21-day (3-week) infectious duration. The rationale behind using a multiplier of four stems from the observation that the reported number of suspected pertussis cases in the preceding two months was four times higher than the number of confirmed cases.

Fifth, we accounted for vaccine impact by assuming a reduction in infection based on vaccine effectiveness (VE). Given a short period of analysis, we did not account for the waning of immunity.

Sixth, we assumed negligible birth and death rates within the population due to a relatively short time interval.

Seventh, we assumed that all model inputs remained constant over time. In this model, we set R_0=5. Evidence suggested that in countries with vaccination coverage of between 53–99%, the R_0 value ranges from 5–6.[19] We also conducted a sensitivity analysis to explore the results in a higher epidemic state (R_0=6).

Eighth, based on reported pertussis deaths in 2023 in Thailand, at the time of the study there was no fatality happening in completely vaccinated individuals.[11] Given that unvaccinated children were more susceptible to contract pertussis and tend to experience more severe disease, we assumed that the mortality rate among individuals completing 3-dose of primary vaccination was 10 times lower than among the unvaccinated population.[20]

Ninth, for vaccine and administration costs, we used the 3-dose DTP vaccine expense as the benchmark for primary infant immunization. We also identified the proportion of infections by age using data from the national surveillance reported in 2023.[11] Based on this proportion, we estimated the direct medical cost by age group, considering the varying rates of hospitalization across different age groups. Infants experience more severe infections and require hospitalization at a higher rate compared to children and adults.[21,22] For non-hospitalized infections, we assumed similar outpatient care costs across age groups.

Tenth, we excluded adverse events following immunization (AEFI) costs, given the pertussis vaccine's long history of minimal serious AEFI (2 out of 100,000 doses).[23,24] Additionally, there were no reports of serious AEFI among adults or pregnant individuals receiving the acellular pertussis vaccine or Tdap booster in 2023.[25]

Simplified key model formulas are presented in Table 2, while essential model parameters are listed in Table 3.

Table 2. Key model formula

Stock	Formula to present outflow of stock
Susceptible incomplete vaccination (dS/dt)	$-\beta S_1 I_1 - \beta S_1 I_2 - \nu S_1$
Susceptible complete vaccination	$-\beta(1-\mathrm{VE})S_2 I_2 - \beta(1-\mathrm{VE})S_2 I_1 + \nu S_1$
Infectious incomplete vaccination	$\beta S_1 I_1 + \beta S_1 I_2 - \gamma I_1$
Infectious complete vaccination	$\beta(1-\mathrm{VE})S_2 I_2 + \beta(1-\mathrm{VE})S_2 I_1 - \gamma I_2$
Recovered incomplete vaccination	γI_1
Recovered complete vaccination	γI_2

Incomplete vaccination: received less than three doses of pertussis vaccine or have never received the vaccine at all. Complete vaccination: completed at least three doses of vaccination regimen. β: basic reproduction number/ infectious period. S_1: susceptible to incomplete vaccination population. S_2: susceptible complete vaccination population. I_1: infectious incomplete vaccination population. I_2: infectious complete vaccination population. v: 1/vaccination period. VE: effectiveness of vaccine against infection. γ: 1/ duration of infection.

Table 3. Essential model parameters

Parameters	Approximate value	Remark or reference	Unit
Basic reproduction number	5	Kretzschmar et al.[19]	Dimensionless
Initial population	20.8 million	Bureau of Registration Administration, Department of Provincial Administration	Persons
Initial infectees	400	Model assumption	Persons
Baseline overall primary vaccination coverage	61.0%	Health Data Center, Office of Permanent Secretary, Ministry of Public Health	Dimensionless
Case fatality rate with incomplete vaccination	0.43%	Division of Communicable Diseases, Department of Disease Control	Dimensionless
Case fatality rate with complete vaccination	0.043%	Model assumption	Dimensionless
Intergroup cross-contact percentage	50.0%	Model assumption	Dimensionless
Infectious duration	21	Lauria et al.[4]	Days
Starting complete vaccinated percentage among infectees	13.0%	Division of Epidemiology, Department of Disease Control	Dimensionless
Vaccine effectiveness against infection among at least 3-dose vaccinees compared to incomplete (less than 3-dose) vaccination	83.5%	E Quinn et al.[10]	Dimensionless
Target vaccination duration	120	Model assumption	Days
Percentage of infants 0–3 months old among all infectees	10.0%	Division of Epidemiology, Department of Disease Control	Dimensionless
Percentage of infants 4–11 months old among all infectees	21.8%	Division of Epidemiology, Department of Disease Control	Dimensionless
Percentage of children 1–4 years old among all infectees	40.8%	Division of Epidemiology, Department of Disease Control	Dimensionless
Percentage of children 5–17 years old among all infectees	23.5%	Division of Epidemiology, Department of Disease Control	Dimensionless
Percentage of adults >18 years old among all infectees	3.9%	Division of Epidemiology, Department of Disease Control	Dimensionless
Percentage of hospitalized infants 0–3 months old among all infectees	65.6%	Botwright et al.[22]	Dimensionless
Percentage of hospitalized infants 4–11 months old among all infectees	28.1%	U.S. Centers for Disease Control and Prevention[21]	Dimensionless
Percentage of hospitalized children 1–4 years old among all infectees	10.3%	U.S. Centers for Disease Control and Prevention[21]	Dimensionless
Percentage of hospitalized children 5–7 years old among all infectees	2.7%	U.S. Centers for Disease Control and Prevention21	Dimensionless
Percentage of adults >18 years old among all infectees	3.0%	Botwright et al.[22]	Dimensionless

Table 3. Essential model parameters (cont.)

Parameters	Approximate value	Remark or reference	Unit
3-dose DTP vaccination cost	23.50	Division of Communicable Diseases, Department of Disease Control	Baht
3-dose vaccination administrative cost	19.14	Modified from Botwright et al.[22]	Baht
Treatment cost for hospitalized child, per episode	36,153.00	Modified from Botwright et al.[22]	Baht
Treatment cost for hospitalized adult, per episode	10,861.00	Modified from Botwright et al.[22]	Baht
Treatment cost for outpatient pertussis, children and adults per infection episode	312.81	Modified from Botwright et al.[22]	Baht

1 US$=36.11 Thai baht as of 15 Jul 2024

Interested Outcomes

We applied the health provider perspective, focusing on daily incident cases, cumulative cases, and cumulative deaths by day 365 for each scenario. The cost of interest included treatment and vaccination costs. We compared outcomes and costs incurred between policy alternatives (Scenarios 2–4) and the status quo (Scenario 1). The key outcome was cost savings (in Thai baht) per case or death averted.

Results

Figure 2a shows pertussis incidence for each scenario over one year. During the initial 100 days, there were minimal differences observed among the scenarios. However, after day 120, distinct patterns emerged. By day 170, Scenario 1 showed a notable increase in daily incident cases compared to Scenario 4 (about a five-fold difference). Over one year, Scenario 1 saw a sharp rise in cases, while Scenarios 3 and 4 had incidences drop to nearly zero.

Figure 2b shows the cumulative incidence of pertussis cases for all scenarios. Likewise, a remarkable difference was observed after day 120. By day 170, Scenario 1 showed twice the cumulative incidence compared to Scenario 4 (5,265 versus 10,586 cases). This disparity was amplified gradually. By the end of the simulation, the cumulative incidence of Scenario 1 was approximately ten-fold higher than the incidence of Scenario 4.

Figure 2c presents cumulative deaths in the current epidemic force. Variations appeared after day 150. By day 250, cumulative deaths in Scenario 1 quadrupled those in Scenario 4. Over the whole one-year period, Scenario 1 experienced a 10-fold increase in cumulative deaths compared to Scenario 4, while Scenarios 2 and 3 varied between 40–90 deaths. Scenarios 3 and 4 had minimal differences in cumulative deaths.

Table 4 presents the total cost, case number, deaths, cost savings, amount saved per case, and amount saved per death of different vaccination scenarios in an

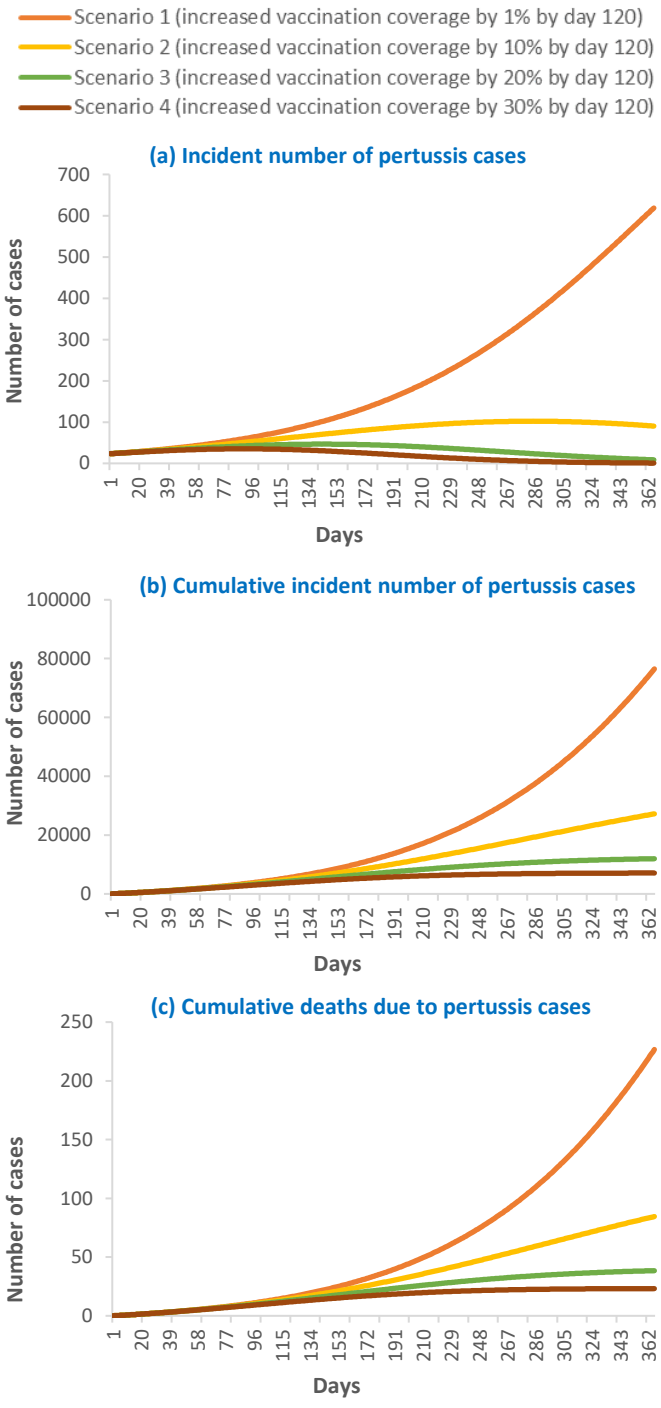

Figure 2. Incident number, cumulative incidence, and cumulative deaths of pertussis cases in Southern Thailand (R_0=5) in different vaccination scenarios

epidemic state (R_0=5) by day 365. Cumulative cases and cumulative deaths in all alternative vaccination policies decreased exponentially compared to the status quo. Scenario 4, which aimed for the highest vaccination target, bore the largest vaccination cost but at the same time experienced the smallest volume of cases and deaths. The total treatment costs decreased as the vaccination target grew (180, 79, and 47 million baht for Scenarios 2, 3, and 4 respectively).

Table 4. Summary of cases, deaths and costs incurred for various vaccination scenarios in current epidemic state (R_0=5) by day 365

Interested outcome	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Cumulative cases (n)	76,501	27,219	11,970	7,098
Cumulative deaths (n)	227	85	38	23
Vaccine and administration cost (million baht)	0.3	3.5	7.0	10.5
Treatment cost (million baht)	505	180	79	47
Grand cost (million baht)	506	183	86	57
Cost saving (million baht)	Ref	322	420	448
Cases averted (n)	Ref	49,281	64,530	69,403
Deaths averted (n)	Ref	142	188	204
Cost saved (in baht) per case averted	Ref	6,540	6,501	6,458
Cost saved (in million baht) per death averted	Ref	2.27	2.23	2.20

Scenario 1: baseline strategy. Scenario 2: 10% increase of vaccination coverage by day 120. Scenario 3: 20% increase of vaccination coverage by day 120. Scenario 4: 30% increase of vaccination coverage by day 120. Ref: reference range.

Scenario 2 showed the least cost-saving (322 million baht) compared to Scenarios 3 and 4 (420–448 million baht) when contrasting with Scenario 1. Scenario 4 projected the largest number of cases (69,403) and deaths (204) averted—approximately 10–40% safer than Scenario 2. Scenario 2 had the most cost-saving policy option (6,540 baht per case prevented and 2.27 million baht for a death prevented) compared with other options despite having a diminutive margin.

Similar to the 'R_0=5' assumption, all vaccination policy alternatives exhibited cost-saving outcomes compared to the baseline scenario in a high epidemic state (R_0=6). The volume of cases and deaths averted in all interested scenarios in a high epidemic state was about 6–8 times as large as that in the current epidemic state. The monetary saving for a case averted varied between 6,585–6,594 baht, which is very close to the saving in the current epidemic state. The distinct change in the high epidemic state was that Scenario 4 became the most cost-saving option for preventing deaths, with a cost of 2.19 million baht per death prevented, as shown in Table 5.

Table 5. Summary of cases, deaths and costs incurred for various vaccination scenarios in high epidemic state (R_0=6) by day 365

Interested outcome	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Cumulative cases (n)	548,714	254,722	85,106	33,513
Cumulative deaths (n)	1,644	726	240	95
Vaccine and administration cost (million baht)	0.3	3.5	7	10.5
Total treatment cost (million baht)	3,624	1,683	562	221
Grand cost (million baht)	3,625	1,686	569	232
Cost saving (million baht)	Ref	1,939	3,056	3,393
Cases averted (n)	Ref	293,992	463,608	515,201
Death averted (n)	Ref	918	1,404	1,550
Cost saved (in baht) per case averted	Ref	6,594	6,591	6,585
Cost saved (in million baht) per death averted	Ref	2.11	2.18	2.19

Scenario 1: baseline strategy. Scenario 2: 10% increase of vaccination coverage by day 120. Scenario 3: 20% increase of vaccination coverage by day 120. Scenario 4: 30% increase of vaccination coverage by day 120. Ref: reference range.

Discussion

Overall, our study elucidates the benefit of policies to expedite primary vaccination against pertussis amongst children in the Deep South region of Thailand, in terms of both case and death reduction and cost savings.

We found that all pertussis vaccination policies that aim to achieve 10–30% additional coverage within 120 days would result in cost-savings compared to the status quo vaccination rate. An increment of 10% in primary vaccination coverage resulted in the most cost-saving for both case and death aversion compared

with other vaccination strategies in existing epidemic states. Although our results suggest favorable outcomes for a 10% augmentation of pertussis vaccination coverage amongst children, this still needs enormous effort in achieving such a target as it means a 10-fold increase from the baseline daily vaccination rate (from 50 to 682 vaccinations per day).

Various strategies to enhance vaccine coverage include community engagement, implementing mobile vaccination units, and targeted messaging to ensure that the information reaches diverse subgroups.[26,27] The MOPH and related health sectors should consider implementing such measures soon. Political commitment to harness resources for rapid vaccine roll-out and steadfast assistance from various stakeholders and residents are indispensable.

Our findings concur with existing evidence despite subtle differences in research questions and design. Wu et al suggested that over the lifetime of 40 birth cohorts, China's immunization program could helped prevent 93% of pertussis cases and 97% of pertussis deaths.[28] Girard underpinned that in England and Wales, maintaining vaccination coverage at a level of at least 90% would ensure the largest cost savings.[29]

It is worth noting that given a higher epidemic force, enhanced vaccination coverage to over 90% (30% increment) likely becomes the most cost-saving option for death aversion. This observation is consistent with a prior study during the COVID-19 pandemic in Thailand, which demonstrated that focusing vaccination efforts in high-epidemic areas, such as Samut Sakhon, where the migrant population faced a higher reproduction number, would yield more cost-effective (cost-saving) outcomes compared to a general population vaccination approach.[30]

Our findings suggest that a reduction in cases and deaths would not be noticeable within the first 100–120 days. Thus, policymakers should not consider these vaccination policies as a silver bullet to immediately halt an outbreak. Other control measures, such as isolation of cases, postexposure antimicrobial prophylaxis adherence, and strengthening of the surveillance system, should be implemented alongside a vaccine roll-out.[31,32] Moreover, communication strategies to enhance vaccine acceptance amongst people in Thailand's Deep South should be established. During the outbreak, the DDC communicated to the public the guidelines to strengthen immunity against whooping cough in southern border provinces in December 2023 and January 2024.[33–35] These measures include a vaccine mop-up policy booster for those under the age of seven years, pregnant women, and for children's caregivers in epidemic areas.[36] According to personal negative beliefs about the benefits of vaccination and religious and local tradition concerns, DDC and the public health authority in the Deep South also communicate about the source of vaccines and the explanation of the advantages of vaccination according to the spirit of religion.[37–39]

This is one of the first studies in Thailand to investigate the cost-effectiveness of the pertussis vaccine using real-world evidence, and we consider this as a methodological strength. Nonetheless, some limitations remain. First, the model did not explore in detail the effect of various influential factors on the model results, such as varying epidemic force by age groups, differences in the likelihood of contacts by geographic areas and age structures, and the interaction of public health programs and non-pharmaceutical interventions that may alter the effective contact rate. Second, we did not account for uncertainties in the model parameter (except for R_0) due to a lack of empirical data from domestic sources. This point comes with a suggestion that if data are available, the stochastic model that considers data uncertainties should be performed. Last, the interpretation of various vaccine programs should be made with caution. This is because, in reality, numerous unpredictable factors may affect vaccine roll-out, such as budget constraints, logistic hurdles, and societal willingness, all of which hold substantial sway over the initial policy intention. Further studies that explore various aspects of vaccine operational programs should be conducted and interpreted alongside our study.

Conclusion

A 10% increase in pertussis vaccine coverage from baseline levels is the most cost-effective for averting cases and deaths during existing epidemic conditions. Achieving higher coverage will incur more cost-savings for preventing deaths if the epidemic escalates. Further research should explore other influential factors and parameter uncertainties. Other control measures, including non-pharmaceutical interventions, should complement vaccination strategies.

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: C.M., C.K., R.S.; Data curation: C.M.; Formal analysis: C.M., R.S.; Methodology: C.M., R.S.; Writing—Original draft: C.M., C.K., T.C., R.S.; Writing—Review and editing: C.M., C.K., T.C., R.S. All authors have read and approved the final manuscript.

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An Investigation of a Community Chickenpox Outbreak with a Fatal Case, Songkhla Province, Thailand, October 2022

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Abstract

In October 2022, a suspected chickenpox death was notified. A field investigation was done to verify the diagnosis and cause of death, describe the epidemiological characteristics, identify risk factors, and control the outbreak. We conducted a descriptive study and a matched case-control study. A case was defined as a person with multiple stages of skin lesions on at least two body areas in Subdistrict from 1 Aug 2022 to 24 Oct 2022. We reviewed medical records and searched for cases house-to-house. For the matched case-control study, cases were chickenpox cases residing in Bo Tru Subdistrict, from 1 Aug 2022 to 14 Oct 2022. Controls were neighbors without symptoms or chickenpox history, matched by age. Samples were tested using the reverse transcription polymerase chain reaction technique. Environmental surveys were performed. We identified 30 cases including the deceased, who was 49 years old. The median (interquartile range) age of the cases was 11 (7–38) years. Seventeen were elementary-school students. None of the cases received chickenpox vaccination or had a history of chickenpox. The secondary attack rate among household contacts was 41.2% (14/34). Reverse transcriptase polymerase chain reaction tests from three cases were all positive. Being a close contact with a case and sharing personal utensils were risk factors. We strengthened the surveillance system for early detection and treatment and provided risk communication in the community. Chickenpox cases should be isolated from susceptible persons. Standard treatment guidelines for complicated cases should be distributed among healthcare services.

Keywords: chickenpox, outbreak investigation, community, complications

Background

The varicella-zoster virus, commonly known as chickenpox, belongs to the herpesvirus group and is a highly contagious disease (R_0=6) with humans as its sole reservoir.[1] The virus usually spreads via droplets, aerosols, and by direct contact.[2] Characteristic symptoms include an itchy rash marked by fluid-filled blisters that eventually burst and form crusts or scabs. These lesions initially appear on the chest, back, and face, gradually spreading to other parts of the body, and last for four to seven days.[3] The incubation period is approximately 14 days (range 10 to 21 days) and individuals are contagious from one to two days before the onset of rashes until all lesions have crusted over.[2] In most cases, infection occurs only once and has lifelong immunity.[4] Susceptibility to infection is typically observed in individuals who have not been vaccinated or have not previously been infected. Close contact with cases and direct contact with chickenpox lesions are significant risk factors contributing to its spread.[2,5]

Chickenpox infection can lead to various complications, including skin and soft tissue infections, pneumonia, sepsis, encephalitis and death. The chickenpox fatality rate among children aged 1 to 14 years is one per ten-thousand and among adults is 21 per ten-thousand. Pneumonia is the most common cause of death. Populations considered at high risk for complications include infants, people over the age of 12, pregnant women, active smokers, and individuals with weakened immune systems.[6,7] It is recommended that individuals

who have never had chickenpox should receive two doses of the chickenpox vaccine. The vaccine has an effectiveness of 90% after two doses.[8]

On 2 Oct 2022, a joint investigation team from the Office of Disease Prevention and Control Region 12 Songkhla, was alerted by the Songkhla Provincial Health Office of a death from unknown cause of a person suspected to have either chickenpox or Mpox. This case was reported by Ranot Hospital in Ranot District, Songkhla Province. Subsequently, a joint investigation team comprising members from the Office of Disease Prevention and Control Region 12 Songkhla, Songkhla Provincial Health Office, and Ranot Hospital initiated a field investigation. The objectives were to verify the diagnosis and cause of death, confirm the outbreak, describe its epidemiological characteristics, identify risk factors, and provide recommendations and control measures.

Methods

Epidemiological Investigation and Descriptive Study

We reviewed the geographic and demographic data of Bo Tru Subdistrict and population. To assess the situation of varicella infection in Ranot District, Songkhla Province from 2021 to 2022, we compared the data of 2022 with a five-year median obtained from the Ranot Hospital database.

We investigated during 3–24 Oct 2022 in Bo Tru Subdistrict, Songkhla Province. We reviewed the medical records of the index case and conducted face-to-face interviews with Ranot Hospital healthcare staff and the family of the index case.

We defined a chickenpox suspected case as an individual residing in Bo Tru Subdistrict, who manifested at least two multi-stage skin lesions (vesicle, papule, macule, and crust), on at least two different locations of the body, between 1 Aug 2022 and 24 Oct 2022. A chickenpox confirmed case was any suspected case that tested positive for the chickenpox virus using reverse transcription polymerase chain reaction (RT-PCR).

An active case finding was performed by reviewing the database and medical records of both Ranot Hospital and Bo Tru Subdistrict Health Center. We compiled a line list of cases, diagnosed with chickenpox (international classification of diseases, 10th edition: B01), whose visit date ranged from 1 Aug 2022 to 24 Oct 2022. We conducted an active case finding in Bo Tru Subdistrict through face-to-face interviews with the individuals from the abovementioned list of cases (or their parents), using a semi-structured questionnaire. We conducted phone interviews with cases who were unable to participate in the investigation on the scheduled days.

To identify further cases that may not have been in our initial line list, local healthcare officers made announcements in Bo Tru Subdistrict for individuals with multi-stage skin lesions to contact the hospital, using a snowball approach. We interviewed the cases and identified their household members. We maintained the active case surveillance for an additional six weeks following the onset of the last identified case.

Laboratory Study

Because the index case manifested generalized multi-stage skin lesions, specimens including one lesion fluid sample were tested for Mpox virus by RT-PCR and sent to the Regional Medical Sciences Center 12 Songkhla. Two serum plasma samples from the index case were also tested for RT-PCR varicella-zoster and herpes simplex I and II viruses and sent to the National Iinstitute of Health. The specimens were all collected by Ranot Hospital's healthcare staff on 2 Oct 2022 before the case was referred to Songkhla Hospital.

On 14 Oct 2022, we collected two specimens from two suspected cases with active multi-stage lesions for RT-PCR testing for varicella-zoster in Bo Tru Subdistrict. The specimens were placed in a viral transport media and packaged at temperatures between 2–8°C and sent to a private laboratory (N-Health Laboratory) for PCR testing for the varicella-zoster virus.

Environmental Study

We conducted a walkthrough survey in Bo Tru Subdistrict to identify environmental factors that could enhance the transmission of the virus. We utilized a subdistrict map, observed daily activities and personal hygiene practices, and interviewed a community leader and three elementary school teachers.

Analytic Study

An age-matched case-control study was conducted to identify potential risk factors for chickenpox among individuals residing in Bo Tru Subdistrict between 1 Aug 2022 and 14 Oct 2022. The sample size was calculated based on an assumed odds ratio of 12.1 for attending activities with individuals who had chickenpox.[9] The required sample size was 23 cases and 23 controls, with a ratio of 1:1. Cases were suspected cases from the descriptive study. We defined a control as a neighbor of a case who lived within three kilometers from case's house and aged within one year of the case, exhibiting no symptoms, and having no history of chickenpox. We chose the controls from a pool of eligible controls living in Bo Tru Subdistrict. Data was

collected via face-to-face or phone interviews using a semi-structure questionnaire.

Statistical Analysis

Descriptive statistics included median with interquartile range (IQR), ratio, and proportion. To calculate the secondary attack rate within each household, we divided the number of second-generation cases (occurring 10–42 days after the primary cases within each household) by the total number of susceptible individuals living in that household (excluding primary cases and those with a history of chickenpox).

Exposure variables included demographic characteristics (gender, being a student at Bo Tru Elementary School) and risk behaviors (being a close contact with a case, sharing personal utensils, sharing room spaces, and attending religious activities). The main outcome was being either a suspected or a confirmed case. We calculated the odds ratio (OR) and 95% confidential interval (CI) for univariable analysis. For multivariable analysis, we used a multiple conditional logistic regression model by including variables with a *p*-value <0.1 from the univariable analysis. Results are shown in the form of adjusted odds ratio (AOR) and 95% CI. We analysed the data using Stata version 16.

Ethics

This study was a part of the routine activities of the Thai Department of Disease Control, Ministry of Public Health.

Results

Bo Tru Subdistrict of Ranot District, Songkhla Province comprises of 1,839 households and has a population of 7,455. There is one elementary school, a community mosque, and a health center. According to the Ranot Hospital database, there was an increase in the number of chickenpox cases in 2022, from two cases in July to 13 cases in late September, which surpassed the five-year median.

Source Case Identification

The index case was a 49-year-old Thai Muslim male living in Bo Tru Subdistrict. He worked in the fishery industry and had no reported underlying health conditions. He also had no history of prior chickenpox infection or vaccination. He was an active smoker, smoking approximately five cigarettes per day for over a decade. He lived with his wife and daughter, who both had history of chickenpox. On 12 September, he visited his 7- and 10-year-old cousins, who were both infected with chickenpox. He developed symptoms 11 days later. Initially he sought medical care at a local private clinic. However, his condition deteriorated quickly. He was initially suspected of having either varicella-zoster or Mpox infection. A chest x-ray revealed signs of severe pneumonia in both lungs. His condition continued to worsen and he passed away on 2 October (Figure 1).

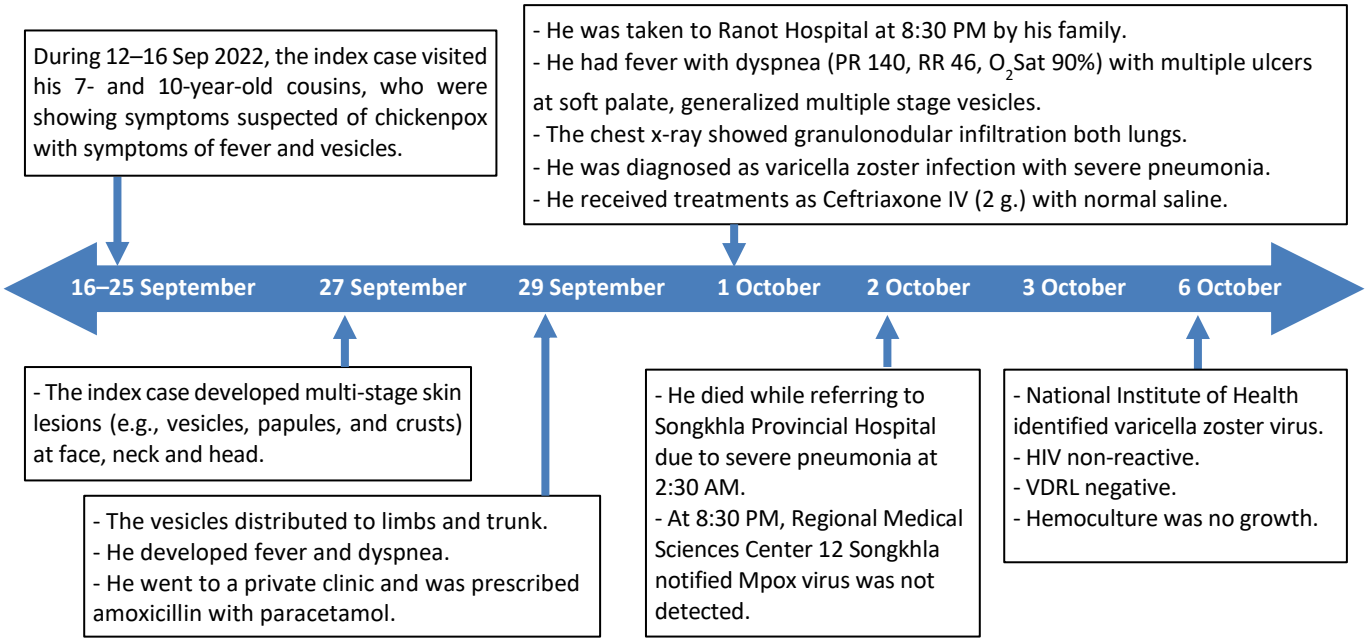

Figure 1. Timeline of chickenpox symptoms progression in the index case from first contact to death in Bo Tru Subdistrict, Ranot District, Songkhla Province, 16 Sep 2022–6 Oct 2022

Following this incident, we performed an active case finding and compiled a line list of 13 cases from the database and medical records of Ranot Hospital and Bo Tru Subdistrict Health Center. The identified cases

were their schoolmates and family members, which consisted of adults, teenagers, and children. The two boys attended Bo Tru Elementary School. A timeline of the epidemic curve in the school is shown in Figure 2.

A 14-year-old male student was suspected to be infected with chickenpox on 16 Aug 2022 by his friend at another secondary school from a nearby district, where no previous outbreaks were reported. He subsequently introduced the virus to his two brothers (the 7- and 10-year-old cousins of the index case), who were residing in the same household.

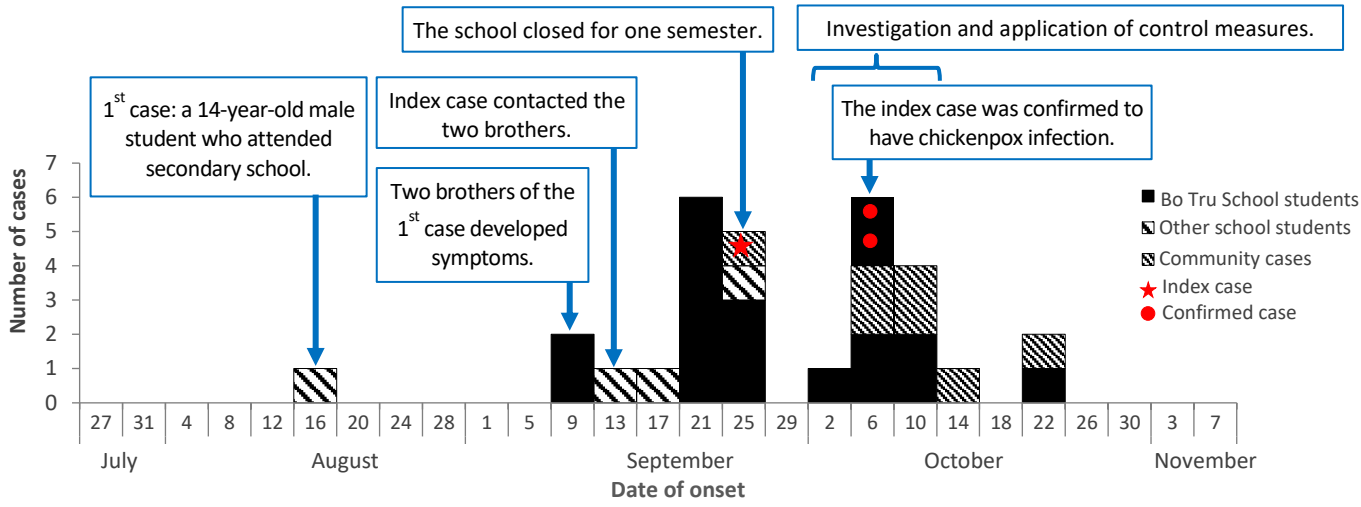

Figure 2. An Epidemic Curve of Chickenpox Cases in Bo Tru Subdistrict, Ranot District, Songkhla province during 1 Aug–24 October 2022 (n=30)

Characteristics of the Chickenpox Outbreak and Risk Factors

We identified 30 cases, including two adults aged over than 18 years, three teenagers and 25 children aged less than 13 years, giving an incidence rate of 4.0 per 1,000 population in Bo Tru Subdistrict. The male-to-female ratio was 1.5:1 and the median age was 11 years (IQR 7–38). The case fatality rate was 3.3% (1/30). Of the cases, 56.7% (17/30) were students from Bo Tru Elementary School and 43.3% (13/30) were other individuals living in the subdistrict. Two were smokers, and none reported consuming alcohol. None of the cases received the chickenpox vaccine nor had a history of prior chickenpox infection. Clinical symptoms were vesicles (100.0%), fever (83.3%) and papule (76.6%). Lesion sites occurred at legs (76.6%), trunk (70.0%) and arms (66.7%). The percentage of cases who visited local drug stores was 46.6% (14/30), and 23.3% (7/30) visited Ranot Hospital (outpatient clinic). There were no hospitalizations.

There were 16 infected households in Bo Tru Subdistrict, of which 14 contained a secondary case. We identified 75 contacts in 16 infected households, of which 41 reported to have a previous chickenpox infection and 34 had no history of chickenpox vaccination (Table 1). Therefore, the overall secondary attack rate among susceptible contacts was 41% (14/34). The number of household contacts of chickenpox cases and the percentage with chickenpox infection among household contacts, by age group, showed that the lowest proportion occurred among individuals under the age of 10 years (Table 1).

Table 1. Number of chickenpox household contacts in Bo Tru Subdistrict and percentage with a previous history of chickenpox infection among household contacts, by age groups, Bo Tru Subdistrict, Ranot District, Songkhla Province during 1 Aug 2022–24 Oct 2022

Age group (years)	Total cases (n=30) n (%)	Primary cases in households (n=16)	Secondary cases in households (n=14)	Number of household contacts (n=75)	Previous history of chickenpox infection among household contacts (n=41) (% (case/total))
≤5	8 (26.7)	4	4	8	12.5 (1/8)
6–9	13 (43.3)	7	6	10	10.0 (1/10)
10–14	7 (23.3)	4	3	9	23.8 (2/9)
15–25	0	0	0	12	50.0 (6/12)
26–40	0	0	0	14	78.6 (11/14)
>40	2 (6.7)	1	1	22	90.1 (20/22)

Laboratory results of a sample from the index case sent for RT-PCR testing for the Mpox virus was negative. A serum plasma sample sent for RT-PCR testing for varicella-zoster was positive. However, a serum sample tested negative for the herpes simplex I and II viruses. RT-PCR testing of samples taken from two suspected cases were positive for varicella-zoster.

From the walkthrough survey, the subdistrict was densely populated. There was a mosque and we observed adequate ventilation. Most individuals attending the mosque were wearing personal protective equipment. Many houses had double or single bedrooms that were shared by multiple individuals. Parents of the children infected by chickenpox were aware of their child's infection and stated that their children stayed at home. However, we noted that some cases were interacting and playing with other healthy children. During our investigation, Bo Tru Elementary School was closed due to the school break.

A total of 42 community households participated in the analytic study. On univariable analysis, being a close contact with a case (OR 6.50, 95% CI 1.46–28.8) and sharing personal utensils (OR 2.03, 95% CI 1.04–3.97), increased the risk of infection. However, on multivariable analysis, no statistically significant factors were associated with chickenpox infection (Table 2).

Table 2. Univariable and multivariable analysis in matched case-control by one year age in risk factors associated with chickenpox infection among residences, Bo Tru Subdistrict, Songkhla Province, during 1 Aug 2022–24 Oct 2022 (n=42, 21 pairs)

Exposure factors	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Gender=male	3.02 (0.60–14.86)	-
Being students at Bo Tru Elementary School	3.50 (0.72–16.85)	-
Being closed contact with cases	6.50* (1.46–28.80)	3.19 (0.52–19.25)
Sharing personal utensils	2.03* (1.04–3.97)	1.52 (0.70–3.30)
Sharing room spaces	1.03 (0.71–1.49)	-
Attending religious activity	2.00 (0.36–10.91)	-

**P-value <0.1*

Action Taken

The joint investigation team worked collaboratively to strengthen the surveillance system for early case detection, notification, and proper management in the community. This involved cooperation with school teachers and local private clinics and drugstores in notifying chickenpox cases to local healthcare workers. Additionally, we provided risk communication and health education to the community, including distributing leaflets and conducting outreach activities at a community mosque. We also approached local religious leaders to request the temporary suspension of religious activities. Furthermore, we encouraged medical staff at Ranot Hospital to establish a service plan for high-risk groups and severe chickenpox cases. This included early detection and treatment of chickenpox cases and chickenpox vaccination for high-risk groups, and the establishment of an efficient referral system.

Discussion

The diagnosis of chickenpox in the deceased case and the outbreak was confirmed. Based on the clinical manifestation, the index case was initially suspected to have Mpox infection.[10] However, RT-PCR laboratory results confirmed the presence of the varicella virus. The diagnosis of this disease was primarily derived from the clinical presentations and further confirmed through laboratory testing, particularly RT-PCR, which is known for its high sensitivity.[11,12]

This index case of chickenpox infection is an active smoker, with no history of vaccination, suggests a possibility of increased risk of severe pneumonia and associated complications.[13] Complications in healthy adults tend to be more severe compared to children, with the risk being approximately 25 times higher.[14] Additionally, smoking can elevate the risk of respiratory complications in chickenpox-infected cases by up to 15-fold.[15,16] This increased risk is attributed to structural changes in the respiratory system and a decrease in immune response.[17] Therefore, it is important to provide risk communication to raise awareness of disease severity among high-risk groups, including adults who smoke, those who are not immunized, and among young children.

The recommended treatment for severe varicella pneumonia is intravenous acyclovir. However, the index case did not receive this treatment during his life-threatening period due to the late detection and unavailability. Intravenous acyclovir has been proven to be a highly successful treatment for chickenpox cases with severe pneumonia and the fatality rate is higher in chickenpox-infected adults who do not receive this treatment.[14,18,19] Therefore, introducing

clinical practice guidelines for management of chickenpox in complicated cases at district hospitals should be considered. This would involve early detection and treatment as well as the establishment of an efficient referral system.

The Centers for Disease Control and Prevention recommends varicella vaccination for outbreak prevention and control to provide protection to people not yet exposed and to shorten the duration of possible outbreaks.[20] Offering the vaccine within 3–5 days of exposure to a varicella rash is important to provide the greatest protection.[21] However, none of the cases in this outbreak had ever received the chickenpox vaccination (the vaccine is not included in Thailand's Expanded Program on Immunization), probably because most (68%) of the Thai population already has varicella antibodies.[22] Moreover, in Thailand, the cost of the vaccine is high ($US 80–100/dose).[23] However, in future outbreaks, vaccination should be taken into consideration and offered to high-risk groups or those without chickenpox immunity.

Risk factors found in this study, being a close contact with a case and sharing personal utensils, were similar to the results of two previous studies.[5,9] Therefore, if chickenpox cases are detected in a household or school, they should be isolated from susceptible persons such as adults with no immunization, and personal utensils should not be shared.[24,25]

In this study, delays in outbreak detection and subsequent actions were identified. The outbreak began in July 2022 and lasted until the beginning of October 2022, roughly spanning around two generations. It was detected among family members in the community. The well-established disease surveillance system within the community and prompt application of control measures for cases until their recovery were crucial in controlling this outbreak.[26,27]

Limitations

Only three cases in this investigation were laboratory confirmed. Our results from the descriptive study and risk factors from the analytic study may therefore be inaccurate. However, as chickenpox symptoms are recognizable, we mainly used history of illness in selecting cases and controls. Moreover, there was information bias of past exposures among varicella cases that were more likely to remember their risk factors compared to the controls, resulting in differential misclassification. This may have resulted in an overestimate of the risk. However, we triangulated our results by having the study subjects ask their family members when they were uncertain.

Recommendations

For effectiveness of the outbreak control, risk communication in the community was crucial. We recommended that chickenpox cases detected in a household be isolated and separate personal utensils used by household members. Introduction of chickenpox clinical practice guidelines in complicated cases at district hospitals was recommended, focusing on early detection and treatment in high-risk and susceptible group, such as adults over the age of 12, pregnant women, and active smokers. The chickenpox vaccination in the future outbreak should be offered after exposure. There should be surveillance system strengthening in specific areas such as elementary schools or households containing high-risk groups. This can be achieved by involving community participation such as private clinics and drug stores to aid early detection and response.

Conclusion

An outbreak of chickenpox occurred in a community resulting in one death from severe pneumonia. The dead case was an active smoker. None of the cases received chickenpox vaccination or had a history of chickenpox infection. The secondary attack rate of the close community contacts was 41%. Potential risk factors associated with this outbreak were being a close contact with a case and sharing personal utensils. We strengthened the surveillance system to facilitate early detection and community risk communication. Coordinating standard treatment guidelines for complicated cases was essential.

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Conflicts of Interest

The authors declared no conflict of interest.

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Accuracy of COVID-19 Prediction Modeling Techniques

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Abstract

The unprecedented impact of the COVID-19 pandemic has revealed that forecasting capability is critically needed in making strategic decisions and formulating reasonable countermeasures. This study aimed to assess the predictive accuracy in forecasting the numbers of COVID-19 cases using Thailand's national COVID-19 surveillance database from January 2020–June 2021 based on three analytical models: a susceptible-exposed-infectious-recovery compartmental model, an auto-regressive integrated moving average model, and a long short-term memory (LSTM) network model. All forecasting methods had model parameters adjusted weekly according to the most recent situation and predictive accuracy measures, including the mean absolute percentage error (MAPE). We found that the MAPE values ranged from 19.65%–22.54%, 28.95%–32.35%, 47.78%–53.55%, and 75.03–84.91% for forecasting one, two, four, and eight weeks ahead, respectively. Among the three models, the LSTM model had slightly higher accuracy than the other two models within the same forecasting range. These prediction models can be used for short-range forecasts in other similar settings while long-range forecasting requires monitoring and updating periodically.

Keywords: COVID-19, forecast, predictive accuracy, compartmental model, ARIMA, LSTM

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 during 2019–2023 has had an unprecedented impact around the world.[1,2] The pandemic was declared a public health emergency of international concern by the World Health Organization in January 2020, and lasted until May 2023.[3] At least 765 million cases and 6.9 million deaths associated with COVID-19 infection were reported worldwide.[4] The speed and scale of the outbreak required countries to mobilize enormous resources including vaccines, medicines, equipment, and medical supplies to prevent the spread of disease.[4,5]

To manage resources more effectively and efficiently, many disease forecasting techniques have been applied in making strategic decisions and formulating reasonable countermeasures. For example, traditional regression models and time series analysis methods, such as auto-regressive integrated moving average (ARIMA), exponential smoothing techniques, and decomposition, were used in forecasting various diseases such as influenza, dengue hemorrhagic fever, and COVID-19.[6–8] The susceptible-exposed-infectious-recovered (SEIR) model, which is a well-known mathematical compartmental model, is another commonly used technique, especially for estimating the effects of interventions.[9,10] Recent advances in digital technology, big data management, and computational capability have also enabled the applicability of data-intensive methods such as machine learning and deep learning. Many techniques, such as random forest, convoluted neural networks, and long short-term memory (LSTM) networks have been used for predicting various kinds of diseases, including COVID-19.[11–13] Machine learning is arguably more flexible than traditional statistical forecasting models, particularly for identifying complex and non-linear relationships. LSTM is a type of machine

learning technique under the framework of recurrent neural network models, and is commonly used in disease forecasting.[14–16]

Thailand was the first country after China to detect a confirmed case of COVID-19, which was reported on 12 Jan 2020.[17] The first large disease cluster started in March 2020, and thereafter cases were continuously reported across the country.[18] The most severe period in terms of cases and deaths occurred in 2021, and it was not until 2022 that the severity started to abate.[19] In October 2022, the Thai Ministry of Public Health (MOPH) announced the end of the epidemic in Thailand and classified COVID-19 as an endemic disease.[20]

The Department of Disease Control (DDC), Thailand's national agency for disease prevention and control under the MOPH, established the National COVID-19 Surveillance (NCS) system in January 2020. The NCS is an electronic surveillance database that stores data of individual COVID-19 cases reported from all hospitals in the country. The data are analyzed and disseminated to all stakeholders via the DDC COVID-19 situation dashboard.[19] During the pandemic, efforts were made to forecast COVID-19 cases based on the NCS data using various modeling techniques.[21,22] However, there was a lack of systematic evaluation of the performance of these techniques when applied to Thailand's context. Since the pattern of COVID-19 cases and the quality of surveillance systems vary among countries, this study aimed to assess the accuracy of forecasting weekly COVID-19 cases at one, two, four, and eight weeks ahead using three models, namely SEIR, ARIMA, and LSTM models, based on data from the Thai NCS database during 2020–2021. Results from this study should provide a rationale on the selection of appropriate forecasting techniques, execution, and interpretation for better responses during future pandemics.

Methods

This is a predictive modeling study based on retrospective data on the number of weekly COVID-19 cases in Thailand, using three modeling techniques as described below.

Data

This study used weekly COVID-19 cases during 1 Jan 2020 to 29 Jun 2021. During the study period, all COVID-19 cases were diagnosed in hospital and every positive case was confirmed either by reverse transcription polymerase chain reaction or rapid antigen test. As of the end of June 2021, COVID-19 vaccination coverage for two doses was less than five percent of the total Thai population.[23] To minimize the influence of immunization coverage on the assessment of predictive accuracy, this study excluded cases diagnosed after 29 Jun 2021.

Prediction Models

Susceptible-exposed-infectious-recovered (SEIR) model

To set up the compartmental model, the population in Thailand was divided into four compartments, namely susceptible (S), exposed (E), infectious (I), and recovered (R), representing those without infection, non-immune and therefore susceptible for getting infection; those contracting the infection but still not-transmissible; those contracting the infection and transmissible; and those recovering from the disease and not transmissible, respectively. Since dying from COVID-19 should only occur among those who developed symptoms, the mortality rate from the disease was added to the "I" compartment. The dynamics of the SEIR model are defined in the following differential equations:

$$\frac{dS}{dt} = -\frac{\beta S I}{N}$$

$$\frac{dE}{dt} = \frac{\beta S I}{N} - \sigma E$$

$$\frac{dE}{dt} = \sigma E - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I$$

$$\frac{dD}{dt} = \mu I$$

where S, E, I, R stand respectively for the numbers of cases in the population in the S, E, I, and R compartments at each time step; N and D are the estimated population and COVID-19-associated deaths each time step, respectively; β is the per capita transmission coefficient (or effective contact rate); σ is the reciprocal of the latency period; γ is the recovery rate; and μ is the COVID-19-associated mortality rate among cases. The total population of Thailand in 2020 was 66,534 thousand and the initial values of S, E, I, and R were estimated and revised weekly based on the numbers of reported cases and deaths.[19,24] The β parameter was estimated using the effective reproductive number (R_t) calculated by the team from the Robert Koch Institute.[25] Parameters σ and γ were calculated using the reciprocal of the latent period of 5.5 days and infectious period of 10 days, respectively.[26,27] Parameter μ is the estimated case-fatality ratio of COVID-19 and equal to 1.37%.[28] The model's initial values were reviewed and adjusted weekly when the mean absolute percentage error of the most recent four weeks was larger than 30%. The adjusted values were approved by an epidemiologist and an infectious disease expert. The model transmission dynamics were run using the R language and environment.[29]

Auto-regressive integrated moving average (ARIMA) model

The general form for the ARIMA (p, d, q) model with auto-regressive parameter (p), moving average parameter (q), and differencing parameter (d) was applied in this study. Due to the seasonal pattern of COVID-19, we also included a seasonal component in the model. The structure of the basic ARIMA (p, d, q) model is given by:

$$Y_t = \theta_0 + \phi_1 Y_{t-1} + \phi_2 Y_{t-2} + \ldots + \phi_p Y_{t-p} - \theta_1 \varepsilon_{t-1} - \theta_2 \varepsilon_{t-2} - \ldots - \theta_q \varepsilon_{t-q} + \varepsilon_t$$

where ϕ_a (a=1, 2,…, p) and θ_b (b=0, 1, 2,…, q) are the auto-regressive and moving average parameters, i.e., regression coefficients, of the model, respectively. Y_t and ε_t represent the value to be predicted and its error at time week t. Parameter θ_0 is the intercept of the regression line. We used the "auto.arima" function in the "forecast" package in R to identify the appropriate and non-stationary data adjustment and ARIMA model structure, including seasonality components.[29,30] The function algorithm uses conditional-sum-of-squares to find starting values, then fits the model using maximum likelihood. We used the AIC, AICc and BIC values to choose the best model.

Long short-term memory (LSTM) model

We employed a two-layer LSTM network structure. We normalized COVID-19 cases using the Min-Max scaling method to scale the data between 0–1. We used a 4-week moving historical data window to predict future cases. We set the 50-neuron unit for both the first and the second layers. The model's weights were adjusted using the backpropagation through time method. We compiled the model using the loss function of the mean square error (MSE), optimizer (Adam), epoch number of 300 and learning rate of 0.005, as suggested by a previous study.[31] All LSTM network models were conducted in R.[29]

Model Training, Testing and Predictive Accuracy Assessment

The number of COVID-19 cases from 1 Jan 2020–29 Jun 2021 was analyzed. Cases reported between 1 Jan 2020–29 Dec 2020 (the first 52 weeks in the dataset) were used as the training set in all three models for predicting the number of cases at weeks 53, 54, 56, and 60. Cases diagnosed in weeks 1–53 were then used to predict the number of cases in weeks 54, 55, 57, and 61. The model fitting and parameter adjustment were conducted weekly and this process continued until the end of the study. After obtaining the predicted values of the targeted future weeks, each of the predicted values was compared with the actual data, (the testing set), for each week. To compare the predictive accuracy of the three models quantitatively, the following metrics were used: mean absolute error (MAE), mean absolute percentage error (MAPE) and the coefficient of determination (R^2) as given by the following equations:

$$\text{MAE} = \frac{1}{N}\sum_{i=1}^{N} |Y_i - \hat{Y}_i|$$

$$\text{MAPE} = \left(\frac{1}{N}\sum_{i=1}^{N} \frac{|Y_i - \hat{Y}_i|}{Y_i}\right) x100$$

$$R^2 = 1 - \frac{\sum_{i=1}^{N}(Y_i - \hat{Y}_i)^2}{\sum_{i=1}^{N}(Y_i - \bar{Y})^2}$$

where Y_i is the actual number of cases, $\hat{Y}_i$ is the predicted number of cases, and $\bar{Y}$ is the average number of actual cases during the study period.

The model development and the evaluation of predictive accuracy were calculated for the whole country and for two sub-national areas: (1) Greater Bangkok Region, consisting of Bangkok and three surrounding provinces: Nonthaburi, Samut Prakan and Pathum Thani, and (2) the remaining provinces of Thailand.

Ethics

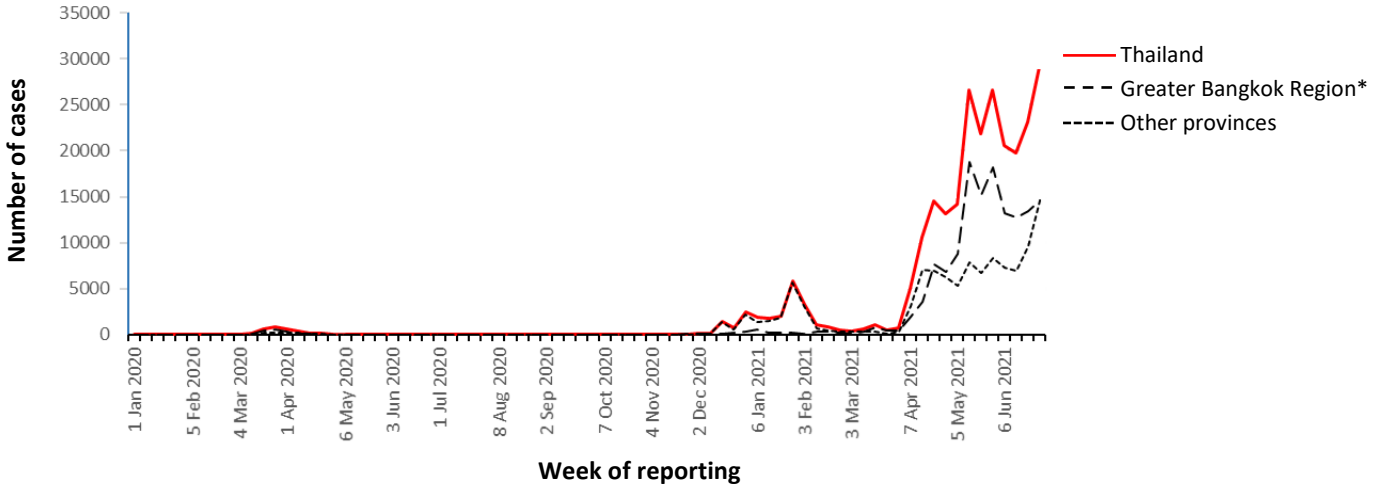
This study used aggregated COVID-19 cases from the NCS database of the DDC with no individual or personal identifiable information. This analysis is one of DDC's public health mandates in preparing for a better response to the next pandemic and was therefore exempted from ethical review for research in humans.

Results

COVID-19 Epidemic Pattern in Thailand, January 2020–June 2021

The first COVID-19 case in Thailand was reported in the second week of 2020 (Figure 1). Subsequently, 1–12 cases per week were reported until the first large-scale outbreak occurred in mid-March, lasting until the end of April. In this first outbreak period, over 100 cases were reported weekly, with the peak week having more than 800 cases. After April 2020, the number of weekly cases decreased to fewer than 100 and this continued until December 2020 when a second large-scale outbreak occurred. The number of cases increased from two to three figures and in some weeks reached four figures. The number of cases in this wave of the outbreak peaked in the last week of January 2021, with more than five thousand cases reported. Subsequently, the number of cases decreased to less than 1,000 per week. However, in early April 2021, another outbreak occurred, with cases increasing to over ten thousand per week. By the end of June, the

outbreak was still present. The epidemic from the beginning until June 2021 revealed cases that were mostly (56%) from the Greater Bangkok Region, with the remainder scattered in other provinces throughout the country. However, the outbreak patterns in both areas were similar.



**Greater Bangkok Region consists of Bangkok Metropolitan, Nonthaburi, Samut Prakan, and Pathum Thani provinces*

Figure 1. Number of reported COVID-19 cases in Thailand, Greater Bangkok Region, and other provinces by week of reporting, 1 Jan 2020–29 Jun 2021

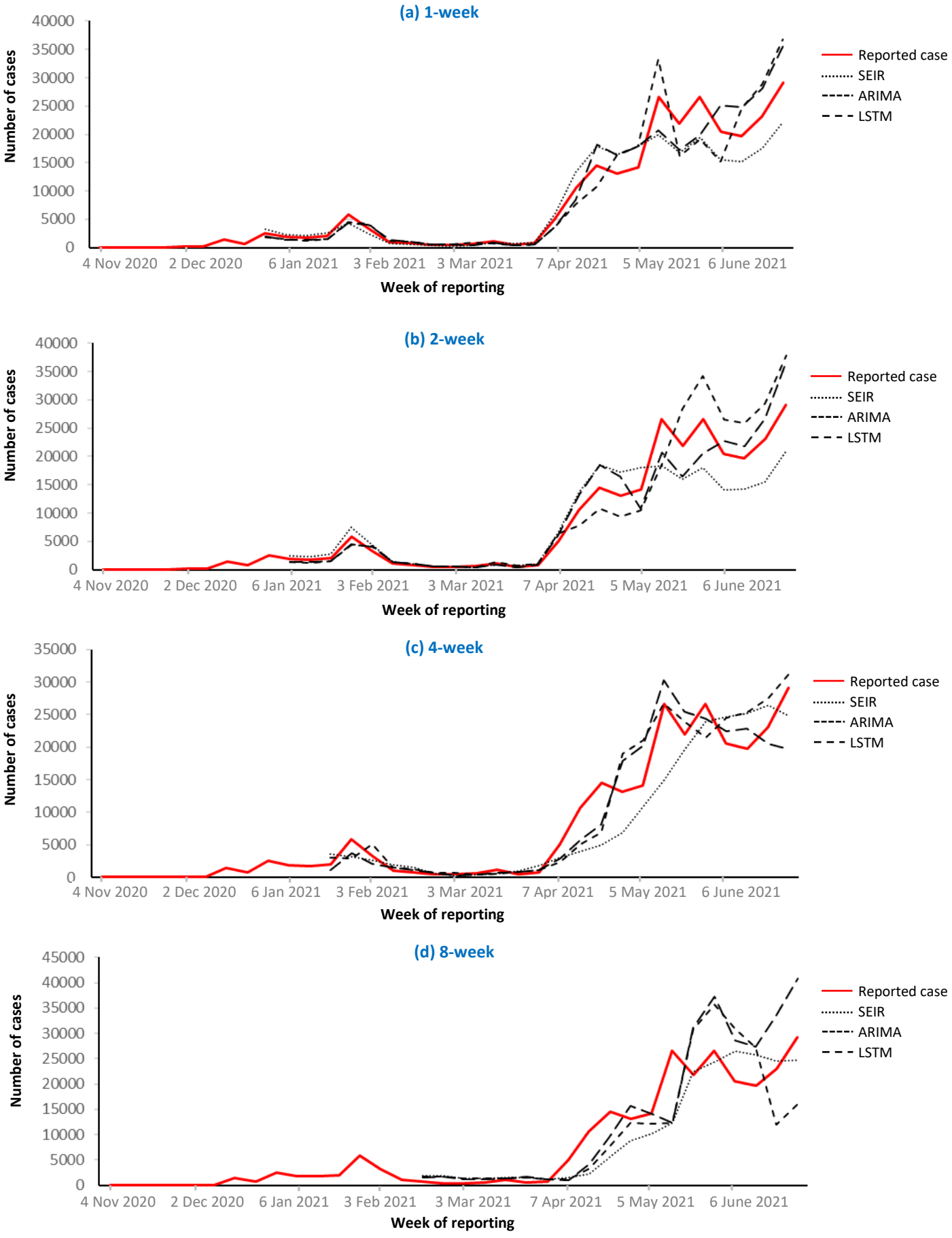
Predictive Accuracy

Figure 2 illustrates the predicted weekly numbers of COVID-19 cases using the SEIR, ARIMA, and LSTM models at one, two, four, and eight weeks ahead (Figure 2a, 2b, 2c, and 2d, respectively) compared to the reported numbers during 30 Dec 2020–29 Jun 2021. The differences between the predicted and reported numbers, i.e., prediction error, varied by forecasting model and time. During periods of severe outbreaks, the prediction error was higher and longer forecasts were associated with larger prediction errors. The relationships between the actual and predicted number of cases are visualized in Figure 3. The pattern was similar to that shown in Figure 2; longer forecasts were associated with weaker correlations, i.e., lower values of R^2. Table 1 quantitatively characterizes the prediction errors for each model and forecast week. The MAE and MAPE values for all models increased with increasing forecasting period. The MAPE values of the three models ranged from 19.65%–22.54%, 28.95%–32.35%, 47.78%–53.55%, and 75.03–84.91% for the forecasts at one, two, four, and eight weeks ahead, respectively. Among the three models, the LSTM model had consistently lower MAE and MAPE values compared to the other two models within the same forecasting range.

Table 1. Accuracy measures of COVID-19 predictions at one, two, four, and eight weeks ahead using SEIR, ARIMA, and LSTM models compared with weekly reported COVID-19 cases in Thailand, 30 Dec 2020–29 Jun 2021

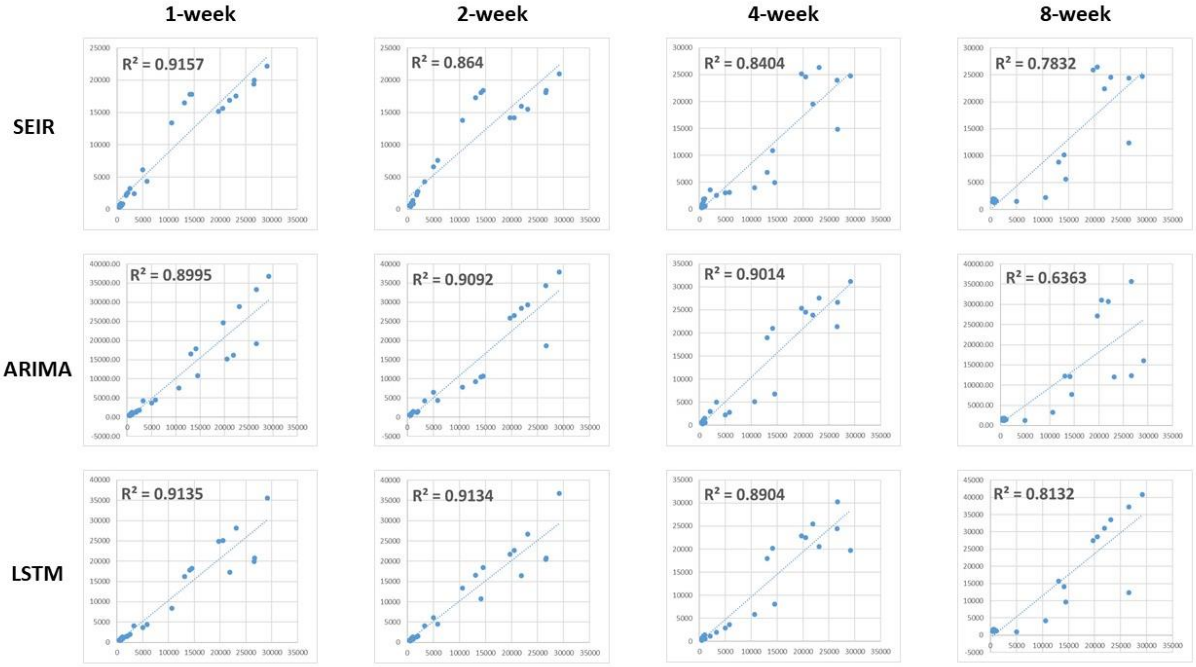
Model	Accuracy measure	Forecasting period (weeks ahead)			
		1	2	4	8
SEIR	MAE	2,349	2,854	3,373	4,169
	MAPE	21.12	32.35	49.84	78.70
	R^2	0.92	0.86	0.84	0.78
ARIMA	MAE	2,466	2,805	3,630	5,002
	MAPE	22.54	30.92	53.55	84.91
	R^2	0.90	0.91	0.90	0.64
LSTM	MAE	2,224	2,111	2,897	3,985
	MAPE	19.65	28.95	47.78	75.03
	R^2	0.91	0.91	0.89	0.81

SEIR: susceptible-exposed-infectious-recovered compartmental model. ARIMA: auto-regressive integrated moving average model. LSTM: long short-term memory network model. MAE: mean absolute error. MAPE: mean absolute percentage error. R^2: coefficient of determination.



SEIR: susceptible-exposed-infectious-recovered compartmental model. ARIMA: auto-regressive integrated moving average model. LSTM: long short-term memory network model

Figure 2. Number of reported COVID-19 cases of Thailand by week of reporting and predicted numbers at one (2a), two (2b), four (2c), and eight (2d) weeks ahead using SEIR, ARIMA, and LSTM models, 30 Dec 2020–29 Jun 2021



SEIR: susceptible-exposed-infectious-recovered compartmental model. ARIMA: auto-regressive integrated moving average model. LSTM: long short-term memory network model.

Figure 3. Scatterplot and coefficient of determination (R2) between numbers of reported COVID-19 cases in Thailand (x-axis) by week of reporting, 30 Dec 2020–29 Jun 2021, and predicted numbers (y-axis) at one, two, four, and eight weeks ahead using SEIR, ARIMA, and LSTM models

Subgroup Analysis for Predictive Accuracy by Area

The predictive accuracy based on the MAE of the two sub-national areas, Greater Bangkok Region and other provinces, are shown in Table 2. For both areas, the predictive accuracy had a similar pattern to that of the whole country. However, based on the forecasting performance, the accuracy was higher in the Greater Bangkok Region.

Table 2. Mean absolute percentage error (MAPE) of COVID-19 forecasts at one, two, four, and eight weeks ahead using SEIR, ARIMA, and LSTM models, compared with weekly reported COVID-19 cases of Greater Bangkok Region* and other provinces of Thailand, 30 Dec 2020–29 Jun 2021

Model	Area	MAPE at forecasting period (weeks ahead)			
		1	2	4	8
SEIR	Greater Bangkok Region	19.10	28.98	47.55	76.55
	Other Provinces	24.55	33.59	55.08	87.39
ARIMA	Greater Bangkok Region	20.22	29.11	50.12	81.44
	Other Provinces	25.78	31.47	56.05	86.67
LSTM	Greater Bangkok Region	18.15	25.02	46.89	72.50
	Other Provinces	21.31	30.40	50.02	78.89

*SEIR: susceptible-exposed-infectious-recovered compartmental model. ARIMA: auto-regressive integrated moving average model. LSTM: long short-term memory network model. *Greater Bangkok Region consists of Bangkok Metropolitan, Nonthaburi, Samut Prakan, and Pathum Thani provinces.*

Discussion

This study demonstrates the real-world performance of three predictive models commonly used for COVID-19 within the context of Thailand's epidemic situation and disease surveillance system. Overall, our study results indicate that longer forecasts were less accurate regardless of the model used. This is consistent with well-known concepts of forecasting, particularly during a highly dynamic situation such as an epidemic of a newly emerging disease.[32,33] We have shown quantitatively the level of forecasting inaccuracy.

The MAPE values of the 1-, 2-, and 4-week ahead forecasts for all three models were approximately 20, 30 and 50%, respectively. These findings are consistent with a study demonstrating accuracy of various models conducted by the U.S. Centers for Disease Control and Prevention for the same forecast horizons while other studies reported either lower or higher values.[34–36] For the 8-week ahead forecasts, all three models gave errors exceeding 70%. Although there are very limited studies on long-range COVID-19 forecasts using the models presented in this study, the marked increase in inaccuracy over longer time horizons (e.g., four weeks

or more) found in this study highlights the fact that these models may only be suitable for short-term forecasts, especially during times of high volatility such as during a pandemic.[32,33]

Among the three models, the LSTM model slightly outperformed the others, consistent with other studies.[37,38] One possible explanation is that LSTM model has a unique algorithm that allows it to "remember" past values (and errors) to inform future predictions longer than many machine learning techniques.[15,16,31,37] For the SEIR and ARIMA models, which were not very different in term of short-term forecast accuracy, what matters may be practical issues. One can conduct ARIMA using an automated tool, e.g., "auto.arima" function in R, that facilitates identifying the best model (as tested in this study), whereas the SEIR model requires modelers to design the structure and set parameters by themselves based on a literature review and data from multiple sources.[30,39,40] In contrast to an SEIR model, traditional ARIMA models require a time series to forecast its future values with or without the use of other exogenous information.[32,33] Therefore, in practice, using ARIMA for general short-range forecasting is likely to be a better option. SEIR will play an important role in forecasting different scenarios, such as comparing the effects of alternative measures of different types.[39,40] Another observation found in this study (Figure 2) is that the predicted values changed more slowly than the actual values. This reflects lags in forecasts usually found in models that rely on calculating forecasts from actual values from the recent past.[33]

Our models could forecast COVID-19 cases in Bangkok and surrounding areas more accurately than in other provinces, although the accuracy trajectories of the two areas were similar to the whole country. This phenomenon may be partly explained by the fact that the population in Bangkok and nearby provinces are denser and have similar characteristics to large cities, i.e., they are more homogeneous, when compared to other provinces, which are divided into urban and rural areas. The pattern of an epidemic spreading in the former were therefore more clear and less diverse than in the latter.

Limitations

One important limitation of this study is that the reported disease information could be incomplete, which is commonly found in disease surveillance systems. This issue might cause the forecasts to be less accurate due to the inaccuracy of the amount and pattern of the input data in the model. However, this limitation should be acceptable as the aim of this study was to assess the predictive performance under real circumstances. Another point to consider is that we chose to analyze the data at a time when most of the country's population were not vaccinated. This was to prevent the rapid increase in vaccine coverage from interfering with the accuracy assessment of our forecasts. This may result in differences in accuracy if these models are deployed at a time when a high proportion of the population has been vaccinated.

Conclusion and Recommendations

This study presented three models for forecasting emerging disease situations whose accuracy could be arguably acceptable for short-range forecasts when knowledge about the disease is limited. We found that the SEIR, ARIMA, and LSTM models had a similar accuracy for short-range (less than two weeks) forecasts and the LSTM model was slightly more accurate than the others. However, long-range forecasts were less accurate. Therefore, researchers using these models should monitor and update the forecasts periodically. Although this study was conducted in the context of Thailand, the results of the study are likely to reflect characteristics of models that can be applied in other countries experiencing similar epidemics.

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Conflicts of Interests

The authors of this study have no conflicts of interest.

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Effectiveness and Safety of Long-acting Antibody (LAAB) to Prevent COVID-19 among High-risk Population in Thailand: a 6-month Retro-prospective Cohort Study

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Abstract

During COVID-19 pandemic, evidence showed lower immunity after infection and vaccination among immunocompromised individuals. In July 2022, a prophylaxis campaign using long-acting antibodies (LAAB), tixagevimab-cilgavimab was launched in Thailand to decrease hospitalizations among high-risk groups. To evaluate the real-world effectiveness and safety of LAAB for high-risk populations, a 6-month retro-prospective cohort study was conducted starting in March 2023. We included 1,249 participants aged ≥18 years with high-risk conditions who tested negative for COVID-19 using antigen test kits during the campaign in Thailand's central, northern, and northeastern regions. Participants provided blood samples for anti-S and anti-N IgG testing and were monitored weekly by phone for six months for acute respiratory symptoms and were screened if COVID-19 was suspected. Positive cases were further tested with RT-PCR and sequencing. We matched 600 individuals who received the study drug tixagevimab-cilgavimab (exposed) by age and comorbidities to 600 individuals who did not receive the drug (non-exposed). Predominant strain was the omicron sublineage XBB. One participant who did not receive the drug was hospitalized without respiratory failure. Anti-N IgG was positive and high levels of anti-S IgG were observed. The effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections or hospitalizations among high-risk groups was not seen. Existing immunity from previous infections and vaccinations likely influenced these results. No serious adverse events related to the drug were reported. Despite these findings, there is a potential prophylactic role of LAAB for immunocompromised groups in the early phase of a pandemic while effective vaccines and treatments are unavailable.

Keywords: effectiveness, long-acting antibody, COVID-19

Introduction

As of 25 Feb 2024, coronavirus disease 2019 (COVID-19) has contributed to the deaths of more than seven million people worldwide, including nearly 40,000 in Thailand.[1] Vaccination is a key strategy to prevent infections and serious outcomes of COVID-19. In Thailand, in May 2023, the coverage for the primary series was 77.2%, while the coverage of at least one booster dose was 48.9%.[2]

As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have evolved, the effectiveness of COVID-19 vaccines has been significantly affected. In Thailand, real-world data indicate that vaccines targeting the original strain are less effective against omicron variants, particularly for preventing infection. This protection varies based on vaccine type, viral strains, and other factors, meaning that immunocompromised individuals, those with chronic kidney diseases, and older adults may have lower immune responses than healthy individuals.[3–5] For these high-risk groups, tixagevimab-cilgavimab, a long-acting antibody (LAAB) used as a pre-exposure prophylaxis, may reduce the incidence and severity of COVID-19. Tixagevimab-cilgavimab neutralizes the SARS-CoV-2 virus by binding to two different epitopes

on the spike protein of the virus. It blocks the virus from binding to angiotensin-converting enzyme 2 receptors on host cells, thus preventing infection.[6]

The US Food and Drug Administration gave authorization for tixagevimab-cilgavimab in December 2021 for emergency use in moderate to severe immunocompromised individuals aged ≥12 years old and recommended a dose of 600 mg against the emergence of omicron BA.1 sub-variants in June 2023.[7]

In June 2022 the Thai Food and Drug Administration approved, under conditional marketing, a 300 mg dose of tixagevimab-cilgavimab, which was subsequently updated to 600 mg in April 2023.[8,9] In addition, the Thai Ministry of Public Health issued guidelines for tixagevimab-cligavimab as prophylaxis in solid organ transplant recipients, patients with end-stage kidney disease, and individuals aged ≥60 years.[10,11]

Thus, we aimed to analyze the real-world effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections and severe outcomes among high-risk groups in Thailand.

Methods

Operational Definitions

Prior to April 2023, tixagevimab-cilgavimab 300 mg was the recommended dose according to the Department of Disease Control (DDC). After April, the recommended dose was increased to 600 mg, derived from B cells of COVID-19 survivors and engineered to prolong the half-life by at least threefold.[10] The drug demonstrated efficacy against COVID-19, including original and mutant strains.

According to the DDC's Disease Surveillance Definition and Reporting Manual for COVID-19, a person was defined as being infected if he or she developed at least two of the following symptoms: fever, cough, nasal congestion, sore throat, or phlegm; or one of these symptoms plus additional signs such as loose stools, muscle pain, headache, nausea/vomiting, fatigue, rash, or shortness of breath, difficulty breathing, olfactory or gustatory changes, confusion, decreased consciousness; or severe respiratory illness (e.g., pneumonia or chest x-ray abnormalities of unknown cause), and was confirmed by antigen test kit (ATK) or reverse transcription-polymerase chain reaction (RT-PCR) testing for COVID-19 viral genetic material.[12]

An adverse event was defined as an illness after receiving the study drug regardless of the causal relationship. A serious adverse event was defined as death, having a life-threatening illness such as anaphylaxis, and prolonged hospitalization after receiving the drug within 30 days, regardless of the causal relationship, and was reported to the DDC adverse events following immunization reporting system.[13]

Study Design

A retro-prospective matched cohort study was conducted, considering an individual pair matched in the same period by age and comorbidity. Matching age groups were 18–30, 31–40, 41–50, 51–60, 61–70, 71–80, and over 80 years. Comorbidity was prioritized based on its association with COVID-19 severity, including chronic kidney disease stages 3–5, diabetes mellitus, chronic lung disease, cancer with chemotherapy/ radiation therapy within two years, autoimmune disease, heart disease, cerebrovascular disease, and obesity (body mass index ≥30 kg/m^2). Participants aged 60 years and older without underlying diseases were matched with others of the same age group.

Participants were enrolled in two phases. During the retrospective phase, hospital-based patients who received tixagevimab-cilgavimab from January to February 2023 had their medical records reviewed and consented for a 6-month prospective observation period. In the prospective phase, participants eligible for the study were recruited from the standard LAAB campaign in the hospital and community during March to July 2023.

Study Site and Population

Both hospital and community settings were chosen purposively, considering the geographic distribution, internal management, and network collaboration. Patients without a history of acute respiratory symptoms in Pranangklao Hospital, Samutprakarn Hospital, Nakhonpathom Hospital in the central region of Thailand were selected to represent hospital-based participants. High-risk individuals residing in provinces covered by the Office of Disease Prevention and Control (ODPC) Regions 3 Nakhon Sawan, ODPC 9 Nakhon Ratchasima, and ODPC 4 Saraburi were selected to represent community-based participants from Thailand's northern, northeastern, and central regions.

We targeted high-risk individuals susceptible to severe COVID-19 infection adhering to DDC's guideline for LAAB administration to establish our study inclusion and exclusion criteria.[10,11] Study participants without COVID-19 infection based on interviews, without any history of acute respiratory symptoms, and who tested negative on ATK screening at enrollment and after seven days

High-risk groups were defined as individuals aged 60 years and older or those with any of the seven specified

chronic diseases used for matching. High-risk groups with low immunity or an inadequate vaccine response included organ or bone marrow transplant recipients on immunosuppressive drugs, patients with hematologic malignancies or solid tumors who are undergoing or have recently completed treatment, HIV-positive individuals with compromised immunity (e.g., CD4 <200 cells/mm^3) who are not on anti-HIV therapy, those with a history of opportunistic infections or ongoing HIV symptoms, patients with end-stage renal disease on kidney replacement therapy, and individuals on immunosuppressive drugs or with immune system impairment as determined by a physician.

Sample Size Assumptions and Calculation

The sample size calculation applied a vaccine effectiveness of 83% as a proxy for LAAB effectiveness with a desired precision width of 20%.[14,15] The attack rate among the unexposed population was estimated at 8%.[16] This yielded a minimum sample size of 1,035 participants. Accounting for a 20% compensation for loss of follow-up, the total sample size was determined to be 1,200.

Sampling Methods

The eligible participants were enrolled through consecutive sampling based on underlying disease records in hospital databases and villagers' family folders. Participants were informed that their participation and treatment choice was entirely voluntary. Those opting for the study drug (exposed) underwent at least one hour of post-injection observation. Participants declining the drug (non-exposed) who were matched by age and comorbidity (Table 1) were also invited to join the study during the same period and within the same region as the LAAB campaign until either there were no more eligible participants in the site or the sample size was reached. Exposed participants were matched with the non-exposed on the same comorbidity if possible, otherwise other chronic diseases were used instead.

Data and Specimen Collection

Participants consented to undergo nasopharyngeal swabs for COVID-19 antigen testing and venipuncture for immune testing before drug administration. Data collected included demographics, risk behaviors, health status, and expenses related to LAAB. Participants were monitored for adverse events at one hour, one day, seven days, and four weeks after injection.

Trained research assistants checked for COVID-19 symptoms and collected nasopharyngeal samples for RT-PCR and whole genome sequencing if symptoms developed. Hospitalizations were reported by hospitals and medical records were reviewed. Weekly follow-up assessments were conducted by phone for six months with additional checks against the DDC COVID-19 database and ongoing monitoring for outbreaks and mutations in Thailand.

Remaining specimens were stored at –70°C at the Thai National Institute of Health and were transferred to a specimen bank where they remain for 10 years for future research and disease control efforts. Participants were informed about the use of their samples in future studies.

Special Laboratory Testing

Baseline antibodies (anti-S and anti-N IgG) against COVID-19 were tested at the Clinical Research Center, Medical Life Sciences Institute, Department of Medical Sciences, Ministry of Public Health using quantitative methods. Serum samples were analyzed for SARS-CoV-2 antibodies to nucleocapsid (N) and spike glycoprotein (S1) proteins using the IgG and Quant IgG-II assay (Abbott Ireland) with the ARCHITECT-i1000SR analyzer (Abbott Diagnostics). Anti-N antibodies were considered negative if the index value was ≤1.40. Anti-S1 antibodies ≥50 AU/mL were considered positive. The reportable range for anti-S1 was 6.8–80,000 AU/mL. For correlation with World Health Organizations international standard, antibodies were converted to binding antibody units (BAU/mL) by multiplying values by 0.142 at the correlation level of 0.999.

CTK-R0182C Onsite COVID-19 Ag rapid tests, were used to screen for SARS-CoV-2 infection during enrollment.

Data Analysis

Categorical variables (gender, age group, underlying diseases, vaccination history including COVID-19, influenza, and LAAB, COVID-19 infection history, risk factors, and prevention behavior in the 14 days before enrollment) were compared using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Baseline COVID-19 antibody concentrations were compared using a t-test on a log scale for geometric mean concentration. A *p*-value <0.05 indicated a significant difference between the two groups.

Effectiveness of Tixagevimab-cilgavimab

The primary outcomes for this study were COVID-19 infection and hospitalization due to COVID-19. Incidence rate ratios were calculated using Poisson regression. Potential confounders and serostatus were

included in the final model. Effectiveness was defined as (1–adjusted incidence rate ratio) × 100.

Ethics

Ethical permission for this study was obtained from the Institute for the Development of Human Research Protections (IHRP). Approval to conduct the study was granted on 28 Mar 2023. The certificate of approval number is IHRP2023040 and IHRP no. 022-2566.

Results

We enrolled 1,249 individuals, of which 49 were excluded (five had COVD-19 infection within seven days after enrollment and 44 exposed could not be matched). Finally, 1,200 participants were included in the analysis, 600 in each group. After the follow-up period, there were 24 COVID-19-infected cases in each group as shown in Figure 1.

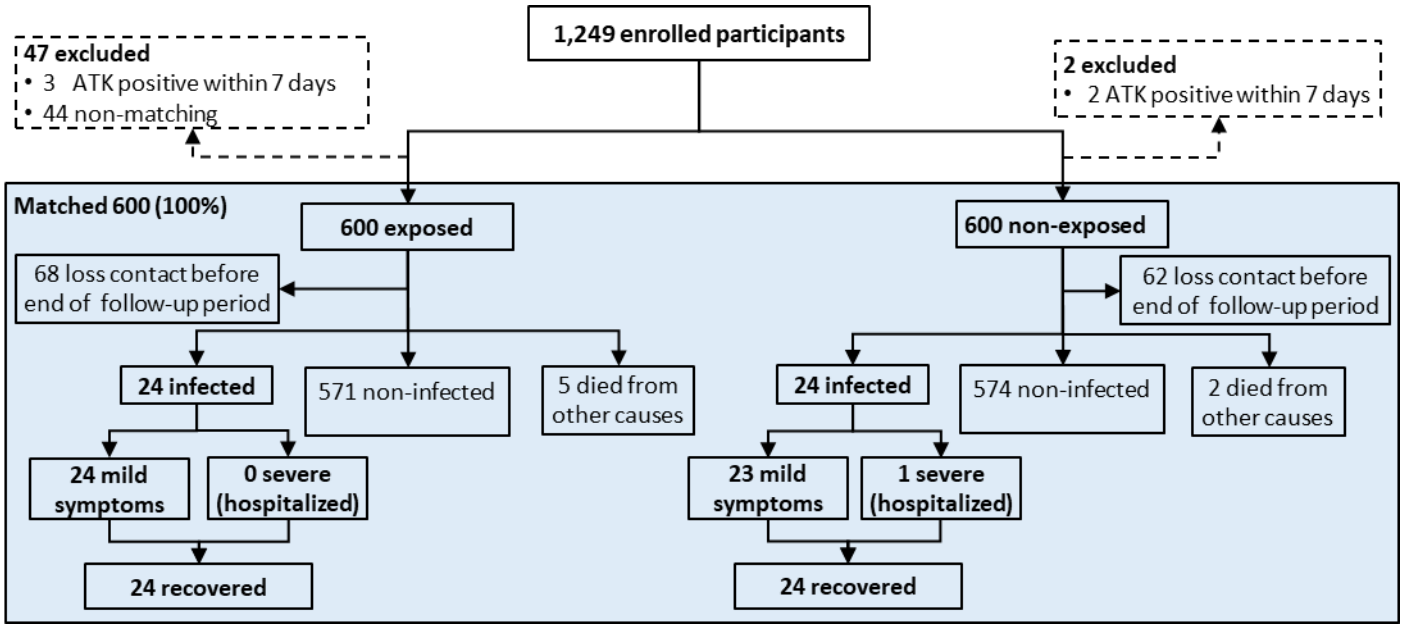

Figure 1. Status of outcomes among enrolled participants with and without long-acting antibody received

Safety Profile or Adverse Event Following LAAB

Among 547 matched pairs who received tixagevimab-cilgavimab 600 mg, 24 exposed and 21 non-exposed were infected. Among 53 matched pairs who received tixagevimab-cilgavimab 300 mg, three non-exposed were infected and no infections were found in the exposed group.

Among seven deaths, the causes, verified through medical records and interviews with hospital staff, were chronic kidney disease with acute renal failure (n=3), hospital acquired pneumonia with negative ATK results (n=2), and heart attack (n=2). Five were from the exposed group who received tixagevimab-cilgavimab for more than 30 days (range 55–166 days), and they did not meet the reporting criteria of serious adverse events. The other two deaths were in the non-exposed group.

Among the 1,200 participants, 972 (81%) were aged 60 years or more. Among these, 220 (23%) had no history of underlying disease (Table 1).

In the non-exposed group, 16 (2.7%) had no prior COVID-19 infection or vaccination, as confirmed by negative anti-S IgG and anti-N IgG results. Of the 24 infected cases, 23 (96%) were vaccinated, and 10 (42%) had a history of prior infection. Only one required hospitalization, and without respiratory failure. The infection, identified as omicron XBB.1.15 by RT-PCR and sequencing, was in a patient who had a prior COVID-19 infection a year earlier and had received three vaccine doses. This patient had positive anti-N IgG (1.87 Index) and anti-S IgG (3,901.3 AU/mL) and eventually recovered.

The effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections and hospitalizations was 11% (95% confidence interval NA–51%), as shown in Table 2. The specific effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections by underlying diseases and COVID-19 vaccination is shown in Table 3.

Among 48 infected COVID-19, whole genome sequencing of SARS-CoV-2 was identified in 32 (67%). Of these, 19 (59%) were identified as the omicron B.1.1.529 sublineage: XBB, with 12 cases (38%) specifically being XBB.1.16. Five strains could not be determined by RT-PCR, and the remaining 11 cases did not have respiratory specimens available for RT-PCR testing, as shown in Figure 2.

Table 1. Baseline characteristics (n=1,200)

Characteristics	Received LAAB n=600 n (%)	Did not receive LAAB n=600 n (%)	*P*-value
Gender			
Male	247 (41.2)	194 (32.3)	0.002
Female	353 (58.8)	406 (67.7)	-
Age (mean±SD)	66.2±9.6	66.0±9.5	0.651‡
(Range)	(19–91)	(23–90)	
High-risk groups (n=1,098)	540 (90.0)	558 (93.0)	0.811
Age ≥60 years old	112* (20.7)	108 (19.4)	0.661
CKD (stage 3–4)	18 (3.3)	24 (4.3)	0.345
Diabetic mellitus	226 (41.9)	213 (38.2)	0.365
Chronic lung disease	2 (0.4)	7 (1.3)	0.106
Heart disease	30 (5.6)	39 (7.0)	0.248
Cerebrovascular disease	13 (2.4)	11 (2.0)	0.835
Obesity†	19 (3.5)	20 (3.6)	0.870
Other high-risk groups	154 (28.5)	176 (31.5)	0.711
High-risk groups with low immunity or inadequate vaccine response (n=102)	60 (10.0)	42 (7.0)	0.078
1) ESRD (CKD stage 5)	46 (76.7)	32 (76.2)	0.565
ESRD with hemodialysis	45 (97.8)	30 (93.8)	-
ESRD without hemodialysis	1 (2.2)	2 (6.2)	-
2) Cancer with chemotherapy/radiotherapy	9 (15.0)	6 (14.3)	1.000
3) Autoimmune diseases	5 (8.3)	5 (11.9)	0.737
History of vaccination before enrollment			
History of receiving COVID-19 vaccine	585 (97.5)	552 (92.0)	<0.001
Not received	15 (2.5)	48 (8.0)	-
1 dose	7 (1.2)	16 (2.9)	0.056
2 doses	133 (22.7)	171 (31.2)	0.002
3 doses	278 (47.5)	253 (46.2)	0.677
>3 doses	167 (28.6)	109 (19.8)	0.001
Last dose ≥6 months	545 (97.3)	508 (96.8)	0.596
Last dose ≥12 months	392 (70.0)	414 (78.9)	0.001
History of received LAAB	20 (3.3)	4 (0.7)	0.001
History of received Influenza vaccination	348 (60.4)	362 (62.4)	0.506
Baseline of COVID-19 antibodies			
Anti-S IgG (GMC±GSD) (95% CI)	3516.2 ± 4.7 (3097.5–3991.5)	2200.8 ± 6.8 (1883.1–2572.2)	<0.001
Anti-S IgG positive	572 (98.3)	552 (93.9)	<0.001
Anti-N IgG (mean±SD) (95% CI)	1.7±2.5 (1.5–1.9)	1.8±2.8 (1.6–2.1)	0.433
Anti-N IgG positive	197 (33.9)	188 (32.0)	0.534
History of previous COVID-19 infection	258 (43.0)	259 (43.2)	1.000
Received 1–2 doses	61 (23.6)	73 (28.2)	0.270
Received >2 doses	190 (73.6)	166 (64.1)	0.023
Anti-N IgG positive	123 (49.4)	108 (42.4)	0.129

**Participants aged ≥60 years without CKD, diabetic mellitus, chronic lung diseases, heart diseases, cerebrovascular diseases, and obesity who received LAAB, 4 of them matched with other 4 participants in the same age group with other chronic diseases who did not receive LAAB. †Body mass index ≥ 30 kg/m2. ‡P-value from Mann-Whitney U test. LAAB: long-acting antibody. ESRD: end-stage renal disease. CKD: chronic kidney disease. GMC: geometric mean concentration. GSD: geometric standard deviation. SD: standard deviation. CI: confidence interval.*

Table 2. Effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections and hospitalizations by high-risk categories (n=1,200)

Outcomes	Exposed n=600	Non-exposed n=600	Crude IRR (95% CI)	Adjusted IRR* (95% CI)	Effectiveness† (95% CI)
High-risk groups					
Person-time (weeks)	12,256	12,600	-	-	-
COVID-19 infection	23	24	0.98 (0.53–1.82)	0.88 (0.49–1.60)	12% (NA–51%)
Hospitalized	0	1	-	-	-
High-risk groups with low immunity or inadequate vaccine response					
Person-time (weeks)	1,237	944	-	-	-
COVID-19 infection	1	0	-	-	-
Hospitalized	0	0	-	-	-
All high-risk populations					
Person-time (weeks)	13,493	13,544	-	-	-
COVID-19 infection	24	24	1.00 (0.55–1.85)	0.89 (0.49–1.60)	11% (NA–51%)
Hospitalized	0	1	-	-	-

**IRR was adjusted for age, gender, history of receiving the COVID-19 vaccine, booster ≥2 doses, last COVID-19 vaccine dose ≥12 months, and positive result for anti-S IgG. †Effectiveness = (1−adjusted IRR) × 100. IRR: incidence rate ratio. NA: not available.*

Table 3. Effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections by number of underlying diseases and COVID-19 vaccination status

Characteristics	Exposed		Non-exposed		Crude IRR (95% CI)	Adjusted IRR* (95% CI)	Effectiveness† (95% CI)
	COVID-19 infection	Person-time (weeks)	COVID-19 infection	Person-time (weeks)			
Underlying diseases							
1	5	3,533	1	4,026	5.70 (0.64–26.96)	16.60 (1.01–27.18)	-
2	6	4,520	8	4,003	0.66 (0.19–2.18)	0.45 (0.13–1.56)	55% (NA–87%)
More than 2	13	5,296	14	5,321	0.93 (0.40–2.14)	0.80 (0.36–1.76)	20% (NA–64%)
COVID-19 vaccination history							
Received ≤2 doses	4	2,890	6	3,842	0.89 (0.18–3.74)	1.30 (0.35–4.90)	-
Received >2 doses	19	10,168	17	8,232	0.90 (0.45–1.85)	0.75 (0.38–1.48)	25% (NA–62%)

**IRR adjusted for age, gender, COVID-19 vaccination, booster ≥2 doses, last COVID-19 vaccination ≥12 months, positive anti-S IgG result. †Effectiveness = (1−adjusted IRR) × 100. IRR: incidence rate ratio. NA: not available.*

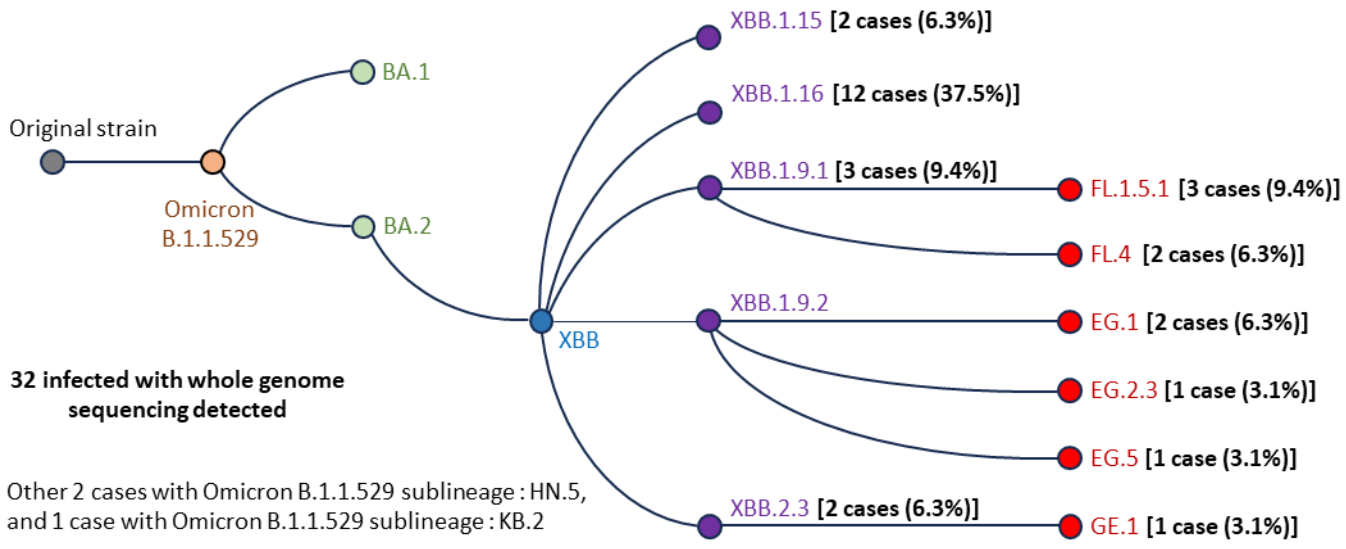

Figure 2. Diagram of SARS-CoV-2 variant strain with sublineages by whole genome sequencing among 32 infected cases

Safety Profile of Tixagevimab-cilgavimab

Among the 647 enrolled with exposed, 42 (6.5%) experienced adverse events; 17 (2.6%) within one hour and 19 (2.9%) 24 hours after receiving the drug. All recovered and there were no hospitalizations. No adverse events were recorded at the four-week follow-up time point, as shown at Figure 3.

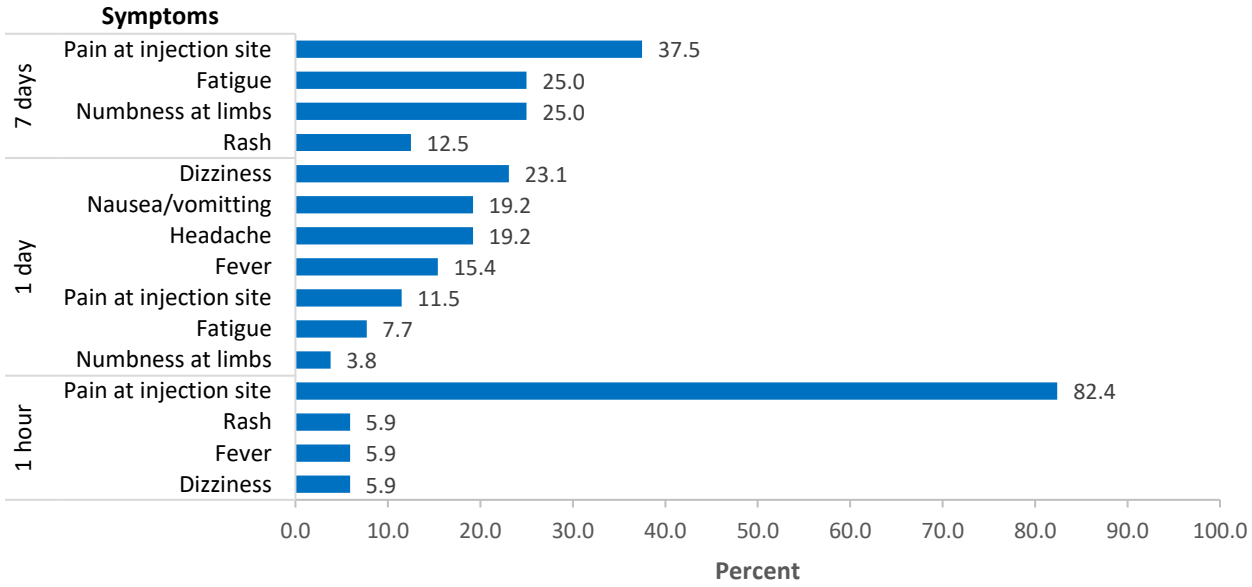

Figure 3. Distribution of adverse events among 42 participants who developed symptoms after receiving tixagevimab-cilgavimab by follow-up time

Discussion

Although there is evidence that the use of LAAB is effective in preventing COVID-19 in high-risk groups, our study found that the effectiveness of tixagevimab-cilgavimab in preventing COVID-19 hospitalizations among high-risk groups was low in both hospital and community settings.[17–19] However, one infected individual from the non-exposed group was hospitalized. Those who did not receive the study drug might have a higher tendency to avoid engaging in several hihg-risk activities since they may perceive themselves as being unprotected. Therefore, they might have a lower "baseline risk" of getting an infection.

Assessing the neutralizing activity of LAAB against variant strains of the virus remains challenging to be timely due to the rapidly changing nature of the virus. In Thailand, the B.1.1.529 omicron variant was subsequently detected in 2022 and lower neutralizing activity of tixagevimab-cilgavimab against the emergence of this omicron sub-variant, including BA.2, BA.5 and XBB, was observed in 2023.[20–24] This observation was similar to SARS-CoV-2 variants circulating in the United States.[25]

A key finding from this study was that nearly 90% of participants, regardless of whether they received the study drug, had immunity from a previous COVID-19 infection or vaccination, as confirmed by positive serostatus for anti-S IgG and anti-N IgG, indicating a history of vaccination or prior infection. Consequently, the observed cases of infection were not severe. Additionally, symptom and ATK screening, along with rapid access to treatment, may have further reduced the risk of severe illness. However, the level of immunity against COVID-19 in preventing severe illness among high-risk groups varies depending on the virus variants, with antibody levels after SARS-CoV-2 omicron infections being lower than those following delta infections.[26]

We found that tixagevimab-cilgavimab is safe for use among high-risk groups. We did not find any serious adverse events in individuals who received the drug, with most individuals experiencing only mild symptoms, such as pain at the injection site, rash, or occasional fever. Although there was one report of an adverse reaction involving difficulty breathing and a skin rash within 40 minutes of drug administration, the majority of adverse events reported were mild.[27,28]

Limitations

In our study, less than four percent of high-risk groups were infected with COVID-19 compared to the expected value of 8%.[2] Since most COVID-19 infections were among the elderly, some with underlying diseases, they tended to avoid engaging in high-risk activities. Therefore, the incidence of COVID-19 reported in our study was lower than expected. Recall bias may be attributable to undetected mild symptoms or asymptomatic cases, which were difficult to identify through weekly phone interviews over six months.

Recommendations

The country's COVID-19 preparedness strategy aims to develop a broad range of prevention and treatment options using both existing and innovative technologies. Early in the pandemic, it could still be crucial to offer pre-exposure prophylaxis or treatments with monoclonal antibodies (including LAAB) to protect high-risk groups, especially those with compromised immune systems who may not respond well to vaccinations, but timely development and administration of the antiboodies is essential in pandemic preparedness.[29–32]

Conclusion

Although tixagevimab-cilgavimab was associated with only mild adverse reactions, there was no statistically significant evidence of its effectiveness in preventing COVID-19 infections or severe outcomes among high-risk groups in Thailand. The year 2023 was during the recovery phase of the pandemic. Most of the population, including immunocompromised and other high-risk individuals, had been vaccinated and had previous natural infections. Tixagevimab-cilgavimab may still have some potential benefit in future pandemics if it is developed rapidly and provided to target populations at appropriate time points.

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Conflicts of Interests

The authors declare no conflicts of interest related to the work presented in this manuscript.

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The Grammar of Science: It's All about Trustworthiness of Your Data

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As mentioned in previous article, several international standards for designing, recording and reporting research studies focus on ethical issues related to rights, safety and wellbeing of study participants and the trustworthiness of the study data.[1–4] The good clinical practice (GCP) guideline indicates that the research team should assure data generated are of sufficient quality to ensure reliable study results.[1] The guideline describes intensively on data governance issues such that there should be appropriate management of data integrity, traceability and security in order to have accurate reporting, verification and interpretation of the study information.[1] Similarly, the UK Office for Statistics Regulation notes that the framework for the code of practice for statistics is generally based on three pillars—trustworthiness, quality and value of the data.[5] There are so many jargons here—let's try to understand them.

Data Management vs. Data Governance

Data management includes tools, procedures, and methods to manage the lifecycle of data, from data initiation to data archive.[6-8] Data validation is one of the critical aspects of data management.[8] Main purpose of data validation is to ensure that the collected data conforms to predefined rules or standards by verifying its accuracy, consistency, and other metrics.[9]

Data governance is a set of processes, roles, policies, standards, and metrics that ensure the effective and efficient control, and utilization of the collected data.[7] Data governance focuses on the processes to increase value of data, while storing, manipulating and using the data, without compromising its security, integrity, or privacy.[6,8,10] Key components of data governance include policies, procedures and standards that govern data management practices regarding data ownership, data stewardship (access, maintenance, use, sharing), data protection, regulatory compliance, and data standardization (using common terminology across different systems).[7,8,11] We can say that data governance can be seen as the blueprint for constructing a new building, whereas data management is the act of construction.[6,11]

Data Quality, Data Security, and Data Integrity

Three fundamental concepts in data management are: data quality, data security and, data integrity. These terms embrace different aspects of data management.

Data quality refers to the condition of a set of values of the data, ensuring that it is fit for its intended use.[7] The purpose of data quality management is to free collected data from anomalies, inconsistencies, inaccuracies, incompleteness, repetitiveness, etc.[9,12] Data quality will streamline data analysis and produce reliable study results. We can say that data quality management consists of practices, methodologies, and tools that systematically identify, rectify, and take preventive measures against potential problems before they can disrupt the data analysis.[9,13]

Data security refers to data protection from unauthorized access and use of the collected data. The security measures should also safeguard the data from breaching or other misconducts.[12] Data security entails technologies, policies, and practices to ensure authentication of the data storage system such that only authorized persons can access to the data.

Data integrity is a broader term encompassing both data quality and security.[12] The "integrity" for data means "wholeness" and "unity".[14] According to international guidelines for research conduct, the generic definition of data integrity means the process of maintenance and assurance of the data quality over its entire data life-cycle.[1–4,14] Specifically, maintaining data integrity involves safeguarding the data against

loss, leaks and falsification, while assurance of data quality is to secure accuracy, completeness and consistency of the data at any point in its lifecycle.[12]

Data Cleaning vs. Data Cleansing

Important parts of the data management procedures after data collection include data assessment, data cleaning, and data cleansing. The purpose of data assessment is to determine if the collected data fulfills the quality standards.[15] If not, we have to perform data cleaning and/or data cleansing. These two terms are often used interchangeably, but they are actually revolved on different concepts and practices.[16] While both processes attempt to improve data quality, the choice between the two often depends on the specific requirements which may vary subject to the complexity and sensitivity of the data analysis tasks.[14]

Data cleaning primarily focuses on ensuring that the dataset is as error-free as possible before it is used for analysis. Data cleaning involves removing or correcting data that is incorrect, incomplete, duplicated, or improperly formatted. The term "data cleaning" is commonly used in academic or scientific communities with the focuses on the accuracy and reliability of data; another related term used in business settings is "data scrubbing" with the focuses on cleaning data for operational efficiency and regulatory compliance.[16] Data cleaning can be automated in the computerized system used for data quality management.[17]

Data cleansing extends beyond cleaning by adding comprehensive process of preparing data. The cleansing involve: checking data irrelevant to the study objectives, removing duplicated data, handling missing values, normalizing or standardizing data formats and structures, and ensuring the data adhere to the relevant data governance standards.[8,9,14,18] The process of data cleansing might involve cross-referencing information with external sources or employing analytic technologies to detect unanticipated patterns of incorrect data.[17,18]

Data Quality Metrics

The idea behind data integrity is to guarantee the reliability, traceability and security of data throughout all processes and systems.[19] The prominent metrics that are universally used to assess data quality in good data management practices and to evaluate document management in the good documentation practices are ALCOA and ALCOA+.[7–9,14,15,18–22]

ALCOA

ALCOA is an abbreviation of Attributable, Legible, Contemporaneous, Original, and Accurate.

A—Attributable (identifiable), being able to trace the persons involving in the processes related to data management including: generating, making corrections, deletions, additions, etc. The "attributable" can be achieved through using validated computerized system with audit trail system functions that can keep records of all activities from data entry to data archiving. For example, the validated computer system contains a journal file with records of who accessing and manipulating the data with date and time-stamped on the data records within the system. It is also captured the original values as well as modified/deleted values (Figure 1).

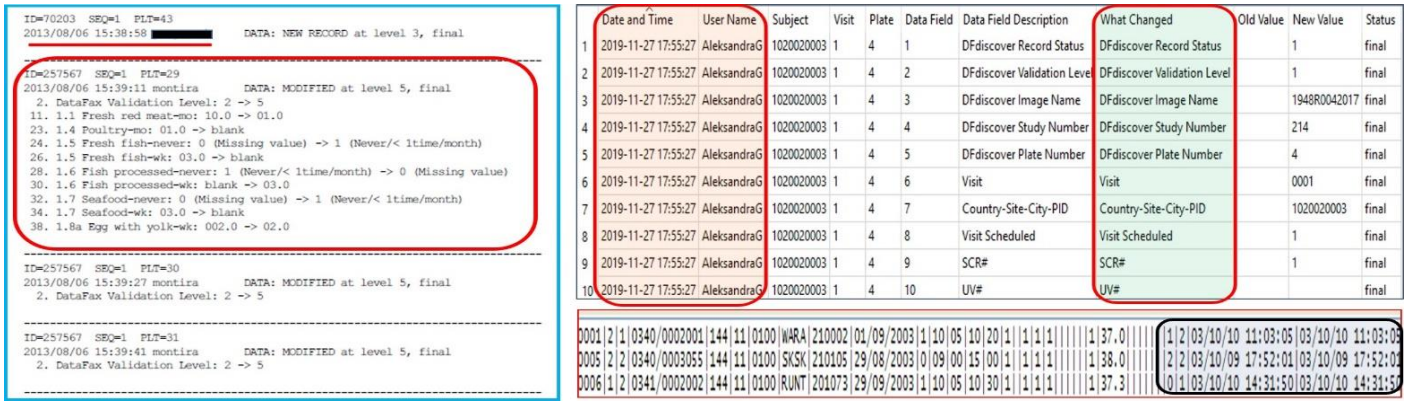

Figure 1. Examples of attributable of data

L—Legible (readable) and understandable of all information to be completed in the study. The data should also be permanent and accessible throughout the data lifecycle. For example, handwritten can be difficult to read and understand. Even though the data entry persons can guess; however, according to GCP, they cannot enter the guessing data but have to query back to the data originator/collector (Figure 2).

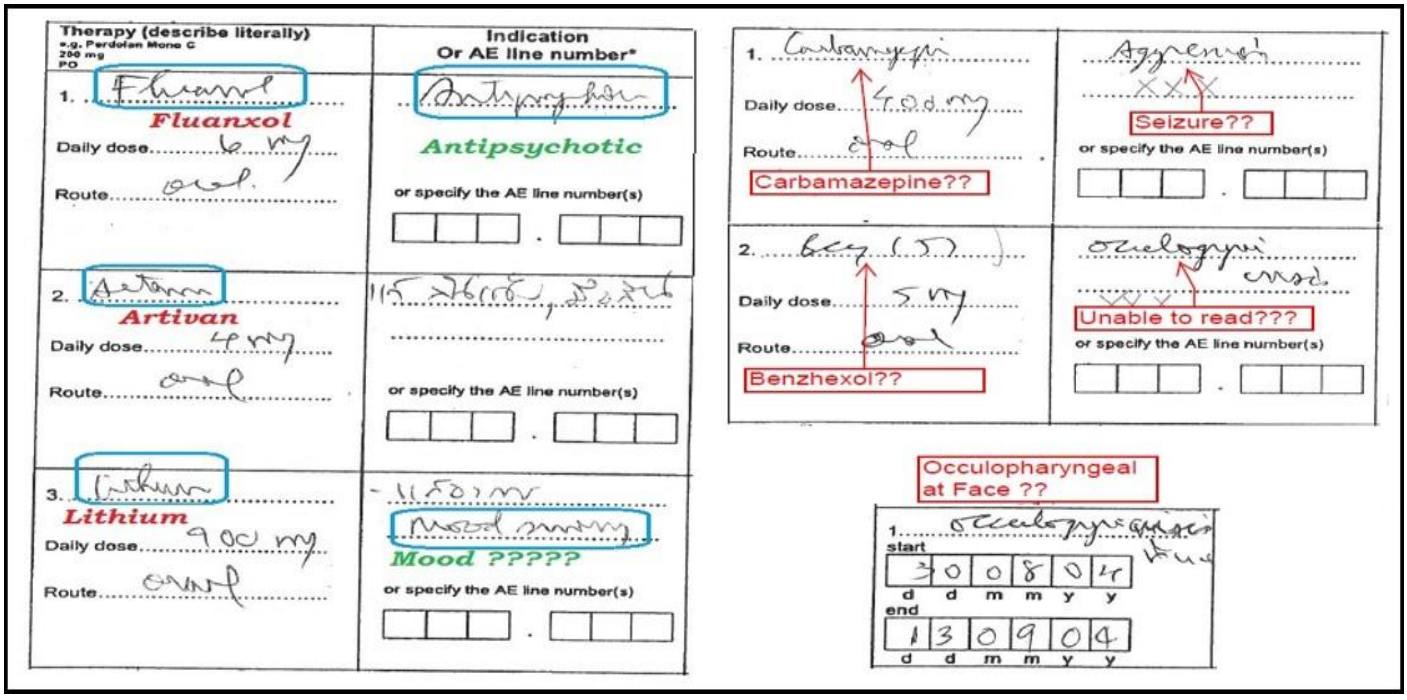

Figure 2. Examples of legible of data

C—Contemporaneous (synchronous), showing the evidence that data are simultaneously or timely documented when the actions or events are actually performed. Contemporaneous is also related to another term, timeliness, ensuring that data are up-to-date and readiness within a certain time frame. For example, as noted on the data records, the study participant enrollment dates (5 Aug 2015) are contradicted with the data submission date (4 Aug 2015). Another scenario shows the issue of unreasonable gap time between data collection date (December 2009) and data submission date (February 2010) (Figure 3).

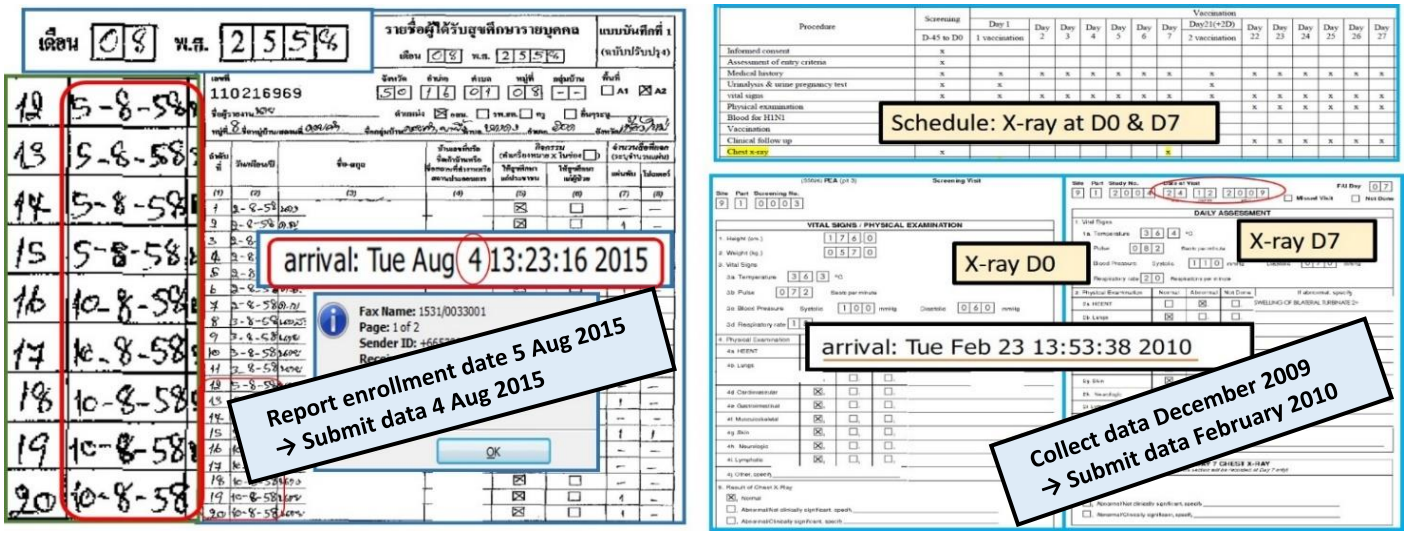

Figure 3. Examples of contemporaneous and timeliness of data

O—Original record (or certified true copy), reflecting the source of the collected information remain available in its original state. Should there be alteration made to the data/records, they should be signed and dated by an authorized person while keeping the reading of the original information. For example, according to GCP, the modification of the data should be traceable with audit trails, the data records were edited by whom and when (Figure 4).

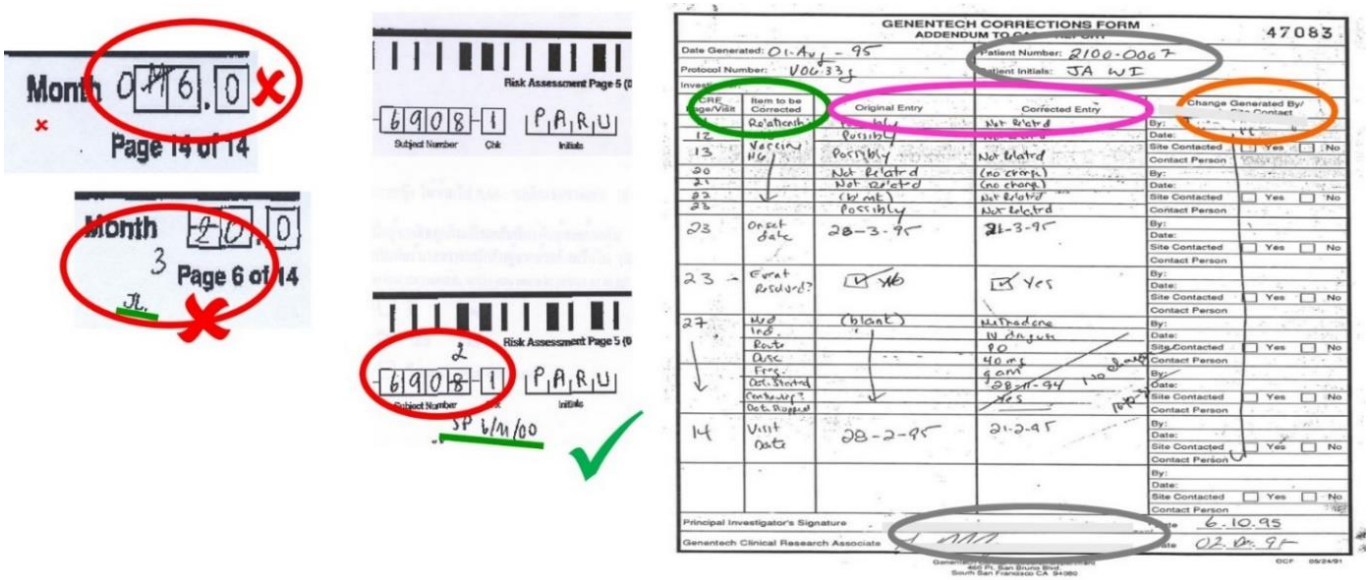

Figure 4. Example of traceable of original data

A—Accurate, verifying that the data values represent reality or are based on the agreed-upon source of truth, ensuring that the data is correct, reliable, and error free. The "accuracy" can be achieved with good automated edit check programs. In certain instances, the automated edit check between contradicting values of variables may not be possible (pre-planned), manual review by data management team is necessary particularly for key outcome variables. For example, the data on a case record form are cross-checked whether they are the same with those on the source document. Manual cross-check is performed between the medication given and the reason for such therapy (Figure 5).

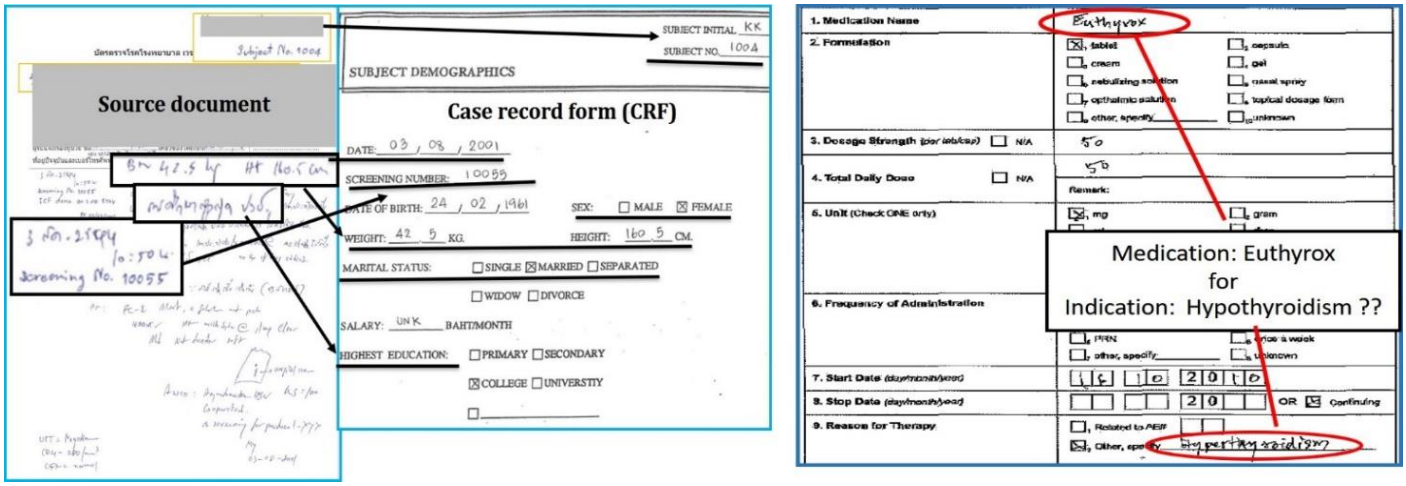

Figure 5. Examples of cross-checking of accuracy of data

ALCOA+

ALCOA+ adds four more quantifiable measurements: Complete, Consistent, Enduring, and Available.

C—Complete (whole), including all necessary data without omissions. The amount of usable or complete data should represent the sample data needed to answer the research questions as planned. Particularly, complete or meaningful data for critical variables related to primary objectives of the study should be acquired. Metadata (information about the collected data) is also important for reproducing information, if needed. For example, rather than leaving blank space for missing data, it is a good practice to assign a missing value with a specific value for each variable. Another approach is assigning "N" (none) or "ND" (not done) or "NA" (not available) for the certain variable, as applicable (Figure 5).

USUBJID	INITIALS	VISDAT	ICDAT	SEX	HEIGHT	WEIGHT	BMI	SYSBP	DIABP
03025	RK	09/APR/2014	09/APR/2014	2	.N	058	.N	130	080
03027	PN	07/MAY/2014	07/MAY/2014	1	.N	051	.N	130	073
03029	SK	07/MAY/2014	07/MAY/2014	1	.N	068	.N	128	070
03040	VS	18/AUG/2014	18/AUG/2014	2	.N	047	.N	142	063
03047	SO	20/AUG/2014	20/AUG/2014	2	.N	083	.N	123	101
03050	KS	27/AUG/2014	27/AUG/2014	2	.N	076	.N	144	077
03053	RV	03/SEP/2014	03/SEP/2014	1	.N	074	.N	132	081
03054	BR	03/SEP/2014	03/SEP/2014	2	.N	048	.N	109	069
01012	SJ	07/FEB/2014	07/FEB/2014	2	.U	067	.N	131	069
03044	VP	20/AUG/2014	20/AUG/2014	1	.U	071	.N	115	066
03049	SR	27/AUG/2014	27/AUG/2014	2	.U	051	.N	148	076
03051	KK	27/AUG/2014	27/AUG/2014	2	.U	040	.N	109	071
03052	TD	27/AUG/2014	27/AUG/2014	1	.U	065	.N	150	070
03057	UA	04/SEP/2014	04/SEP/2014	1	.U	067	.N	123	067
03060	PS	05/SEP/2014	05/SEP/2014	2	.U	075	.N	139	071
15019	TS	23/JAN/2014	23/JAN/2014	2	132	042	24.10	141	089
01019	DJ	28/FEB/2014	28/FEB/2014	2	135	067	36.76	146	071
06030	KK	24/MAR/2014	24/MAR/2014	2	138	043	22.57	160	098
17033	SS	01/MAY/2014	01/MAY/2014	2	140	036	18.36	118	081
11001	TC	25/JAN/2014	15/JAN/2014	1	140	040	20.40	136	060
20058	MS	15/MAY/2014	15/MAY/2014	2	140	046	23.46	120	080
13024	RS	23/APR/2014	23/APR/2014	2	140	049	25.00	117	068
03014	NC	18/FEB/2014	18/FEB/2014	2	140	058	29.59	130	080

Figure 6. Example of completeness metric of data

C—Consistent, ensuring data uniformity without contradictory information across the data collection forms/systems. Cross-checking related data to assure congruent values. The "consistency" can be examined by synchronizing different data sources and/or comparing data records from different datasets. For example, the researchers must investigate if a variable "sex" on a screening data collection form is "male" but on the enrollment form is "female." Query is needed when merging clinical database and laboratory worksheet, and data from the same specimen shows discordant information between reported values in clinical database versus those in the laboratory worksheet (Figure 7).

E—Enduring, securing data throughout the data lifecycle or the study duration. The data records should remain intact, accessible, and readable in a permanent and maintainable form within the study period for which they are intended.

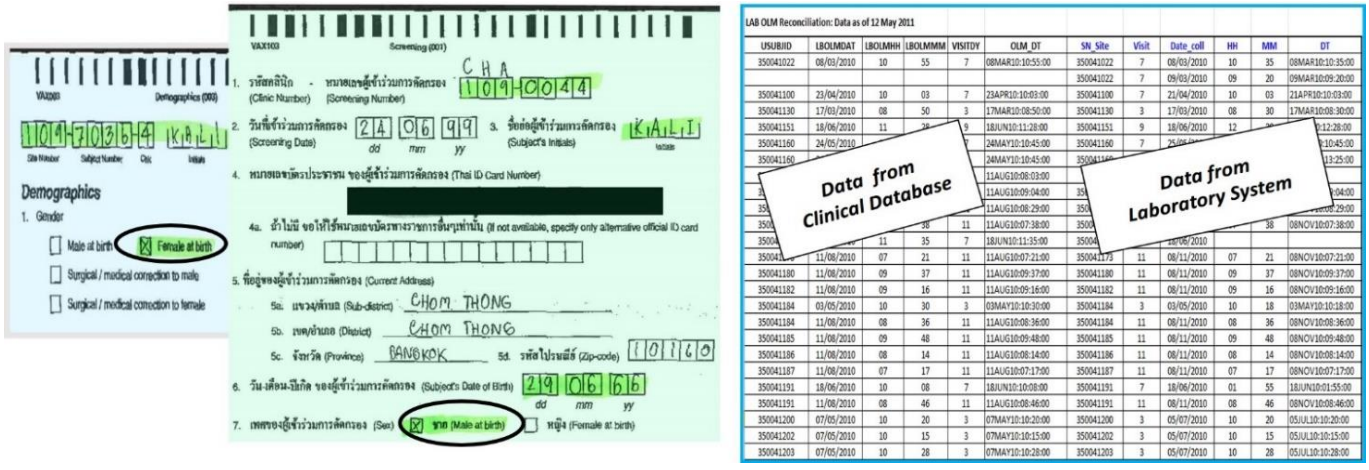

Figure 7. Examples of cross-checking of consistency between data

A—Available, warranting that data records are available throughout the data lifecycle or within the study period. The data records must be ready and accessible for review by responsible persons. The data records should be released or reported according to the pre-planned schedule.

Others

Other metrics that have been used in assessing the data integrity and data quality include uniqueness, validity, reliability, and relevance.

U—Uniqueness, verifying that data records are distinctively identifiable for each study participant. Each study participant should have only one study identification. There should be no duplicate data entries of the same event. For example, the data records of the same events/activities of a particular study participant must be deleted to avoid data repetitiveness. It is also important to cross-check the same study participant with different ID numbers to avoid multiple enrollments to the study (Figure 8).

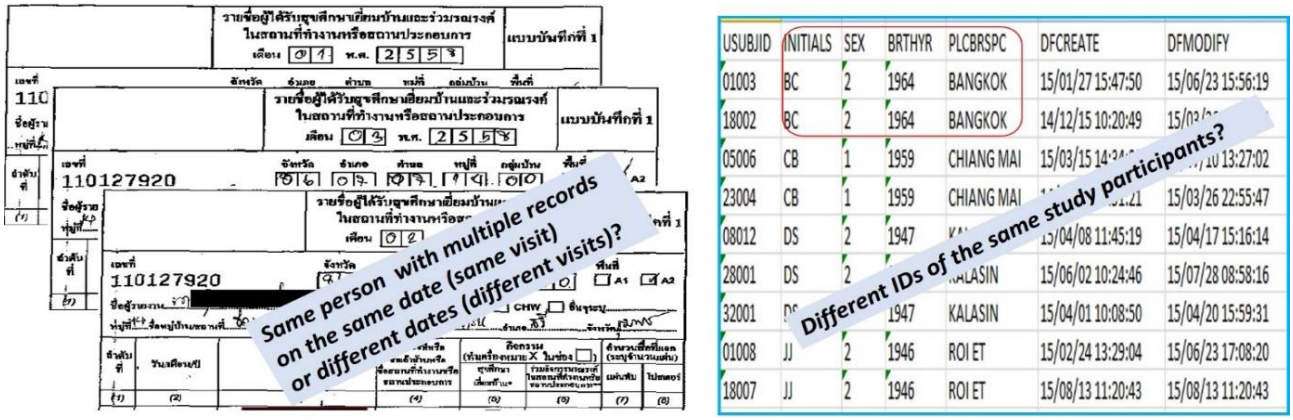

Figure 8. Examples of cross-checking of uniqueness in a set of data

V—Validity, validating the collected data whether they conform to acceptable format, type, or size according to the pre-set rules. The edit check program should be able to detect data values that are out-of-range or deviated from the normal range with unreasonable explanation. There should be standard coding for the open-ended variable. For example, the system should have edit check for unusual white blood cell count. The verbatim of adverse event as reported by the hospital staff must be converted to standard coding scheme (e.g., ICD-11 or MedDRA coding) for data analysis. It is important to train research staff to enter the data according to the data collection manual, e.g., not reporting drug name for the variable that should capture adverse event data.

Figure 9. Examples of checking validity of data

R—Reliability, assuring that analysis of data produces consistent results over time within an individual study participant and/or across different records within the dataset. Reliability of the data can be detected by the inconsistency and/or illogical reason of the data values. Such quality of the data may be observed by basic calculation or after performing data analysis. For example, is it possible that a study participant who has been reported with "confirmed HIV positive" for several visits became "not infected" in the last visit? Is it correct that survival time of the patients, calculated from (date last visit–date diagnosis), are negative, extremely high, or zero? (Figure 10).

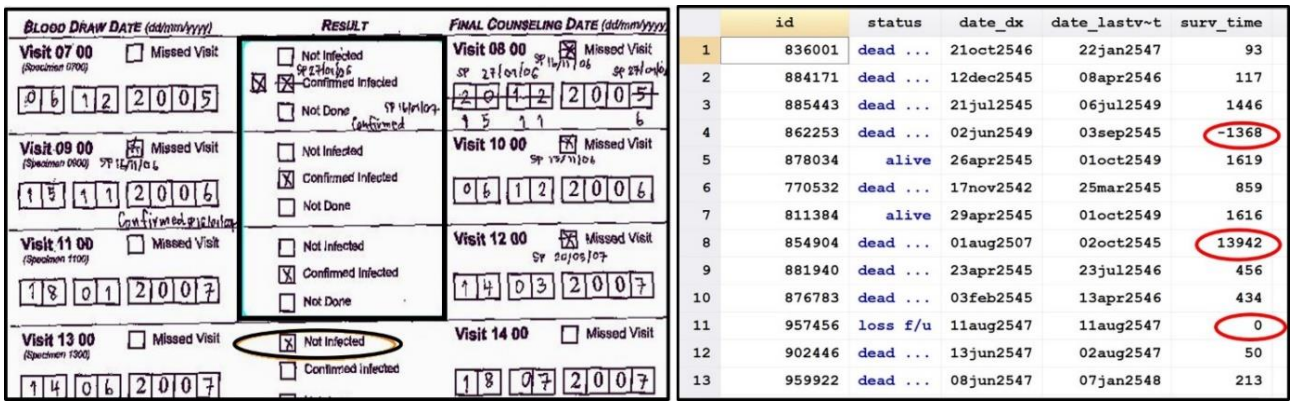

Figure 10. Examples of checking reliability of data within the dataset

R—Relevance, affirming that the data collected according to the protocol requirement. This metric reflects back to the step of data design—what critical variables, including type and size, are needed to answer the research question. Edit check program for the data entry and validation plan are helpful to ensure the collected data are within the format and scope of the study. For example, data values are set according to the validation plan by automated edit check program within the data entry system (Figure 11).

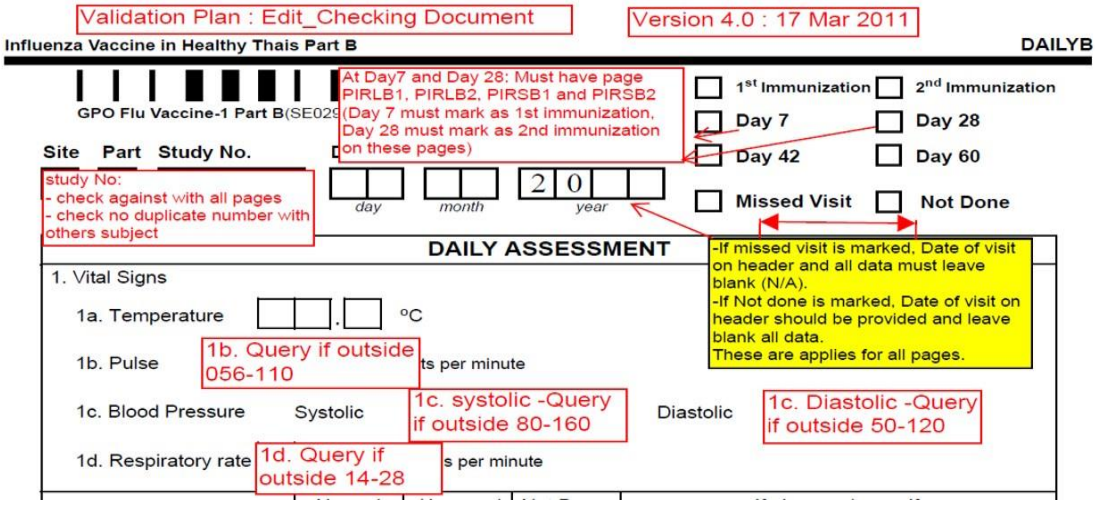

Figure 11. Example of checking data values on data entry screen

Framework for Monitoring Data Quality

One of the frameworks proposed in literature for monitoring data quality include, but not limited to, the followings: ratio of data to errors (how many issues are raised?), number of empty values (how many empty fields are there?), data transformation error rate (if the data are transformed, how often that they are performed incorrectly?), data storage or management costs (how much is the cost of data archival or maintenance?).[21]

In assuring data quality, the data management procedures are required to leave the so-called "audit trail" which will show traceable activities from initial data entry to interim and final reports.[1,20,23] The aim of audit trail is to confirm the whole process such that: the data reported are the data analyzed; the data analyzed are the data recorded on data collection tools; the data on the data collection tools are the data generated from original source; and the data generated are compliant to the study protocol.[23]

Conclusion

A good data quality management with help improve the trustworthiness of your data.[22] Trustworthiness is a product of the people, systems and processes that enable and support the management and production of data.[5] It is important to train research team on data management and governance best practices and provide ongoing monitoring and reeducation.[18] It is essential to assure the quality of study conduct and the trustworthiness of data to achieve the reliable study results.

Suggested Citation

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