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Editorial

Rabies Elimination in Thailand—Still a Ways to Go

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Rabies is a viral, zoonotic disease that is almost uniformly fatal after the onset of symptoms. Though rabies is the cause of approximately 60,000 human deaths each year, it can be prevented by post-exposure prophylaxis with rabies immune globulin and rabies vaccine. Thailand is one of nine Southeast Asian countries that have areas in which rabies is still endemic. Dogs are responsible for more than 99% of human cases globally and the main cause of cases in Thailand.[1]

The World Health Organization (WHO) has determined that it is feasible to eliminate dog-mediated rabies by vaccinating dogs, managing dog populations, preventing dog bites, and making sure that post-exposure prophylaxis is available to all persons.[2] In 2015, a global goal of zero human rabies deaths from dog exposures by 2030 was proposed and the United Against Rabies collaboration, comprising the WHO, the World Organization for Animal Health, and the Food and Agriculture Organization of the United Nations.[3] In 2017, at the urging of Professor Dr Her Royal Highness Princess Chulabhorn Mahidol, Thailand declared a goal of making Thailand human rabies-free by 2020.[4] This goal was set in part because of the progress the country made in reducing rabies cases from more than 50 annual cases before 2000 to less than 10 cases in most years after 2010. The reduction was due in large part to mass dog vaccination and increased accessibility of post-exposure prophylaxis for persons bitten by dogs.[4]

The Thai Ministry of Public Health's Department of Disease Control, in collaboration with the Thai Ministry of Agriculture and Cooperative's Department for Livestock Development and the Thai Ministry of Interior's Department of Local Administration have developed criteria for rabies free zones, which include: 1) no human rabies deaths in the previous two years; 2) no animal specimens positive for rabies in the previous two years; 3) twice yearly surveys of dogs and cats demonstrating that ≥80% are registered; 4) 100% of owned dogs and >80% of all dogs have been vaccinated against rabies; 5) areas have a management system in place that includes shelters for and sterilization of unowned dogs; and 6) commitment to and plan for sustaining the areas as free of rabies.[5] Phuket is in the process of getting an official declaration to become Thailand's first rabies-free province in 2024 and it is expected that more provinces will soon be declared rabies-free.[6]

Challenges to rabies elimination include difficulty accurately estimating, controlling, and vaccinating animal populations; low awareness of the disease among the general population; the limited economic impact from rabies; and the difficulty and cost of reaching residual populations of unvaccinated free-roaming dogs.[7]

Thailand has an estimated one million stray dogs, but has one of the highest all-animal rabies testing rates per 100,000 human population in the world.[8,9] In 2022 detected rabies in more than 100 animal specimens collected in 27 provinces, and Thailand's date for achieving the goal of rabies elimination nationwide has been pushed back to 2030.[8] Maintaining government support and funding; using a One Health approach to engage multiple sectors and local communities; building public awareness about the disease and its risks and conducting mass dog vaccination campaigns; using innovative strategies such as vaccination of dogs with oral rabies vaccine (shown to be effective in vaccinating 65% of the free-roaming dogs in five Thai provinces), and availing WHO guidance and support will assist Thailand in achieving the goal of eliminating human rabies in Thailand by 2030.[7,10]

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SARS-CoV-2 Infections, Vaccination, and Vaccine Effectiveness in Thailand, January 2021–January 2022: Results of a Cohort Study in Four Provinces

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Abstract

We implemented a sero-epidemiological survey of SARS-CoV-2 antibodies in an age-stratified sample of people in Thailand. We used two-stage sampling employing stratified random sampling with official residence lists to recruit 1,200 people in three age strata in Bangkok, Chiang Mai, Nakhon Phanom and Phuket provinces. Serum was screened for SARS-CoV-2 antibodies using enzyme-linked immunosorbent assay (ELISA) and microneutralization assay. We collected symptom and vaccination data weekly and tested participants who met a COVID-19-like illness (CLI) case definition by rRT-PCR. Serum for SARS-CoV-2 antibodies was collected and tested again in January 2022. We estimated vaccine effectiveness using multi-level Poisson regression with propensity score stratification to control for differences in healthcare-seeking behavior. Of 1,200 people enrolled in January 2021, 5 (0.4%; 95% confidence interval 0.16–1.16) had antibody detected by ELISA at baseline, and none tested positive by microneutralization. From January 2021 to January 2022, 23% of participants (278/1,200) reported CLI and 18% of CLI cases (50/278) tested positive for SARS-CoV-2 by rRT-PCR. In January 2022, 87% of participants (955/1,101) had SARS-CoV-2 antibodies detected by ELISA. Ninety-eight percent (1,034/1,045) received at least one dose of COVID-19 vaccine and did not get infection. Vaccine effectiveness against hospitalization was 72% for two doses and 98% for three doses of any vaccine. Low SARS-CoV-2 seroprevalence in 2021 suggests that Thailand successfully prevented COVID-19 infections through non-pharmaceutical interventions during the first year of the pandemic. High seroprevalence in 2022 was driven by vaccination.

Keywords: antibodies, SARS-CoV-2, seroprevalence, Thailand, vaccine effectiveness

Background

Thailand was the first country after China to identify a laboratory-confirmed case of severe acute respiratory coronavirus 2 (SARS-CoV-2) infection. Between 13 Jan 2020 and 1 Apr 2021, Thailand reported 28,889 laboratory-confirmed coronavirus disease 2019 (COVID-19) infections.[1] Studies suggest that quarantine for international travelers and other nonpharmaceutical interventions (NPIs) implemented by the government of Thailand, as well as high compliance with NPIs, contributed to limiting transmission of SARS-CoV-2 during the first 15 months of the pandemic.[2–8]

As Thailand transitions from a pandemic to an endemic model of SARS-CoV-2 response, data on antibody profiles and vaccine effectiveness are needed to assess the impact of pharmaceutical and nonpharmaceutical interventions. To gauge the proportion of persons in Thailand with prior SARS-CoV-2 infections or vaccinations and estimate vaccine effectiveness, a sero-epidemiological survey was conducted based on the World Health Organization Unity studies protocol between January 2021 and January 2022 in four major provinces in Thailand.[3]

Methods

We selected one major province in each of the four regions of Thailand: Chiang Mai, Nakhon Phanom, Bangkok and Phuket provinces. In Bangkok Province, a two-stage sampling was employed. We randomly selected 5 (of 50) districts with probability proportional to size of the population. Stratifying the official list of Thai registered citizens into three age groups (5–18, 19–59, and ≥60 years), we then conducted simple random sampling within each age group. We recruited 75 persons aged 5–18, 150 persons aged 19–59, and 75 persons aged 60 years and older in each province. If participants could not be contacted or refused, we replaced them with the next person on the official list within the same age group until achieving the specified sample sizes. Estimate sample size equation was,

$$n = \frac{Z_{1-\alpha/2}^2\, p(1-p)}{d^2}$$

Where Z (assuming significance 0.05) was 1.96, d was margin of error (0.05), and p was 0.5.

We determined that 300 people in each province would permit seroprevalence estimates of up to 50% prevalence with confidence limits of ± 5%; 1,200 total participants were thus required for four provinces. We back-calculated power to detect a prevalence of 1% based on the same assumptions, using the formula below:

$$n = \left[\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\frac{p_1 - p_0}{\sqrt{p_1(1-p_1)}}}\right]^2$$

Where $Z_{1-\alpha/2}$ (assuming significance 0.05) was 1.96, $Z_{1-\beta}$ (assuming power 80%) was 0.84, p_0 was hypothesized proportion (50% seroprevalence) and p_1 was the measured proportion (1%).

We included people who could communicate in Thai language, were on the official lists and resided in the four provinces at the time of survey enrolment. Exclusion criteria included contraindications to venipuncture and nasopharyngeal or throat swabs.

We collected the blood specimens and the data on demographics, risk factors, mask use, history of COVID-19-like illness (CLI) (presence of one or more of the following: fever, cough, shortness of breath, myalgia, sore throat, loss of taste or smell, or diarrhea) since the beginning of the pandemic, history of positive SARS-CoV-2 rRT-PCR test results since the beginning of the pandemic, and travel history. Blood was again collected from all participants in January 2022.

After enrolment, participants were weekly contacted by phone and asked about CLI symptoms or vaccination in the preceding week. If participants reported CLI, they were asked to visit the nearest health facility for a nasopharyngeal swab, subsequently tested for SARS-CoV-2 by rRT-PCR.

Serum was received within two weeks at Mahidol University and screened within two weeks for SARS-CoV-2 total immunoglobulin using the sandwich enzyme-linked immunosorbent assay (ELISA) (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., China), which uses the receptor binding domain (RBD) of the SARS-CoV-2 spike protein as the test antigen. Previously tested in a Thai population found sensitivity of the Wantai test to be 100% and specificity 99.2%; multiple studies outside of Thailand reported sensitivities from 62% to 98%.[4–7]

The sandwich ELISA assay was performed per the Wantai kit instructions. Staff at Mahidol University performed cytopathic effect based microneutralization assay following the protocol previously described in a biosafety laboratory level 3.[4]

For descriptive statistics, we computed number and percent of participants by gender and mean with standard deviation by province and age group. *P*-values for analysis of variance were generated. All analyses were performed using STATA 14 (College Station, TX, USA). We calculated the crude seroprevalence and 95% confidence intervals (CI) of SARS-CoV-2 as the percentage of participants with

positive SARS-CoV-2 antibodies. The national seroprevalence estimations were calculated, weighted by age, gender and provincial population size in Thailand, using 2021 population data.[8]

Associations between demographic variables and vaccination, hospitalization were estimated with negative binomial regression. Vaccine effectiveness (VE) was estimated as 100% x (1–rate ratio of rRT-PCR-confirmed COVID-19 infections in vaccinated cohort versus unvaccinated cohort). VE was estimated for infection with fever and infection with hospitalization. These outcomes represented any, mild to moderate, and severe infection.[9] Propensity score stratification was included in the VE estimation to approximate likelihood of accessing and receiving COVID-19 vaccine. To measure time-to-event duration of vaccine dose in multivariable model, the duration of each dose started after receiving the vaccine for 14 days and ended when either the next vaccine dose duration started, developing the study outcome, or loss to follow-up. Propensity scores were constructed using multivariable logistic model that included pre-vaccination variables (age, gender, educational, occupational, smoking status, income, comorbidity, body mass index, history of influenza vaccination in the previous year, and facemask using in public) to estimate the probability of booster 3rd dose of COVID-19 vaccination. Poisson regression with log person-time at risk as an offset was used for VE estimate calculation. A multi-level mixed effect model was applied to the Poisson regression to account for propensity score stratification.

The protocol was approved by the Ethical Review Committee for Research related to COVID-19 Disease or Public Health Emergency, Department of Disease Control, Thai Ministry of Public Health.

Results

During 18 Dec 2020 to 2 Feb 2021, we identified 1,898 people for enrollment. Of those, 440 (23%) people were not available, 33 (8%) refused to participate, and 21 (5%) did not show up at the clinic. In total, 698 (37%) refused or were not available; 384 men and 816 women were included in the survey. Of these 1,200 participants, 452 (37.7%) reported experiencing at least one CLI prior to enrolment, none reported a previous laboratory-confirmed SARS-CoV-2 test result or infection at time of baseline serum collection, and 92% reported "always" or "mostly" wearing masks outside of the home (Table 1).

Serum testing at baseline identified five positive results for total antibody to SARS-CoV-2 by ELISA (0.4%, 95% CI 0.16–1.16), and 5 borderline results. Four of the five positive cases were present in the 19–59-year-old group and one positive in the 60 year and older age group. One positive result was found in each of Nakhon Phanom and Phuket provinces, and three were in Chiang Mai Province. Of note, none of these five ELISA positive cases was confirmed positive for neutralizing antibodies to SARS-CoV-2 by microneutralization assay, suggesting that these were recent infections and neutralizing antibodies had yet to develop.

Table 1. Baseline characteristics of survey participants in the four provinces, December 2020–January 2021 (n=1,200)

Characteristics	Total (n=1,200)	Bangkok (n=300)	Nakhon Phanom (n=300)	Phuket (n=300)	Chiang Mai (n=300)	*P*-value
Gender, n (%)						
Male	384 (32.0)	85 (28.3)	103 (34.3)	98 (32.7)	98 (32.7)	0.433¶
Female	816 (68.0)	215 (71.7)	197 (65.7)	202 (67.3)	202 (67.3)	
Age in years, mean (SD)	**41.4 (21.4)**	**40.2 (21.8)**	**41.5 (21.7)**	**41.5 (21.0)**	**42.4 (21.4)**	**0.926#**
Age group (years), mean (SD)						
5–18	11.9 (3.6)	11.0 (3.7)	12.2 (3.6)	12.0 (3.4)	12.4 (3.7)	0.914#
19–59	43.4 (11.6)	41.5 (12.1)	42.7 (10.8)	43.9 (11.1)	45.4 (12.0)	0.404#
≥60	66.9 (5.4)	66.5 (5.8)	68.6 (5.7)	66.0 (4.8)	66.5 (4.9)	0.195#
Body mass index*, mean (SD)	**25.3 (5.0)**	**24.7 (4.8)**	**24.7 (4.6)**	**26.5 (5.9)**	**25.3 (4.4)**	**<0.001#**
Obesity†	143 (16.1)	28 (12.6)	30 (13.5)	55 (24.6)	30 (13.8)	0.002¶
Face mask—ever used when travelling outside‡, n (%)	**1,196 (99.7)**	**299 (99.7)**	**299 (99.7)**	**298 (99.3)**	**300 (100)**	**0.906¶**
Always	889 (74.8)	253 (84.3)	147(49.0)	246 (82.0)	243 (81.0)	<0.001¶
Mostly	203 (16.9)	40 (13.3)	75 (25.0)	42 (14.0)	46 (15.3)	<0.001¶
Sometimes	92 (7.7)	6 (2.0)	65 (21.7)	10 (3.3)	11 (3.7)	<0.001¶
Rarely	12 (1.0)	0 (0)	12 (4.0)	0 (0)	0 (0)	-
Never	4 (0.3)	1 (0.3)	1 (0.3)	2 (0.7)	0 (0)	0.906
Change in or loss of taste§, n (%)	**1 (0.1)**	**1 (0.3)**	**0 (0)**	**0 (0)**	**0 (0)**	**1.000¶**
Change in or loss of smell§,n (%)	**2 (0.2)**	**0 (0)**	**2 (0.7)**	**0 (0)**	**0 (0)**	**0.249¶**

**For age ≥20 years only. †Body mass index ≥30 (age ≥20 years). ‡Self-reported, "ever wear a face mask when travelling outside the home". §Self-reported. ¶p-value calculated using Exact probability test. #p-value calculated using one-way ANOVA, comparing across participants in each province. SD: standard deviation.*

From enrollment to January 2022, 23% (278/1,200) of participants reported CLI. All participants with CLI were tested for SARS-CoV-2 and 18% (50/278) were positive (Table 2). The epidemic curve of CLI and SARS-CoV-2 cases on the cohort approximated the national curve of cases, both peaking in late July/early August (Figure 1). Among the 50 SARS-CoV-2 cases, the most common symptoms reported were sore throat (62%) cough (60%), and fever (42%), and 78% were hospitalized (Supplementary table 2).

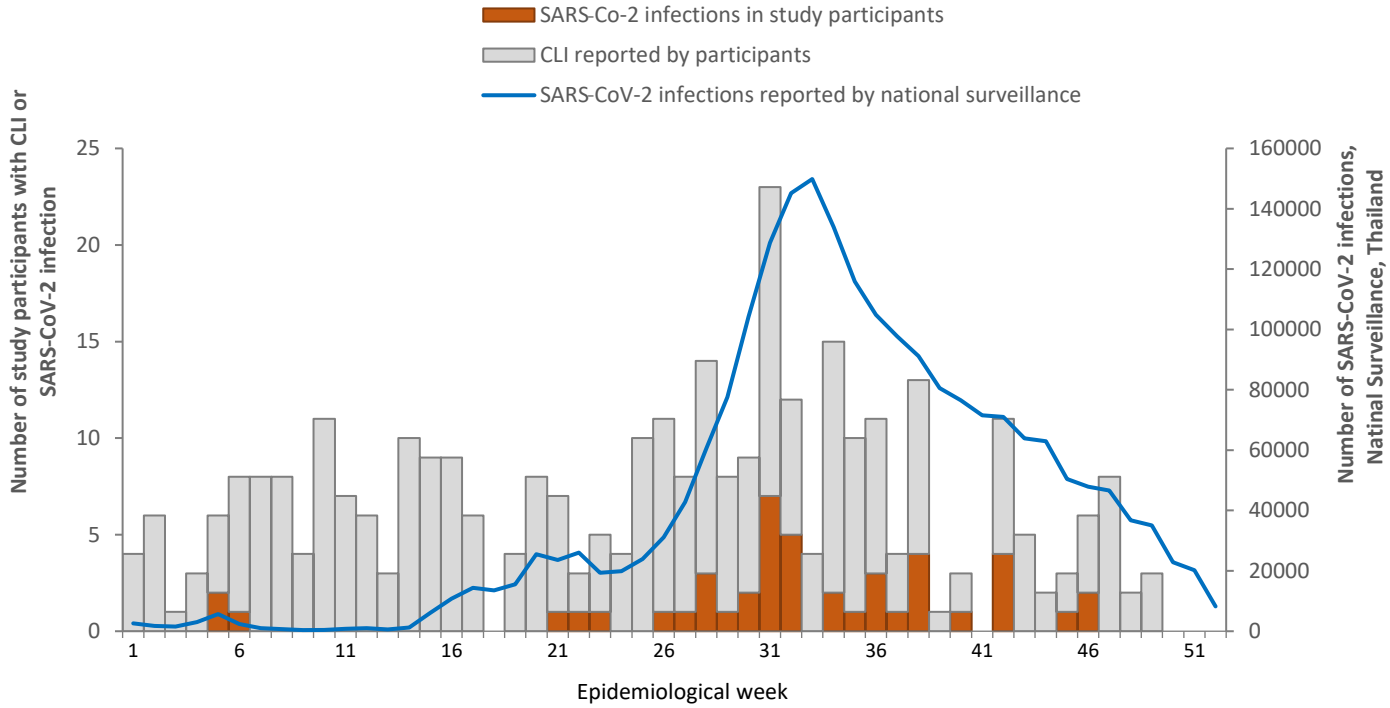

Figure 1. SARS-CoV-2 infections and cases of COVID-19-like illness among study participants and from national surveillance data, Thailand, 2021

In January 2022, 1,034 (93%) study participants reported being vaccinated with one to four doses of a combination of Sinovac, Sinopharm, AstraZeneca, Pfizer and Moderna vaccines; participants received 24 different combinations of vaccine (Supplementary figure 1). Of 1,200 participants, 1,003 had received two doses of vaccine by the end of January 2022, and an additional 31 had received one dose.

On 10 Jan 2022, we drew serum from 1,101 participants. ELISA test results indicated that 955 (87%) of participants had SARS-CoV-2 antibodies, suggesting that they had been either infected or vaccinated or both (Table 2). Weighted by age, gender, and population size, we estimated that national overall prevalence was 87% (95% CI 85.0–88.5). Weighted by gender and population size, we estimated that national age-specific prevalence of people with total antibodies to SARS-CoV-2 detectable by ELISA was 64.7 (95%) CI 58.8–70.6) for ages 5–18, 94.9 (95% CI 93.0–96.7) for ages 19–59, and 93.0 (95% CI 90.0–96.0) for ages 60 and older. By province, total antibodies were 89.6 (95% CI 86.5–92.7) for Chiang Mai Province, 78.4 (95% CI 73.8–82.9) for Nakhon Phanom Province, 88.7 (95% CI 85.6–91.8) for Phuket Province and 90.8 (95% CI 85.6–91.8) for Bangkok Province (p-value <0.001).

Of 124 participants who were not vaccinated and had not tested positive for COVID-19, 16.1% had antibodies to SARS-CoV-2, suggesting they either did not report symptoms and were not tested or they did not report vaccination, or they had asymptomatic infection (Table 2).

Groups of participants with multiple vaccinations or booster doses tended to have larger proportions of people in the group test positive for SARS-CoV-2 antibodies (Table 2). Of 18 participants who had received one dose of vaccine and had not tested positive for COVID-19, 8 (44%) had SARS-CoV-2 antibodies detected by ELISA. Of participants who received two doses of vaccine and had not tested positive for COVID-19, 93.3% had antibodies to SARS-CoV-2, and of participants who received more than two doses of vaccine, 98.9% had antibodies to SARS-CoV-2. Six of seven (86%) participants who were not vaccinated but tested positive for COVID-19 had SARS-CoV-2 antibodies, and 100% of participants who received one or more doses of vaccine and had also tested positive for COVID-19 by rRT-PCR had SARS-CoV-2 antibodies.

Table 2. Antibody result stratified by COVID-19 vaccination and SARS-CoV-2 infection (CLI and vaccination update 31 Jan 2022)

	Not vaccinated (n= 166)		1 dose (n= 31)		2 doses (n= 434)		More than 2 doses (n= 569)		Total
PCR result after CLI	COVID – (n=155)	COVID + (n=11)	COVID – (n=26)	COVID + (n=5)	COVID – (n=413)	COVID + (n=21)	COVID – (n=556)	COVID + (n=13)	1,200
CLI cases, month 0 to 12	36	11	4	5	70	21	118	13	278
Positive ELISA results, month 12	16.1% 20/124*	85.7% 6/7*	44.4% 8/18*	100.0% 4/4*	93.3% 346/371*	100.0% 18/18*	98.9% 540/546*	100.0% 13/13*	86.7% 955/1101
COVID positives with fever, n (%)	-	5 (45.5)	-	2 (40.0)	-	11 (52.4)	-	3 (23.1)	
COVID positives hospitalized, n (%)	-	10 (90.9)	-	5 (100.0)	-	16 (76.2)	-	8 (61.5)	

**Denominator is participants who could visit for blood draw at 12-month time point. CLI: COVID-19-like illness.*

Approximately 4% of participants were exposed to SARS-CoV-2 antigen either through vaccination or infection but did not test positive for SARS-CoV-2 antibodies at the one-year timepoint. For these participants, the median number of days from exposure to the one-year blood draw ranged from 16 (for participants who received only one dose of vaccine) to 189 (in the participant who was infected) (Supplementary table 3).

Of 1,003 participants who had received two or more doses of vaccine, 34 (3.3%) later reported CLI symptoms and tested positive for SARS-CoV-2 by rRT-PCR at least two weeks after the second dose of vaccine. None had multiple infections.

Two doses of any vaccine were 61% (95% CI 10–84%) effective against infection, and three doses were 93% (95% CI 70–99%) effective. Similarly, two doses of vaccine were 72% (95% CI 25–90%) effective against hospitalized infection, and three doses were 98% (95% CI 80–99%) effective. Two or more doses were 80% (95% CI 33–94%) effective against rRT-PCR-confirmed infection with fever (Table 3). We repeated the analysis with common combinations of vaccine. We found the AstraZeneca-AstraZeneca-Pfizer combination to have effectiveness of 94% (95% CI 40–99%) against infection (Supplementary table 4).

Table 3. VE against laboratory confirmed SARS-CoV-2 infection, infection with hospitalization, and infection with fever*

	Person-year	Positive PCR[†] n (rate/100 person-year)	Rate ratio[‡] (95% CI)	VE (95% CI)	*P*-value
Total infection					
Unvaccinated (reference group)	158.69	11 (6.93)	Reference	-	-
Partial vaccinated[¶] (1 dose)	31.21	1 (3.20)	0.42 (0.05, 3.47)	58% (-247, 95%)	0.421
Complete vaccinated (fully 2 dose)	441.77	14 (3.17)	0.39 (0.16, 0.90)	61% (10, 84%)	0.028
Booster 3 dose	449.37	3 (0.67)	0.07 (0.01, 0.30)	93% (70, 99%)	<0.001
Booster 4 dose	124.58	0 (0.00)	-0.07 (-0.11, -0.03)[§]	-	0.001
At least 2 doses	1,015.39	17 (1.67)	0.23 (0.10, 0.52)	77% (48, 90%)	<0.001
At least 3 doses	573.95	3 (0.52)	0.05 (0.01, 0.24)	95% (76, 99%)	<0.001
Hospitalized infection					
Unvaccinated (reference group)	158.69	10 (6.30)	Reference	-	-
Partial vaccinated (1 dose)	31.21	1(3.20)	0.46 (0.05, 3.89)	54% (-289, 95%)	0.475
Complete vaccinated (fully 2 dose)	441.77	10 (2.26)	0.28 (0.10, 0.75)	72% (25, 90%)	0.011
Booster 3 dose	449.37	1 (0.22)	0.02 (0.002, 0.20)	98% (80, 99.8%)	0.001
Booster 4 dose	124.58	0 (0.00)	-0.06 (-0.10, -0.02)[§]	-	0.003
At least 2 doses	1,015.39	11 (1.08)	0.14 (0.05, 0.36)	86% (64, 95%)	<0.001
At least 3 doses	573.95	1 (0.17)	0.01 (0.001, 0.16)	99% (84, 99.9%)	<0.001

Table 3. VE against laboratory confirmed SARS-CoV-2 infection, infection with hospitalization, and infection with fever* (cont.)

	Person-year	Positive PCR† n (rate/100 person-year)	Rate ratio‡ (95% CI)	VE (95% CI)	*P*-value
Infection with Fever					
Unvaccinated (reference group)	158.69	5 (3.15)	Reference	-	-
Partial vaccinated (1 dose)	31.21	0 (0.00)	-0.03 (-0.06, -0.004)§	-	0.408
Complete vaccinated (fully 2 dose)	441.77	8 (1.81)	0.46 (0.14, 1.54)	54% (-54, 86%)	0.206
Booster 3 dose	449.37	0 (0.00)	-0.03 (-0.06, -0.004)§	-	0.001
Booster 4 dose	124.58	0 (0.00)	-0.03 (-0.06, -0.004)§	-	0.055
At least 2 doses	1,015.39	8 (0.79)	0.20 (0.06, 0.67)	80% (33, 94%)	0.011
At least 3 doses	573.95	0 (0.00)	-0.03 (-0.06, -0.004)§	-	0.005

**Fever was the main symptom.[11] †Vaccinated group, included only episodes which after final vaccination dose >14 days in the analysis. ‡Multilevel poison regression with propensity score (to booster vaccination) stratification analysis. §Rate difference. ¶ To classify the number of vaccination dose, for the first dose was counted after take blood draw at least 14 days, second dose was after first dose 21 days and third dose was after second dose 90 days and fourth dose was after third dose 90 days. VE: vaccine effectiveness = (1 – rate ratio) x 100. CI: confidence interval.*

We found no characteristics, including age group or obesity, associated with infection and hospitalization among vaccinated participants. Twenty-two percent of men and 10% of women were unvaccinated, as were 43% of participants aged 5–18. Factors associated with not being vaccinated were male (rate ratio (RR) 0.67, 95% CI 0.56–0.79), and young age group (age 5–18 RR 0.22, 95% CI 0.18–0.25) (Table 4). (Supplementary tables 5, 6).

Table 4. Characteristic and prognostic factor for vaccination

Characteristics	Vaccinated (n=1,034) (n, %)	Not vaccinated (n=166) (n, %)	Rate ratio§ (95% CI)	*P*-value
Gender				
Male	296 (28.6)	87 (52.4)	0.67 (0.56, 0.79)	<0.001
Female	738 (71.4)	79 (47.6)	-	-
Age in years, mean (SD)	**45 (19)**	**19 (20)**	**-**	**<0.001¶**
Age group (years)				
5–18	172 (16.6)	128 (77.1)	0.22 (0.18, 0.25)	<0.001
19–59	579 (56.0)	22 (13.2)	4.23 (2.85, 6.26)	<0.001
≥60	283 (27.4)	16 (9.6)	2.84 (1.76, 4.57)	<0.001
Body Mass Index*, mean (SD)	**25 (5.0)**	**25 (4.7)**	**-**	**0.461¶**
Obesity†	136 (16.0)	6 (16.2)	0.99 (0.47, 2.09)	0.972
Face mask—ever used when travelling outside‡				
Always	2 (0.2)	2 (1.2)	0.16 (0.02, 1.13)	0.066
Mostly	784 (75.8)	106 (63.9)	1.19 (1.05, 1.34)	0.005
Sometimes	169 (16.3)	34 (20.5)	0.80 (0.57, 1.11)	0.180
Rarely	70 (6.8)	22 (13.3)	0.51 (0.33, 0.80)	0.003
Never	9 (0.87)	2 (1.20)	0.72 (0.16, 3.31)	0.676
Household income (USD)#				
<145 USD	146 (14.1)	19 (11.5)	1.03 (0.97, 1.10)	0.317
145–<290 USD	173 (16.7)	31 (18.7)	0.98 (0.92, 1.05)	0.551
290–<581 USD	265 (25.6)	51 (30.7)	0.96 (0.91, 1.02)	0.189
581–<871 USD	171 (16.5)	31 (18.7)	0.98 (0.92, 1.04)	0.512
871–<1,161 USD	120 (11.6)	14 (8.4)	1.05 (0.98, 1.11)	0.175
≥1,161 USD	20 (12.1)	159 (15.4)	1.04 (0.98, 1.10)	0.223

**For age ≥20 years only. †Body mass index ≥30 (age ≥20 years). ‡Self-reported, "ever wear a face mask when travelling outside the home". §Rate ratio, negative binomial regression. ¶t-test. SD: Standard deviation. CI: confidence interval. #Based on 1 US dollar (USD) was equivalent to 34.43 Thai Baht (THB).*

There were more women in the 19–59 and more than 60 age groups, women in the study had higher risk of being obese (RR 1.53, 95% CI 1.08–2.17), and were more likely to report wearing face masks. (Supplementary table 7).

Discussion

In January 2022, 955/1,101 (87%) people in the cohort had antibodies to SARS-CoV-2 detected by ELISA. Of the study population, 1,034/1,200 (93%) reported being vaccinated, 50/1,200 (4.2%) had CLI symptoms and rRT-PCR-confirmed infection, and 20/124 (16.1%) who were not vaccinated, did not report CLI symptoms or test positive for COVID-19 by rRT-PCR, had antibodies for SARS-CoV-2 by ELISA. Two doses of any combination of vaccine were 72% (95% CI 25–90%) effective against hospitalized infection, and three doses were 98% (95% CI 80–99%) effective. These results suggest that there is a high degree of immunity in the Thai population, and they highlight the importance of delivering a third booster dose. Continued monitoring of VE and antibody waning will be important in the future.

At baseline we found very low (<1%) prevalence of SARS-CoV-2 antibodies, suggesting that a low proportion of people in Thailand had been infected at the time of data collection.

At the time of baseline data collection, national COVID-19 surveillance had identified 11,649 cumulative COVID-19 cases in Bangkok Province (42.9/100,000 persons), 24 (1.3/100,000 persons) in Chiang Mai Province, 0 in Nakhon Phanom Province, 44 (10.6/100,000 persons) in Phuket Province, and a total of 11,649 (16.8/100,000 persons) cases nationally.[10]

A review of population seroprevalence estimates from 47 studies in several countries worldwide found the range was 0.4–22.1% with a pooled estimate of 3.4% (95% CI 3.10–3.73%).[11] Our point estimates in Thailand in January 2021 (<1%) are at the low end of this range was similar to the global pooled estimate. One reason of high seroprevalence later in 2022 is the omicron variant that render the 2021 non-pharmaceutical intervention not effective. Our findings are consistent with Thai national surveillance data, which indicated a lower cumulative incidence of cases in Thailand during 2020 relative to most other countries in the world, followed by waves of infection and robust vaccination efforts in 2021.[12]

Self-reported vaccine coverage of at least two doses was 84% in the cohort; this was higher than national coverage estimates of ~70% at the time.[13] It is possible that because our study population lived in urban areas, they had better access to vaccine. In January 2022, 87% of participants had antibodies to SARS-CoV-2 by ELISA, while 4% (of vaccinated participants and a natural infected case) had no detectable antibodies by ELISA. Explanations for finding fewer participants with antibodies than had been vaccinated and infected include: one dose of vaccination may not be enough to induce the antibody response, the date of blood collection may have been too soon after vaccination for antibody development, or antibodies may have waned after initial exposure. These antibody profiles may help to explain the prolonged Omicron peak (January–May) Thailand experienced in 2022. When compare the antibodies to SARS-CoV-2 by ELISA between age group we found antibodies level was lowest in participants ages 5–18 years. Thailand started to provide the vaccine for children age above 5 years in January 2022.[13] Late vaccination in this age group may affect to antibody response.

Low prevalence through mid-2021 may be explained by widespread NPIs implemented by the Thai government, such as masking requirements, restrictions on gatherings and population movements, quarantine for international travelers, high local rates of adherence to these NPIs, and rapid identification and response to clusters of COVID-19 cases.[14–17] The low seroprevalence in Thailand, and some other countries of the Lower Mekong Delta during the first year of the pandemic, has also been attributed to ongoing investments in pandemic preparedness and outbreak response, and in the training of community responders. [18] As such, there may be more to learn from the first year of Thailand's pandemic response that may be applied to the future preparedness of both high- and low-income countries globally. All high seroprevalence among 4 provinces in the study at the end of 2022 showed the real situation in the Thailand when we consider by region.

We estimated VE of 72% to prevent hospitalization for two doses of all vaccine combinations against all SARS-CoV-2 variants circulating in Thailand during the study period, and 98% for three doses. VE tended to increase with increasing doses of vaccine and with vaccination plus infection. These results are similar to those reported elsewhere.[19,20] VE of these vaccines against Omicron and Omicron subvariants may be less than against other variants.[21] The Omicron wave occurred in Thailand during January–May 2022 and our data likely do not reflect VE against Omicron.

Groups with lower vaccine coverage included men, people aged 5–18 years, and people reporting low-income status. Low coverage in the young (5–18 years) age group may have been due to later implementation of vaccination programs due to delays in regulatory approval.

Limitations

There were 23% of participants could not able to be contacted. Many people were not available because they had returned to their home villages, especially from Phuket and Chiang Mai because they had lost their jobs due to the depressed tourist economy. We did not have sufficient sample size to asess VE for each combination of vaccine or for SAR-CoV-2 variants. Early in the pandemic, national policy required that all people testing potitive for COVID-19 be hospitalized regardless of severity of severity of infection; this may account for the high rate of hospitalization reported, although it is not likely that this biased VE estimates because vaccines were not available during this period this perios. Participants in this survey were randomly selected from four provinces, and although we weighted for gender, age and population structure, results may only approximate prevalence in the national population of Thailand. This may be especially true when comparing data beteween urban and rural areas. Other limitations for VE estimation are 1) the VE could decline over time due to immunity waning, and 2) the calendar period of follow-up time between comparison groups may not be the same.

Recommendations

Next study should assess T-cell responses to measure longer-term immunity and estimates of longer-term protection against severe disease. An exploration of antibody of antibody waning over time and factors associated with this would be useful to inform continuing pandemic response policy.

Conclusion

A high proportion of study participants had SARS-CoV-2 antibodies, and VE for three doses of vaccine was 98%. As Thailand shifts from a pandemic to endemic model of response, ensuring high coverage of third booster doses of vaccine will be important.

Suggested Citation

Nakphook S, Davis WW, Prasert K, Ditsungnoen D, Lerdsamran H, Puthavathana P, et al. SARS-CoV-2 infections, vaccination, and vaccine effectiveness in Thailand, January 2021–January 2022: results of a cohort study in four provinces. OSIR. 2023 Dec;16(4):174–82. doi:10.59096/osir.v16i4.264238.

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Evaluation of a Surveillance System on Multidrug-resistant Tuberculosis in Bangladesh

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Abstract

In 2017, the World Health Organization reported that 558,000 people were diagnosed with multidrug-resistant tuberculosis (MDR-TB) or rifampicin-resistant tuberculosis. In Bangladesh, the MDR-TB rate is 1.6% of new cases and 29.0% of previously treated cases. We evaluated the MDR-TB surveillance system to assess its simplicity, timeliness, data quality, stability, flexibility, and usefulness following the guideline of the United States Centers for Disease Control and Prevention. Stakeholders reported that the system was simple and useful for monitoring the program's performance. However, there was a need to improve the timeliness, data quality and overall coordination between health facilities and the National Tuberculosis Control Program (NTP). Data from all reporting centers did not reach the NTP timely. There were duplication of data and missing demographic characteristics. The surveillance system needs specific objectives, permanent funding and more attention from the government to ensure its stability. A unified electronic data entry mechanism can be achieved using the District Health Information System software in collaboration with the Management Information System of Directorate General of Health Service, Bangladesh National Tuberculosis Program with unique patient identification.

Keywords: multidrug-resistant tuberculosis, National Tuberculosis Control Program, surveillance, Bangladesh, United States Center for Disease Control and Prevention

Introduction

In 2017, the World Health Organization reported 558,000 new cases of multidrug-resistant tuberculosis (MDR-TB) and approximately 230,000 related deaths.[1] Every year, 90 to 100 MDR-TB cases are reported in the United States.[2] However, most cases live in India, South Africa, China, and Russia.[3] In Bangladesh, the MDR-TB prevalence is 1.6% among new cases and 29.0% among previously treated cases.[4]

To address the MDR-TB problem in Bangladesh, the country obtained support from the Global Fund to Fight Against AIDS, Tuberculosis, and Malaria. This was a pilot project at the National Institute of Diseases of the Chest and Hospital (NIDCH). Enrollment of patients started in August 2008.[5] Several non-governmental organizations and institutes became official partners of the National Tuberculosis Control Program (NTP). The relationship between NTP and most of these partner agencies is governed through a memorandum of understanding.

In Bangladesh, tuberculosis surveillance is conducted by the National TB Control Program in collaboration with 34 non-governmental organizations (NGO).[5] The NTP defines MDR-TB as tuberculosis that is resistant to isoniazid and rifampicin, the two most powerful first-line drugs used to treat tuberculosis.[5]

Surveillance can be used to identify public health emergencies, seasonal patterns of disease, monitor interventions, and document disease burden. The primary goal of the NTP MDR-TB surveillance system is to prevent the emergence of resistance to second-line drugs and transmission of drug-resistant tuberculosis.[6] The objective of this study was to evaluate the MDR-TB surveillance system in Bangladesh in terms of simplicity, timeliness, data quality, stability, flexibility and usefulness. This first-

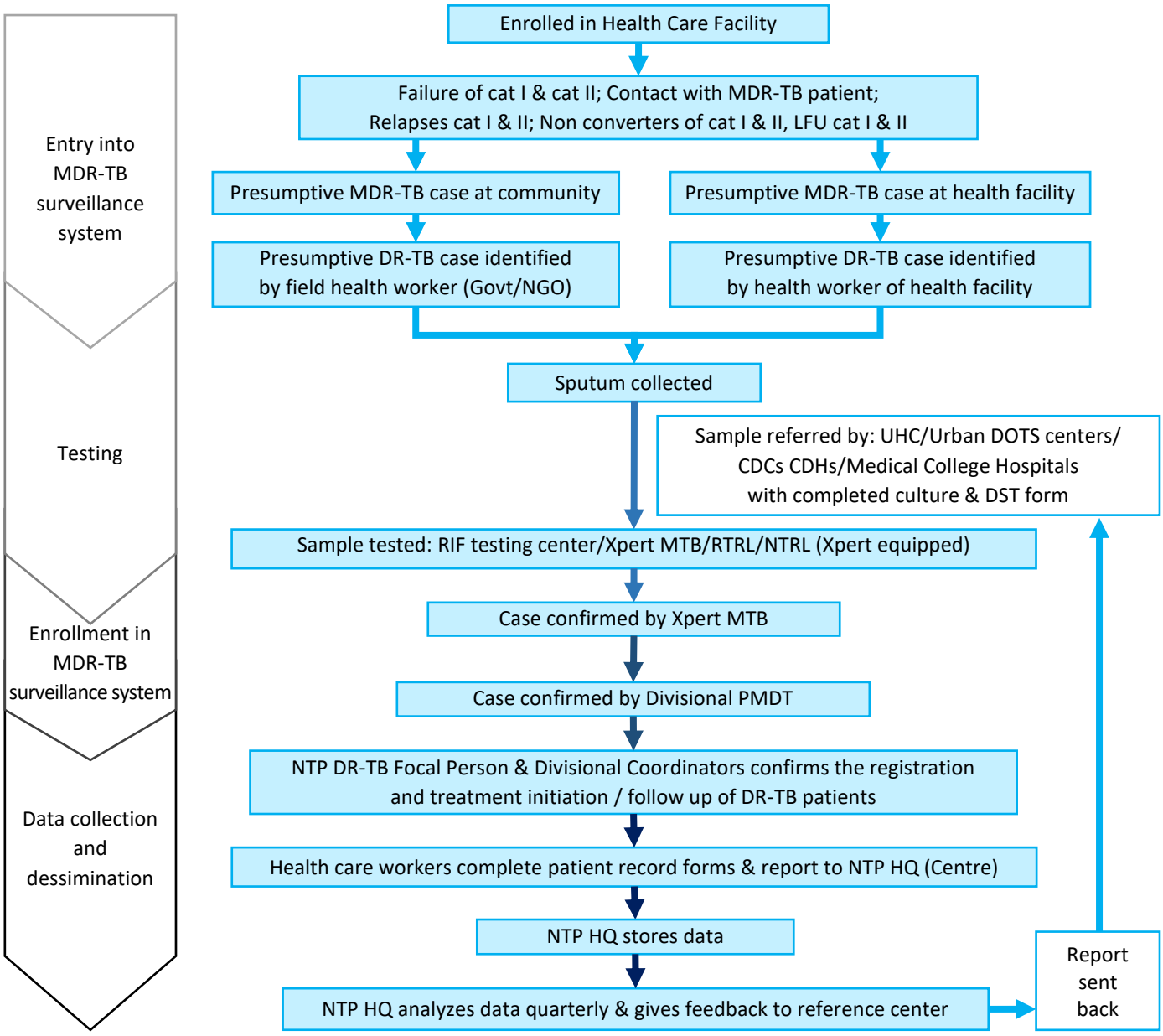
time evaluation will help to improve the quality of the surveillance system.

Methods

We followed the United States Centers for Disease Control and Prevention (U.S. CDC) 2001 guidelines for assessment using a mixed methods approach.[7] The evaluation obtained surveillance data between 2008 and 2015 from the NTP and interviewed the key focal persons and laboratory personnel at surveillance sites.

Key Informants

Stakeholders were those who received data from the surveillance system and who provided input on the system attributes to be evaluated. The major stakeholders were the MDR-TB focal persons at the NTP, NIDCH, National Tuberculosis Reference Laboratory (NTRL), programmatic management of drug-resistant tuberculosis coordinator, Regional Tuberculosis Reference Laboratory, NGO partners and relevant staff at the surveillance sites. Face-to face interviews were conducted with directors and key staff of these organizations to understand how the data were used and if the evaluation would be beneficial to their program. Based on stakeholder engagement, interest and evaluation objectives, the following attributes were assessed: simplicity, timeliness and data quality (quantitative variables) as well as stability, flexibility, and usefulness (qualitative variables).



cat: category. LFU: lost to follow up. DR-TB: drug resistant tuberculosis. NGO: non-government organization. UHC: Upazilla Health Complex. CDC: chest disease clinic. CDH: Chest Disease Hospital. DST: drug susceptibility testing. RIF: resistance to rifampicin. MTB: Mycobacterium tuberculosis. RTRL: Regional TB Reference Laboratory. NTRL: National TB Reference Laboratory. NTP: National TB Control Program. HQ: headquarters. PMDT: Programmatic Management of Drug-resistant TB

Figure 1. Flow chart of data for surveillance of MDR-TB by the Bangladesh National Tuberculosis Control Program

Selection of Site

We included four of the six sentinel hospitals in the MDR-TB surveillance system for the evaluation. The NIDCH is the referral hospital for MDR-TB and was chosen purposively. Three other sites, namely Chittagong, Sylhet and Rajshahi, were selected randomly. Direct observation was done only at the NIDCH.

Data Sources and Data Collection

We interviewed 35 key informants face-to-face using a pretested semi-structured questionnaire. The key informants were surveillance-related NTP personnel, focal persons of partner organizations, medical officers, public health nurses, district coordinators, laboratory personnel, and data entry officers. Interviews with three District Coordinators of Chittagong, Sylhet, and Rajshahi were conducted over the phone and by email using open-ended questions to assess their district's surveillance system. Meetings were held with staff from the surveillance sites and relevant NGO partners to evaluate the case identification process, sample collection process, sample storage, transportation procedure, and reporting system. Consent was obtained before starting each interview.

We randomly selected 10 out of 85 MDR-TB cases reported from the NIDCH and laboratory register books of the National Tuberculosis Reference Laboratory between January and April 2016. We also received an aggregated dataset of MDR-TB cases from January 2008 to December 2015 from the NTP. We examined the drug-resistant tuberculosis (DR-TB) form 06 for patient ID and disease type; DR-TB form 05 for laboratory ID, sample collection date, and demographic history of patients, and DRTB 02 form for the unique register number, treatment outcome and radiological investigations. We matched all datasets and laboratory registers using the unique patient identification number to obtain demographic characteristics, date of sample collection, feedback result of sample test, and treatment outcomes. We also asked stakeholders to provide comments and recommendations about their surveillance system.

Statistical Analysis

Quantitative data were entered into a Microsoft Excel spreadsheet (version 2013). We checked the dataset for discordant data and resolved any discrepancies. We calculated frequencies and proportion for the institutes of respondents and study attributes and presented descriptively in the tables and figures.

Results

We approached 35 staff from the four study sites and all agreed to be interviewed (Table 1). Among them, 46% were focal persons from different hospitals and organizations, 17% were lab technicians, 17% were public health nurses, 11% were data entry operators, and 9% were medical officers or consultants.

Table 1. Respondent's institutions for evaluation of MDR-TB surveillance system, Bangladesh, 2016

Serial no.	Institute	Number of respondents n (%)	Focal person n (%)	Medical officer n (%)	Nurse n (%)	Lab technician n (%)	Data entry operator n (%)
1	National TB Control Program Headquarters (NTP HQ)	11 (31)	7 (64)	2 (18)			2 (18)
2	National Institute of Diseases of the Chest and Hospital (NIDCH)	10 (29)	1 (10)	1 (10)	6 (60)		2 (20)
3	National TB Reference Laboratory (NTRL)	7 (20)	1 (14)			6 (86)	
4	Bangladesh Rural Advancement Committee	3 (8)	3 (100)				
5	Damien Foundation	1 (3)	1 (100)				
6	Challenge TB (US Agency for International Development)	1 (3)	1 (100)				
7	Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) Hospital	1 (3)	1 (100)				
8	TB Hospital, Shyamoli	1 (3)	1 (100)				
	Total	**35 (100)**	**16 (46)**	**3 (9)**	**6 (17)**	**6 (17)**	**3 (11)**

The percent in the 'number of respondents' column represents column percentage, while others percentage in other column represent row percentages.

Simplicity

All NTP personnel, focal persons, and data entry operators reported that sample collection and transportation was easy and convenient. Simplicity was demonstrated by 76% of the data arriving at the NTP via a standard form. A coordination meeting among the eight stakeholders was held to simplify, coordinate, and streamline processes such as data and sample collection, logistics, and administration issues. However, 82% of the stakeholders sent data in a paper format, while 18% sent their data electronically (either format is acceptable).

Timeliness

Seventy percent of GeneXpert results were reported between 2 and 3 days, which met the programmatic management of drug-resistant tuberculosis guidelines. Additionally, 60% of monthly and quarterly reports were received by the NTP within 7 days, which is the recommended timeframe for sending the reports (Table 2).

Table 2. Timeliness of GeneXpert test reports and monthly and quarterly reports of MDR-TB surveillance system, Bangladesh, 2016

	Duration (days)	Percentage[†]
GeneXpert report received by patients	2–3*	70
	6–10	20
	>10	10
Monthly and quarterly reports received by NTP headquarters	1–7*	60
	8–30	20
	>30	20

*[†]Based on stakeholder's report. *Recommended time.*
NTP: National TB Control Program.

Data Quality

Ten MDR-TB case records were randomly selected and checked for data quality. Tuberculosis disease type, treatment history, laboratory identification number, registration number, date samples were collected and received, and address of the referring health authority were 100% complete (Table 3). The variable with the lowest completeness was the patient's contact number. Stakeholders reported few duplicate cases and any identified duplicates were removed. Training for national and subnational staff conducting surveillance was routinely conducted by the NTP and 81% of respondents confirmed that training was provided to surveillance staff. A training logbook was cross-checked, revealing that three training sessions were conducted in each quarter. This aligned with the programmatic management of drug-resistant tuberculosis guideline.

Table 3. Completeness of case record forms for selected variables of the MDR-TB surveillance system, Bangladesh, 2016

Variable	Completeness (%)
Registration number	100
Patient ID	100
Disease type	100
Date of sample collection	100
Address of referring health authority	100
HIV status	90
Date GeneXpert report sent	90
Laboratory investigations	90
Demographic characteristics	84
Patient's contact number	60

Stability

We assessed the stability of the surveillance system based on long-term financial support and involvement by partners. Among 34 partners (i.e., Global Fund to Fight Against AIDS, TB & Malaria and United States Agency for International Development), most (61%) stakeholders reported having long-term financial support.

Flexibility

As the surveillance system is dependent on financial donations, expansion for new sites is difficult. This difficulty arises from the need to establish more laboratories equipped with a GeneXpert machine for MDR-TB testing. In addition, securing funding for additional staff and attracting qualified staff for surveillance activities pose challenges. Data are archived on a single desktop computer managed by one person, limiting flexibility because the computer is not connected to a network and access to the database must be through this desktop computer only.

Usefulness

Data from the MDR-TB surveillance system was used to monitor program-based activities. The data described the burden of MDR-TB by reporting the age group with the highest prevalence and trends in mortality and morbidity. In Bangladesh, 0.7% of new cases and 11% of previously treated cases were treated with the second line anti-TB drugs. According to Bangladesh TB report 2017, the treatment success and death rates of MDR-TB were 74.3% and 10.3%, respectively.[6] Based on these statistics, policy makers could take initiatives to reduce MDR-TB infection transmission and treatment costs. For example, the data facilitated and targeted distribution of medicines to areas with a higher prevalence of MDR-TB. Moreover, they could identify training needs for physicians and resources needed.

Discussion

The MDR-TB surveillance system was useful for prevention and control tuberculosis in Bangladesh. Despite MDR-TB not being a notifiable disease and having no formal surveillance system in Bangladesh, the MDR-TB surveillance system became part of the tuberculosis surveillance system. Utilizing sentinel hospitals to monitor the disease, the system demonstrated good data quality with minimal missing values and duplicate records. Data were timely reported for proper strategic preventive and control actions. For example, the NTP surveillance identified people with MDR-TB, allowing for prompt isolation and treatment in hospitals. In addition, MDR-TB patients could be monitored to ensure that they continue their treatment. Moreover, the data informed the demand of NTP services, guiding drug provision and laboratory testing capabilities.

When the MDR-TB surveillance system in Bangladesh started, they used the World Health Organization definition for MDR-TB. A simple programmatic approach for the MDR-TB surveillance case definition played an essential role for case detection by using a standard format from the central office through assigned focal persons, much like an umbrella scheme. This is an advantage because standard reporting made data easy to analyze, centralized reporting allowed automatically collating of data from all sentinel sites, and thus stakeholders could obtain complete and updated information on the MDR-TB situation.

Almost all the variables in the MDR-TB reporting form were complete. A few gaps in exposure and demographic variables did not present a problem for describing the burden or providing adequate MDR-TB treatment. Stakeholders mentioned that approximately 1% of patient data was duplicated, but we could not verify this number. Monthly and quarterly reporting was timely for most of the sentinel sites. This assists with timely policy making, allocation of resources, and treatment of patients.

We compared our study favorably with the two publications that used the U.S. CDC guidelines to evaluate the MDR-TB surveillance.[8,9] Both studies concluded that the system was useful, and its quality was good. Further, the authors concluded that private doctors needed to be sensitized about MDR-TB in order to increase public and private collaboration. As in our study, these studies did not assess quantitative attributes such as sensitivity and specificity. These limitations are similar with a study from Yemen.[8] In our study, we did not specifically compare the involvement between public and private sectors in the surveillance. This is a disadvantage because some private hospitals in Bangladesh do not report MDR-TB cases. However, studies from Yemen and Pakistan reported on the both public and private reporting of MDR-TB cases. We also could not compare different tuberculosis reporting systems within the same country as was done in a study from Thailand.[10]

Limitations

Our study had the following limitations. Time constraints did not allow us to have detailed discussions with NTP staff. We also could not visit all surveillance sites. However, we did use direct observations and conducted intensive meetings with stakeholders.

Conclusion

The MDR-TB surveillance system provided useful data that described the burden of disease, monitored trends, and evaluated program demands for resources in order to manage MDR-TB patients. However, concerns remain about the flexibility and stability of the program.

Recommendations

Given these operating conditions, we recommend that the hospitals should use a single electronic platform such as the district health information system used throughout Bangladesh. In addition, each patient should have a unique identification to decrease the number of duplicates. There is a need to improve timeliness, data quality, and overall coordination among the NTP. Increasing the number of MDR-TB surveillance sites to cover the whole country would exhibit the true burden of disease.

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Conflict of Interest

There was no conflict of interest.

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Close Contacts among Students Contributing to an Influenza Outbreak in a Semi-boarding Sports School, Chiang Mai Province, Thailand, 2022

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Abstract

On 11 Sep 2022, the Department of Disease Control was notified of a cluster of influenza-like illnesses (ILI) in a semi-boarding sports school in Sanpatong District, Chiang Mai Province, Thailand. The investigation objectives were to confirm the outbreak, describe its epidemiological characteristics, determine risk factors, and recommend control measures. A descriptive study followed by a retrospective cohort study was conducted. A case was defined as a person presenting at the school from 22 Aug to 20 Sep 2022 and having at least two symptoms compatible with ILI. We observed dormitory conditions and students' activities and collected throat and nasopharyngeal swab specimens. We identified 113 cases, resulting in an attack rate of 26.5% among the screened population and 18.9% among the total population. Almost all cases were students and none developed serious illness. Of 11 specimens tested, nine were positive for influenza A (H3N2). Key risk factors included attending a sports program with adjusted odds ratio (AOR) 2.9, 95% confidence interval (CI) 1.2–6.8, and being in close contact with other cases (AOR 2.3, 95% CI 1.4–3.7). Dormitory overcrowding and close contact during football practice were observed. We recommended regular ILI screening, especially for sports students, and adjusting the dormitory environment to maintain physical distancing.

Keywords: influenza A, influenza-like illnesses, ILI, school, outbreak investigation, Thailand

Background

Influenza A and B viruses are transmitted by direct contact through droplet spreading or via indirect contact with contaminated surfaces. The average incubation period is 2 days (range 1–4 days), with transmission more likely during the first 3–4 days of illness.[1] Common symptoms include fever or feeling feverish, dry cough, runny nose, and fatigue.[2]

The annual global influenza attack rate is 5–10% in adults and 20–30% in children.[3] In Thailand, the Ministry of Public Health (MOPH) through the Division of Epidemiology (DOE), Department of Disease Control (DDC), established an influenza-like illness (ILI) surveillance system in 2009. Currently, patients presenting at about 600 MOPH affiliated hospitals with symptoms compatible with ILI such as common cold, or related diagnoses such as acute pharyngitis, are reported to the DOE. The submitted reports are analyzed and presented in the form of weekly aggregated data on the DOE website.[4] From 1 Jan to 31 Dec 2022, the national incidence of influenza was 122.2 per 100,000 population.[5] In Chiang Mai Province, the corresponding incidence was 263.8 per 100,000 population.[6]

On 11 Sep 2022, the DDC was notified by the Office of Disease Prevention and Control Region 1 Chiang Mai (ODPC-1) that 57 students in a semi-boarding sports school in Sanpatong District, Chiang Mai Province had presented with influenza-like symptoms. The joint investigation team of the DDC, Sanpatong Hospital, and Sanpatong District Health Office initiated an on-site investigation during 12 to 14 Sep 2022. The

objectives of the investigation were to confirm the outbreak, describe its epidemiological characteristics, determine risk factors, and provide recommendations and control measures.

Methods

Descriptive Study

To confirm an outbreak, we extracted in-service patient data of influenza cases in Sanpatong District from 1 Jan 2017 to 17 Sep 2022 from Sanpatong Hospital's database and extracted data of the cases in Chiang Mai Province during the same period from the national surveillance system.

In this event, a suspected case was defined as a student or teacher in the school who had at least two of the following symptoms: fever, cough, sore throat, rhinorrhoea, myalgia, dyspnea, headache, and fatigue during 22 Aug to 20 Sep 2022. A confirmed case was defined as any suspected case with a positive result for influenza virus based on the reverse transcription polymerase chain reaction (RT-PCR) technique.

We conducted an active case finding among school students and teachers during 12 to 14 Sep 2022 via self-administered semi-structured questionnaires which traced back to the symptoms of the respondents approximately two weeks prior to the investigation. We monitored any other coming cases approximately two weeks thereafter. Phone interviews were conducted with participants who were not available during the initial investigation. We collected demographic data on gender, age, grade/class, enrolment in the education or recreation program, dormitory resident status and influenza vaccination history. Clinical variables included history of symptoms and treatment (if any).

We estimated the proportion of the cases on the day of the investigation to assess if the outbreak would continue, assuming that the reproductive number (R_0) ranged between 2.3–3.3.[7–9] Descriptive statistics included median with interquartile range (IQR), ratio, frequency, and proportion.

Laboratory Study

We reviewed laboratory findings of specimens collected by local health staff on 8 Sep 2022, consisting of throat swab specimens for influenza by RT-PCR, dengue NS1 antigen, and severe acute respiratory syndrome coronavirus 2 by antigen test kit. We collected nasopharyngeal specimens for RT-PCR for influenza on 13 Sep 2022 from students randomly selected from the pool of suspected cases who still had symptoms during the investigation.

Environmental Study

We conducted a walkthrough survey by performing a thorough observation of the school environment (dormitories, restrooms, classrooms and cafeteria), accompanied by school staff. We assessed the dormitory capacity and density using a cut-off value of 1.6 m^2/person.[10]

Analytic Study

We conducted a retrospective cohort study starting since the onset of the first case on 22 Aug 2022 until 20 Sep 2022. The source population was school students. The sample size was calculated using a hypothesised risk ratio of 2.67 for being in close contact with influenza cases.[10–13] By assuming 25% incomplete information, we aimed to obtain at least 190 respondents. We distributed the questionaries to all 560 students via a secure online website. Due to difficulties in internet access, 10 students completed paper-based questionnaires instead.

The main outcome was being either a suspected or a confirmed case. We calculated the risk ratio (RR) and 95% confidence interval (CI). For multivariable analysis, we used a multiple logistic regression model, including variables with a *p*-value <0.2 from the univariable analysis. In this step, we excluded certain variables that captured the same constructs to avoid multicollinearity, for example, dropping "senior class" while keeping "age group" or discarding "being male" while keeping "being in a sports program". We grouped variables that measured the same related behaviour together, for example, creating a new variable "being a close contact with other cases" was defined as a person who had a history of sitting, sleeping near, or having meals with a case. Results were shown in the form of an adjusted odds ratio (AOR) and 95% CI. We analysed the data using Stata v16.

Results

Descriptive Study

A surveillance report in Sanpatong District from January 2017 to September 2022 showed an increase in the number of influenza cases by the end of August 2022. The study school is located in Sanpatong District, Chiang Mai Province. It is a semi-boarding school accommodating (290 boarding students, 270 non-boarding students, and 37 teachers). Among the 597 persons in the school, males outnumber females by a factor of 2:1 (397 males: 200 females). There are two academics tracks: a general program and a sports program. Classes range from grade 7 to grade 12, and there are 23 classes.

We identified 113 cases (from 427 screened students and teachers), for an attack rate of 26.5% and 18.9% among the total school population. The median age of the cases was 15 years (IQR: 12–19). The attack rate among males and females was 27.1% and 25.3%, respectively. The highest attack rate was found among students aged 16–17 years (35.2%). The majority of cases (112/113, 99%) were students. The attack rates were highest among students in senior classes (33.2%) and in those enrolled in the sports program (35.0%) (Table 1).

Table 1. Attack rates of influenza cases in a semi-boarding sports school in Sanpatong District, Chiang Mai Province, 22 Aug–20 Sep 2022 (n=597, including both students and teachers)

Student/teacher	No. of population	No. of screened population (%)	No. of cases	Attack rate by screened population (%)
Gender (n=597)				
Male	397	273 (68.8)	74	27.1
Female	200	154 (77.0)	39	25.3
Age, years (n=597)				
12–13	102	97 (95.1)	14	14.4
14–15	173	134 (77.5)	36	26.9
16–17	189	142 (75.1)	50	35.2
≥18	133	54 (40.6)	13	24.1
Type of person (n=597)				
Teacher	37	10 (27.0)	1	10.0
Student	560	417 (74.5)	112	26.9
Student grade* (n=560)				
Junior	276	206 (74.6)	42	20.4
Senior	284	211 (74.3)	70	33.2
Residence (n=560)				
Dormitory student	290	211 (72.8)	66	31.3
Non-dormitory student	270	206 (76.3)	46	22.3
Student education program (n=560)				
Sports	207	157 (75.9)	55	35.0
General	353	260 (73.7)	57	21.9

**Junior = grades 7–9; Senior = grades 10–12; Missing data were excluded.*

Among the cases, there was no hospitalizations or deaths. The most common clinical symptoms were runny nose (83.6%), cough (82.8%), fever (75.9%), headache (66.4%), sore throat (56.0%), fatigue (55.2%) and myalgia (42.2%). Most cases visited the school infirmary (39.1%) and local drugstores (34.7%). History of influenza vaccination among students was 11.8% (49/417).

On 19 Aug 2022, a student attended an inter-school sports tournament. The first three cases developed symptoms on 22 Aug 2022. Those students went to school and then came into contact with other students. The number of cases reached its peak on 9 Sep 2022. The epidemic curve showed a propagated pattern (Figure 1).

Laboratory Study

Specimens from 11 student cases, including six nasopharyngeal and five throat swab specimens, were sent for RT-PCR. Nine tested positive for influenza A subtype H3N2. Mixed organisms were identified in two specimens (one showing influenza A and rhinovirus; the other showing influenza A with respiratory syncytial virus). Tests for other viruses, namely dengue (n=16) and severe acute respiratory syndrome coronavirus 2 (n=57) performed by local healthcare staff were negative.

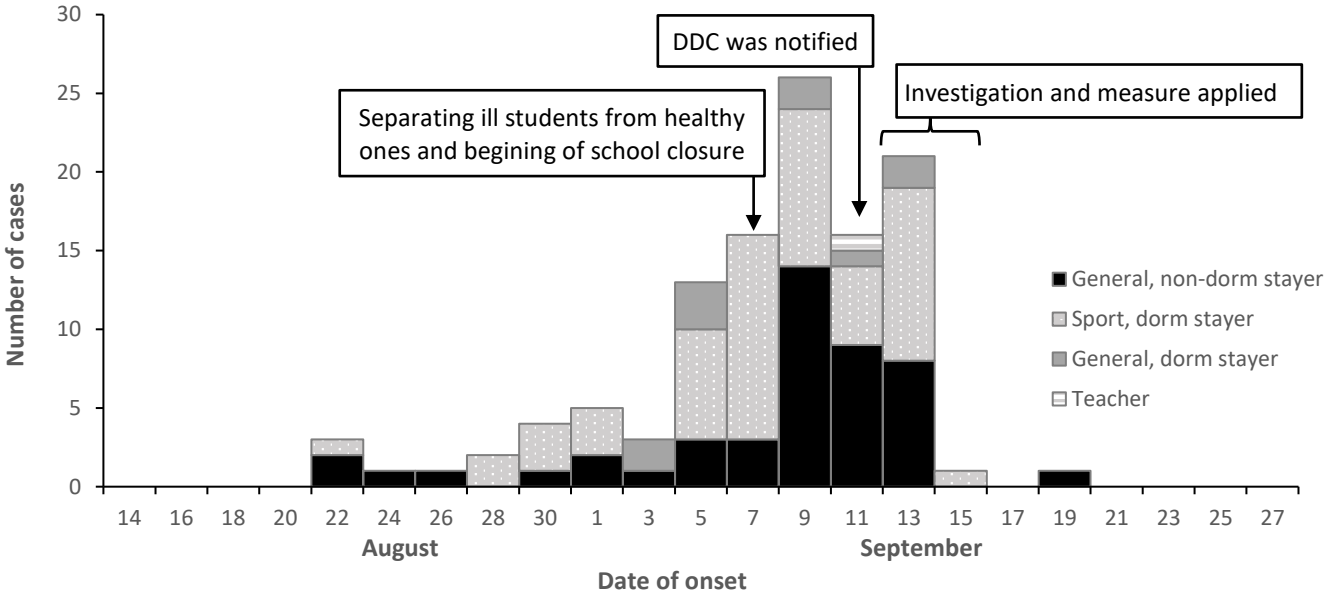

Figure 1. Number of influenza cases among students and teachers according to academic track and dormitory resident status in a semi-boarding sports school in Sanpatong District, Chiang Mai Province, 22 Aug–20 Sep 2022 (n=113)

Environmental Study

The school contained eight dormitories (five male and three female). Each dormitory was divided into four rooms on average. Each room contained a few small windows, and some were air-conditioned. Between 15–20 students stayed together in one room. There were five dormitories with an area density of less than 1.6 m^2/person.[10] The attack rate was high in these dormitories. The room specific attack rate varied between 0–67%. One male dormitory had the highest overall attack rate (AR) (Figure 2).

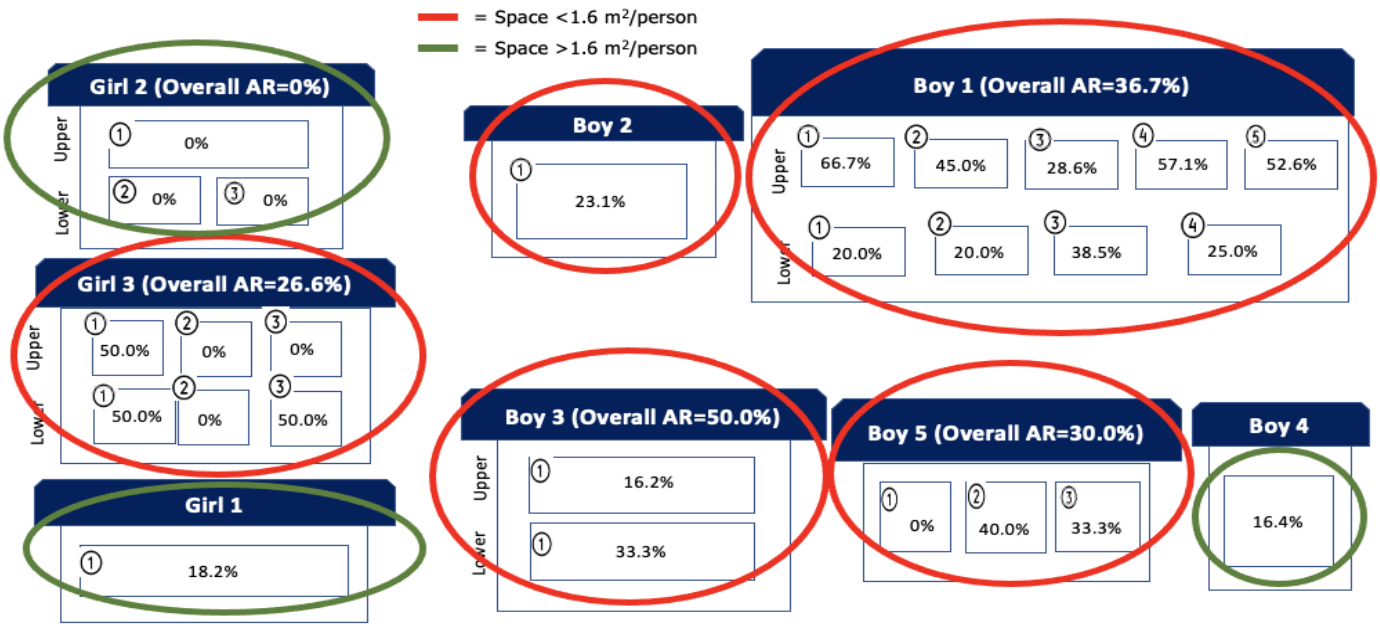

Figure 2. Attack rates in male and female dormitories by density in a semi-boarding sports school in Sanpatong District, Chiang Mai Province, 22 Aug–20 Sep 2022

Prior to the investigation, the school director terminated all onsite learning and separate ill students from the others. Some students did not wear masks consistently while staying in their dormitories. Most of the students had meals together in a canteen, studied in the same classes, and stayed in a crowded dormitory (Table 2). Sports students spent extended periods in close proximity with one another throughout the day. They were required to practice football in the morning (6:00–7:00 AM) and in the afternoon (4:00–6:00 PM). During football practice, mask wearing was not enforced.

Table 2. Daily schedule of students at a semi-boarding sports school, Sanpatong District, Chiang Mai Province, 22 Aug–20 Sep 2022

Time	Academic track/type of resident		
	Sports track, dormitory resident	General track, dormitory resident	General track, non-dormitory resident
6:00–7:00 AM	Football practice	-	-
7:00–8:00 AM	Breakfast at the canteen		-
8:00–8:30 AM	Enrol in the national anthem assembly at the football field		
8:30 AM–12:00 PM	Study		
12:00–1:00 PM	Lunch		
1:00–4:00 PM	Study		
4:00–6:00 PM	Football practice	-	-
6:00 PM	Dinner at canteen		-

Analytic Study

A total of 417 students participated in the analytic study resulting in a response rate of 74.5%. On univariable analysis, being at least 16 years old, being in a senior class, enrolled in the sports program, staying in a crowded dormitory, and being in close contact with other cases contributed to an increased infection risk with a *p*-value <0.2 (Table 3). History of vaccine administration had a non-significant protective effect. On multivariable analysis, being enrolled in the sports program (AOR 2.9, 95% CI 1.2–6.8), being in close contact with cases (AOR 2.3, 95% CI 1.4–3.7) and age ≥16 years (AOR 1.75, 95% CI 1.10–2.75) were significant risk factors for influenza infection (Table 4).

Table 3. Univariable analysis of risk factors associated with influenza infection among students at a semi-boarding sports school, Sanpatong District, Chiang Mai Province, 22 Aug–20 Sep 2022

Exposures	Exposed (person)		Non-exposed (person)		Risk ratio	95% CI	
	Case	Non-case	Case	Non-case		Lower	Upper
Individual factors (n=417)							
Male (vs female)	74	184	38	121	1.20	0.85	1.68
Age ≥16-years (vs <16 years)	64	128	48	177	1.57‡	1.13	2.16
Senior class (vs junior class)	70	141	42	164	1.62‡	1.16	2.26
Sports program (vs general program)	55	102	57	203	1.59‡	1.16	2.18
Staying in a crowded dormitory* (vs staying in uncrowded dormitory or not staying in a dormitory)	57	117	55	188	1.44†	1.05	1.98
Risk behavior and hygiene							
Sharing utensils with others (vs not sharing) (n=407)	41	108	66	192	1.07	0.77	1.50
Sharing utensils with cases (vs not sharing) (n=402)	9	15	97	281	1.46	0.84	2.51
Taking off masks (vs always wearing mask) (n=407)	95	254	12	46	1.31	0.77	2.24
Not washing hands after touching surfaces (vs always washing hands) (n=407)	7	13	100	287	1.35	0.72	2.51
Not covering nose while coughing (vs always covering nose) (n=407)	5	10	102	290	1.28	0.61	2.67
Being close contact to cases							
Sitting near cases (vs not sitting near cases) (n=404)	27	37	80	260	1.79‡	1.26	2.53
Sleeping near cases (vs not sleeping near cases) (n=404)	29	45	78	252	1.65‡	1.17	2.33
Having meal with cases (not having meal with cases) (n=399)	15	28	89	267	1.39§	0.89	2.18
Receiving Influenza vaccine (vs not receiving) (n=417)	11	38	101	267	0.81	0.47	1.41

**Staying in a crowded dormitory with an area <1.6 m²/person was compared against staying in an uncrowded dormitory (with an area ≥1.6 m²/person) or not staying in a dormitory. Missing data were excluded. †p-value <0.05. ‡p-value <0.01. §p-value <0.2. vs: versus.*

Table 4. Multivariable analysis of risk factors associated with influenza infection among students at a semi-boarding sport school, Sanpatong District, Chiang Mai Province, 22 Aug–20 Sep 2022 (n=417)

Exposures	Adjusted odds ratio	95% CI	
		Lower	Upper
Age ≥16 years (vs < 16 years)	1.75†	1.10	2.75
Staying in crowded dormitory (vs staying in uncrowded dormitory or not staying in a dormitory)*	0.58	0.24	1.41
Sport program (vs general program)	2.86†	1.20	6.81
Being a close contact with cases (vs not being a close contact)	2.27‡	1.38	3.73

*We excluded the following variables despite demonstrating p-value <0.2 from univariable analysis to avoid multicollinearity problems: being male (due to high collinearity with sport program) and being in senior class (due to high collinearity with age at least 16 years). We also grouped variables, "sitting near a case", "sleeping near a case" and "having meal with a case" together and renamed them as "being a close contact with a case". *Staying in crowded dormitory with an area <1.6 m²/person was compared against staying in uncrowded dormitory (with an area ≥1.6 m²/person) or not staying in a dormitory. †p-value <0.05. ‡p-value <0.01. CI: confidence interval. vs: versus.*

Control Measures

Control measures were still useful and recommended to be promptly implemented. At the time of the investigation, the proportion of cases was approximately one-fifth of the school population. We foresaw the outbreak had not reached its peak as the proportion of cases remained below the immunity threshold, estimated to be between 56–70% ($1–1/R_0$).[14]

Approximately 7–10 days after the outbreak's onset (Figure 1), the school director endorsed school closure and switched all onsite activities to an online platform. We also established an ILI surveillance system among students and school teachers. This entailed assigning one student per class or dormitory room to observe their peers for ILI symptoms. Additionally, we requested the school director to designate infirmary teachers to report findings to the investigation team. We also conducted health education sessions to promote personal hygiene and correct use of personal protective equipment to students and teachers at the school.

Discussion

This investigation confirmed the presence of an influenza A (H3N2) outbreak within the school. Both epidemiological investigation findings and laboratory results were compatible with influenza A, although the possibility of co-infection in a few cases could not be entirely ruled out.

The attack rate of this outbreak among the screened population was 26.5%, which was similar to the attack rate observed in other school settings.[15] The attack rates among sports students and senior-class students were higher than their counterparts. This may be attributed to the daily activities of these students that facilitated influenza transmission. Although there was a substantial overlap between students enrolled in the sports program and senior students, both variables were independent risk factors for infection.

We found that fever was not the most prevalent clinical presentation. Hence, relying solely on temperature screening may be insufficient for ILI surveillance. Prior evidence indicated a broad range of seasonal influenza presentations.[16] In this study, fever was present in 76% of cases, while other studies reported percentages ranging from 42 to 86%.[17–19]

This outbreak was likely to have originated from an imported case within the community with the initial case being a student enrolled in the sports program who had played football with students from other schools. At that time, there was a gradual rise in the number of influenza cases in Sanpatong District. Subsequently, the joint activities within the school environment likely facilitated the spreading of the disease, as evidenced by the propagated pattern of the epidemic curve.

The risk of influenza infection was notably higher among those having close contact with cases and those enrolled in the sports program. Sports students in particular had an increased likelihood of physical contact with their peers. Additionally, the nature of football games made it challenging to maintain mask-wearing and proper personal hygiene practices. These findings were similar to other epidemiological studies that also supported an elevated risk of infection among those in close contact with a case.[20–22]

In the univariable analysis, influenza vaccination was shown to have a protective effect against influenza infection but without statistical significance. Previous evidence confirmed its efficacy in preventing hospitalization and severe illness.[27–29] The lack of statistical significance may be attributed to several factors. For example, some participants were uncertain about their recent influenza vaccination status, and for those who reported to have received the vaccine, we could not trace back to the lots of vaccines administered to each individual to assess whether the antigenic strain in the vaccine matched the viral strand present in this outbreak.

Although crowded dormitories did not show statistical significance in the multivariable analysis, they had the potential to enhance disease transmission, as suggested by previous studies. For example, Wongsanuphat et al. showed that being in an area with a density of less than 1.1 m^2/person could result in an attack rate as high as 33.2%, although that study was conducted in a prison setting and the 1.1 cut-off value may not precisely match the school setting.[23] Another study reported that the risk of developing influenza infection during a New Year's party was higher among attendees who shared the same dining table with a case.[24]

The school closure probably had a significant role in controlling the outbreak. The school director had endorsed this once the outbreak was realized. Prior studies suggested that timely school closure, ideally within a week after the outbreak's onset, could be an important measure for halting an outbreak.[25–26] Moreover, the implementation of ILI surveillance among students and teachers could help limit the transmission and enhance awareness.[27]

Limitations

Firstly, not all students and teachers participated in the questionnaire survey due to the school closure prior to our investigation. However, we tried to enrol additional participants as much as possible by conducting phone interviews to complement the self-administered survey. If we had been able to include all students and teachers in the survey, the attack rate might have been lower (assuming that the absent participants posed a lower risk of infection). Secondly, there was a possibility of response bias among students due to the online distribution of questionnaires. However, guidance by the investigation team was provided alongside the questionnaire and we also interviewed the teachers to triangulate their answers. Lastly, there may have been recall bias as ill individuals were prone to recall the history of contact than those who were not. This potential bias could lead to an overestimation of the measure of association.

Recommendations

We recommended that the school maintain the ILI surveillance system after the end of the outbreak. Daily monitoring of the symptoms of students, especially among sports students, by teachers or volunteer students would be helpful.[30] We also recommended implementation of intensive health education on personal hygiene and the proper use of personal protective equipment. We also suggested that the dormitories' environment should be adjusted to make them less crowded under guidance of local health authorities. Furthermore, it is advisable to have yearly influenza vaccination administered to all students and teachers in the boarding school as prior evidence suggests its benefit in preventing severe illness.

Conclusion

We report an influenza A (H3N2) outbreak at a semi-boarding sports school in Sanpatong District, Chiang Mai Province. The overall attack rate was 26.5% among the screened population and 18.9% among the total population with the majority of cases being students. There were no hospitalizations or fatalities. The source of the infection likely originated from the community, potentially introduced by students participating in an inter-school sports competition. Being involved in a sports program and being in close contact with a case posed a significant risk of infection. We recommended implementing ILI surveillance system within the school. Adjustments to the dormitories' environment, particularly their density, should be considered to mitigate the risk of future outbreaks.

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Rapid Assessment of Cost-effectiveness of COVID-19 Vaccine against Severe Illness in Thailand

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Abstract

Though the benefit of COVID-19 vaccine in preventing severe illness is universally accepted, little is known about its benefit relative to its investment in monetary value. This study aimed to assess the cost-effectiveness of the national COVID-19 vaccination campaign compared to a scenario where this had not been introduced. This study used a test-negative matched case-control study design to analyze the occurrence of severe illness. Then, a societal perspective was applied for cost-effectiveness analysis. The cost calculation involved aggregating expenses from both COVID-19 treatment and productivity loss during sickness or premature death. The incremental cost-effectiveness ratio (ICER) was calculated to compare the hypothetical scenario (no vaccination campaign) with the status quo (the vaccination campaign in place). The study found that the three-dose regimen vaccine effectiveness remained over 80% over a year, 0.99 (95% CI 0.96–1.00) in August 2021 to 0.80 (95% CI 0.62–0.89) in June 2022, potentially preventing 71,913 severe illness cases. The ICER analysis showed that preventing one death incurred an extra cost of USD 23,938. Similarly, preventing one intubated case resulted in an additional cost of USD 45,646. Notably, a reduction of vaccine related cost (including administration cost) greatly improved the cost-effectiveness of the campaign. However, a sole reliance on ICER may be insufficient to determine the vaccine campaign's effectiveness. Therefore, this study suggests further analyses, such as research on willingness to pay threshold and budget impact, to gain a more comprehensive understanding for future policy decision-making.

Keywords: COVID-19, vaccination, vaccine effectiveness, incremental cost-effectiveness ratio, ICER, Thailand

Background

The sudden surge in cases and fatalities from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) posed severe challenges to public healthcare systems in all nations. Challenges included intensive care bed capacity, insufficient medical personnel and resources, and disrupted patient delivery and isolation systems.[1] Many governments responded to the pandemic by implementing measures such as compulsory mask-wearing in public spaces, social distancing, and city lockdowns.[1,2] Additionally, introducing COVID-19 vaccines was considered pivotal when combined with these public health interventions.[3]

From the detection of the first COVID-19 case in January 2020 to June 2022, the number of COVID-19 infections among Thailand's population reached 4,522,915, resulting in a death toll of 30,648.[4,5] To address the pandemic, Thailand's government initiated the national COVID-19 immunization plan in early 2021 with introducing multiple vaccines including CoronaVac, ChAdOx1 nCoV-19, Sinopharm, BNT162b2, and mRNA-1273. The vaccination target groups are in line with the vaccination priorities outlined by the Center for COVID-19 Situation Administration's policy. These groups encompass frontline medical and public health personnel, individuals with underlying conditions such as severe chronic respiratory diseases, heart and coronary artery diseases, chronic kidney diseases, various cancers undergoing treatment, diabetes, and obesity. Additionally, the groups include individuals aged 60 and over, those actively involved in COVID-19 control, pregnant women, public health personnel beyond the frontline, occupational sectors like tourism, international travelers, the population comprising

both Thai and foreign nationals, diplomats, industrial and service sector workers, students aged 12–18 years old, and students studying abroad, regardless of registration status. Following the vaccination of those, the government extended vaccine coverage to the entire population, targeting an 80% vaccination rate.[6]

As of June 2022, COVID-19 vaccination rates were at 82% for the first dose, 76% for the second dose, and 43% for the third dose and beyond, among Thailand's population.[7] Prior domestic studies had suggested the clinical effectiveness of various vaccine regimens in Thailand.[8,9] Nevertheless, those studies have not delved into their cost-effectiveness. The cost of vaccines in this study depends on various factors, including the price of the vaccines themselves, the costs associated with their administration, and the cost of treatment. Additionally, the indirect cost of productivity, including the gross domestic product (GDP) loss based on the duration of absenteeism from work should not be ignored.

Following the emergence of the ancestral COVID-19 strain in early 2020, Thailand subsequently witnessed various mutations, notably the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529, BA.2, BA.2.75, BA.4/BA.5, BA.4, and BQ.1) variants.[10,11] This study, conducted in Thailand from 1 Jul 2021 to 30 Jun 2022, revealed that during the latter half of 2021, the Delta variant (B.1.617.2) from India held primary dominance, whereas throughout 2022, the Omicron variant (B.1.1.529) from South Africa prevailed.[9,11]

In comparison to the ancestral variant, both the Delta and Omicron variants exhibited higher transmission rates, likely attributed to their increased transmissibility and enhanced capacity to evade the immune response and recognition by T-lymphocytes, as evidenced by a higher reproductive number when compared to earlier variants. During the scenario of the specific variants predominating in Thailand, the Delta variant (with a basic reproductive number: R_0=1.22 and 95% confidence interval (CI) 1.22–1.22) and the Omicron variant (R_0=1.91 and 95% CI 1.87–1.95) were approximately 1.13 and 1.77 times more transmissible than the Alpha variant (R_0=1.08 and 95% CI 1.08–1.08) from England, which was prevalent at the beginning of 2021. [12-14]

Disease severities varied among variants. Alpha, Gamma, and Delta showed comparable profiles, while Omicron infections were less severe. However, breakthrough infections were more common with Omicron. Delta posed a higher mortality risk than the Alpha variant, while Omicron, despite high transmissibility, was less deadly.[15]

Vaccine distribution challenges prompted this research on the cost-effectiveness of COVID-19 vaccines in Thailand. The study aimed to guide policymakers by evaluating costs and outcomes related to the vaccine campaign from July 2021 to June 2022. Assessing economic feasibility in preventing severe illness, the study provided insights for prioritizing strategies to reduce morbidity, mortality, and direct costs from a payer's perspective. Therefore, the objective was to evaluate the cost-effectiveness of the national COVID-19 vaccination campaign compared to a scenario where the vaccination policy was absent.

Materials and Methods

Study Design

This study conducted a test-negative matched case-control study to examine the occurrence of severe illness from 1 Jul 2021 to 30 Jun 2022 by utilizing nationwide data of individuals who were tested for SARS-CoV-2. For each case in this study, two controls were selected who closely matched in terms of age, testing date, and the location where their samples were collected. Then, cost calculation involved aggregating expenses from a societal perspective and the incremental cost-effectiveness ratio (ICER) by comparing the status quo (vaccination campaign in place) with a hypothetical (no vaccination campaign) were calculated.

Data Collection

Data were collected from the Co-Lab, Co-Ward, COVID-19 death, and Ministry of Public Health Immunization Centre (MOPH-IC) databases. These databases are managed by the Department of Medical Sciences, Department of Medical Services, Department of Disease Control, and Bureau of Digital Health under the Ministry of Public Health, respectively. The Co-Lab database serves as the national laboratory recording system, encompassing health service records of individuals undergoing the polymerase chain reaction test or the professional-use antigen-detecting rapid diagnostic test for SARS-CoV-2 across both public and private health facilities. The Co-Ward database nationally monitors hospital bed capacity and clinical severity. The COVID-19 death contains all death records associated with COVID-19 infection. The study received a nationwide immunization history from MOPH-IC.

Case-control Study

In this study, severe illness was characterized by either severe pneumonia requiring intubation support or resulting in a fatal outcome. A case was identified as a Thai national testing positive for SARS-CoV-2,

either through the polymerase chain reaction testing or professional-use antigen-detecting rapid diagnostic testing, and experienced severe illness between 1 Jul 2021 and 30 Jun 2022. Each occurrence of severe pneumonia requiring intubation and subsequent death was counted as a single case. Conversely, a control was an individual testing either negative for SARS-CoV-2 or positive without experiencing severe illness throughout the study period.

Cost Evaluation

This study conducted a comprehensive cost evaluation, considering both direct and indirect costs from a societal perspective. Provider-related costs, specifically treatment expenses, were sourced from the National Health Security Office, providing average direct medical costs for severe illness cases.[16] The market cost of each vaccine type at the end of 2021 was utilized, and GDP per capita data for the Thai population in 2021 from the World Bank informed the calculation of indirect costs.[17,18] The contribution of GDP per capita by age groups was assumed to follow the income distribution by age groups, as recommended by the Office of the National Economic and Development Council.[19-21] No cost discounting was applied in this study.

Direct cost

From the healthcare provider's viewpoint, encompassing entities or individuals responsible for healthcare service payments, costs considered included vaccine prices, administration costs, and treatment expenses for intubated patients, along with admission costs in the intensive care unit. A rough assumption was made for fatalities, equating their intensive care unit stay duration to that of intubated patients.

Indirect cost

Indirect costs were evaluated from broader social and economic perspectives, examining the societal implications of financial decisions. The focus was on quantifying the economic impact, specifically GDP loss, due to the daily absence of the workforce among admitted patients and instances of fatalities. This calculation considered two age categories: individuals under aged 60 and those aged 60 and beyond.

Data Analytic

A conditional logistic regression, implemented with the sklearn package and linear model module in Python 3.12, estimated the odds of intubation or fatality among vaccinees compared to the unvaccinated group. Results were expressed in odds ratios (OR) with a 95% CI. Vaccine effectiveness (VE) was calculated as VE = 1 – OR. Expected numbers of severe illness cases were determined by dividing actual cases by OR. This study then subtracted the actual number of severe illness cases from the expected number to obtain the number of cases averted by the vaccine campaign.

ICER Calculation

For cost calculation, two scenarios were considered: the status quo (the vaccination campaign in place), and a hypothetical scenario (no vaccination campaign). A 14-day productivity loss for severe illness patients was assumed.[22] Regarding mortality, the time remaining until life expectancy was calculated by subtracting the median ages of deaths from the overall life expectancy of the Thai population. This result was multiplied by age-specific GDP contribution.[23] The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in the total costs between two scenarios by the difference in health outcomes (number of intubated cases and fatalities averted).

The status quo (the vaccination campaign in place)

The total costs included medical costs, vaccine costs, vaccine administration costs, and GDP loss. The total vaccine expenses were calculated by adding up the result of multiplying the cost of each vaccine brand (based on market cost) with its corresponding share of vaccine uptake among the Thai population, as sourced from the MOPH-IC databases.

Hypothetical scenario (no vaccination campaign)

The total expenses were computed using a method similar to the status quo, excluding vaccination costs. The expected severe illness numbers were deduced from OR.

Moreover, to gain a broader understanding of the cost-effectiveness of the COVID-19 vaccination campaign, this study performed a sensitivity analysis by adjusting the cost related to vaccine administration (vaccine vial expense and logistic cost) by reducing these costs from 100% to 80% and 50% respectively. This approach allowed us to explore potential impact of cost reductions on the overall effectiveness and feasibility of implementing the vaccination policy in the future given the change in the market price of vaccines.

Results

Descriptive Study

Receiving a higher number of vaccine doses resulted in greater effectiveness against severe illness (Table 1). Despite showing a declining trend, the three-dose and four-dose regimens maintained over 80% effectiveness throughout a one-year duration. The one-dose regimen lost its protective effect after a one-year period.

Table 1. Odds ratio and vaccine effectiveness of developing severe infection in different vaccine regimens over time

Month (year)	Doses received	Odds ratio (95% CI)	Vaccine effectiveness (95% CI)
July 2021	1	0.33† (0.29–0.37)	0.67† (0.63–0.71)
	2	0.07† (0.06–0.09)	0.93† (0.91–0.94)
	3	NA	NA
August 2021	1	0.34† (0.30–0.38)	0.66† (0.62–0.70)
	2	0.10† (0.08–0.13)	0.90† (0.87–0.92)
	3	0.01† (0.00–0.04)	0.99† (0.96–1.00)
September 2021	1	0.40† (0.35-0.45)	0.60† (0.55–0.65)
	2	0.13† (0.11-0.16)	0.87† (0.84–0.89)
	3	0.02† (0.01-0.05)	0.98† (0.95–0.99)
October 2021	1	0.53† (0.44–0.63)	0.47† (0.37–0.56)
	2	0.13† (0.11–0.16)	0.87† (0.84–0.89)
	3	0.02† (0.01–0.03)	0.98† (0.97–0.99)
November 2021	1	0.54† (0.42–0.70)	0.46† (0.30–0.58)
	2	0.15† (0.12–0.18)	0.85† (0.82–0.88)
	3	0.01† (0.00–0.22)	0.99† (0.98–1.00)
December 2021	1	0.77 (0.55–1.07)	0.23 (-0.07–0.45)
	2	0.24† (0.19–0.30)	0.76† (0.70–0.81)
	3	0.04† (0.02–0.08)	0.96† (0.92–0.98)
January 2022	1	0.88 (0.48–1.61)	0.12 (-0.61–0.52)
	2	0.37† (0.27-0.53)	0.63† (0.48–0.73)
	3	0.07† (0.03–0.16)	0.93† (0.84–0.97)
	4	NA	NA
February 2022	1	0.77 (0.47–1.26)	0.23 (-0.26–0.53)
	2	0.46† (0.34–0.61)	0.54† (0.39–0.66)
	3	0.15† (0.10–0.23)	0.85† (0.77–0.90)
	4	0.04† (0.01–0.13)	0.96† (0.87–0.99)
March 2022	1	0.60* (0.42–0.85)	0.40* (0.15–0.58)
	2	0.27† (0.22–0.34)	0.73† (0.66–0.78)
	3	0.08† (0.06–0.11)	0.92† (0.89–0.94)
	4	0.00† (0.00–0.02)	1.00† (0.98–1.00)
April 2022	1	0.59* (0.41–0.85)	0.41* (0.15–0.59)
	2	0.42† (0.34–0.52)	0.58† (0.48–0.66)
	3	0.13† (0.09–0.17)	0.87† (0.83–0.91)
	4	0.04† (0.01–0.10)	0.96† (0.90–-0.99)
May 2022	1	0.66 (0.34–1.30)	0.34 (-0.30–0.66)
	2	0.35† (0.24–0.50)	0.65† (0.50–0.76)
	3	0.16† (0.10–0.26)	0.84† (0.74–0.90)
	4	NA	NA
June 2022	1	1.66 (0.77–3.60)	NA
	2	0.44† (0.27–0.70)	0.56† (0.30–0.73)
	3	0.20† (0.11–0.38)	0.80† (0.62–0.89)
	4	0.13† (0.03–0.61)	0.87† (0.39–0.97)

*Before January 2022, as the number of those receiving four doses was extremely small, thus we focused on one to three doses only. *p-value < 0.01. †p-value < 0.001. NA: denotes not applicable as the number of the vaccinees in particular vaccine category was too small to perform valid calculation (such as causing negative vaccine effectiveness).*

The actual recorded severe illness cases amounted to 65,165 (Table 2). Had the vaccine campaign not been established, the number of severe illness cases would have reached 137,078 (95% CI 111,618–191,922). As a result, 71,913 (95% CI 46,453–126,757) cases of severe illness, including 33,822 fatalities, were effectively averted. The volume of prevented cases was prominent among individuals aged 60 years or older.

Table 2. Number of severe illness cases in actual situation and in the scenario with an absence of vaccine campaign

Scenario	Illness level	Age groups—10^3 persons (95% CI)		
		All age groups	<60 years	≥60 years
Actual situation	Intubated cases	34.52	9.67	24.85
	Fatalities	30.65	8.58	22.07
	Total severe illness cases	65.17	18.25	46.92
No vaccination campaign	Intubated cases	72.61 (59.12–101.66)	20.33 (16.55–28.46)	52.28 (42.57–73.19)
	Fatalities	64.47 (52.50–90.26)	18.05 (14.70–25.27)	46.42 (37.80–64.99)
	Total severe illness cases	137.08 (111.62–191.92)	38.38 (31.25–53.74)	98.70 (80.37–138.18)
Prevented cases	Intubated cases	38.09 (24.61–67.14)	10.67 (6.89–10.67)	27.43 (17.72–48.34)
	Fatalities	33.82 (21.85–59.62)	9.47 (6.12–16.69)	24.35 (15.73–42.92)
	Total severe illness cases	71.91 (46.45–126.76)	20.14 (13.01–35.49)	51.78 (33.45–91.27)

CI: confidence interval.

During the study period, the total cost of the vaccine campaign amounted to US dollar (USD) 1,846 million and the total treatment cost for all severe illness cases under the status quo consequently reached USD 176 million. Considering these altogether with the GDP loss (USD 861 million), a total cost incurred for the status quo was USD 2,882 million (Tables 3, 4).

In the hypothetical scenario (no vaccination campaign), the estimated total treatment cost was USD 369 million (95% CI USD 300–517 million). When stratified by age group, the treatment cost for individuals under 60 years was USD 103 million (95% CI USD 84–145 million), accounting for 28% of the treatment cost. The remaining 72% of the total treatment cost, equivalent to USD 266 million (95% CI USD 217–372 million), was attributed to individuals aged 60 years and above.[24] The expected overall GDP loss for all age groups combined was USD 1,812 million (95% CI USD 1,475–2,536 million), leading to the grand cost for the hypothetical scenario of USD 2,181 million (95% CI USD 1,776–3,051 million).

Table 3. Treatment cost (in million USD) due to severe infection in actual situation and in the scenario with an absence of vaccine campaign

Scenario	Illness level	Age groups—million, USD* (95% CI)		
		All age groups	<60 years	≥60 years
Actual situation	Intubated cases	93.04	2,602	6,682
	Fatalities	82.61	231.19	59.49
	Total severe illness cases	175.65	49.06	126.31
No vaccination campaign	Intubated cases	195.38 (159.29–273.76)	54.98 (44.55–76.69)	140.69 (114.75–197.36)
	Fatalities	173.67 (141.25–243.03)	48.49 (39.47–67.95)	125.18 (101.78–175.08)
	Total severe illness cases	369.05 (300.83–516.79)	103.47 (84.30–144.63)	265.87 (216.53–372.16)
Prevented cases	Intubated cases	102.62 (66.26–180.72)	28.76 (18.61–45.11)	73.87 (47.65–130.25)
	Fatalities	91.07 (58.92–160.70)	25.37 (16.35–45.11)	65.69 (42.29–115.59)
	Total severe illness cases	193.69 (125.18–341.42)	54.13 (34.96–95.58)	139.56 (90.22–245.85)

**Based on 1 US dollar (USD) was equivalent to 35.47 Thai Baht (THB). CI: confidence interval.*

Table 4. GDP loss (in million USD) due to severe infection in actual situation and in the scenario with an absence of vaccine campaign

Scenario	Illness level	Age groups—million, USD* (95% CI)		
		All age groups	<60 years	≥60 years
Actual situation	Intubated cases	4.51	3.38	1.13
	Fatalities	856.81	856.81	-
	Total severe illness cases	861.32	860.19	1.13
No vaccination campaign	Intubated cases	9.59 (7.61–12.97)	7.33 (5.92–10.15)	2.26 (1.69–3.10)
	Fatalities	1,802.14 (1,467.48–2,523.33)	1,802.14 (1,467.48–2,523.33)	-
	Total severe illness cases	1,811.73 (1,475.09–2,536.30)	1,809.47 (1,473.40–1,473.40)	2.26 (1.69–3.10)
Prevented cases	Intubated cases	4.80 (3.10–8.74)	3.67 (2.54–6.77)	1.13 (0.85–1.97)
	Fatalities	945.61 (610.67–1,666.53)	945.61 (610.67–1,666.53)	-
	Total severe illness cases	950.41 (614.06–1,675.27)	949.28 (613.21- 1,673.29)	1.13 (0.85–1.97)

**Based on 1 US dollar (USD) was equivalent to 35.47 Thai Baht (THB). CI: confidence interval.*

When total cost was accounted, this study separately calculated ICERs for averting one additional intubated case and one additional death. It was important to note that intubated cases and fatal cases were analyzed mutually exclusively. The ICER for an intubated case averted was USD 45,646 (95% CI USD 24,675–72,210) and for a death averted was USD 23,938 (95% CI USD 320–53,856) respectively. The ICER for preventing an intubated case would decline to USD 35,952 (95% CI USD 19,176–57,204) and USD 21,412 (95% CI USD 10,926–34,694) in presumptive scenarios where total vaccination cost diminished to 80% and 50% of the total original cost respectively. The same pattern was also observed in the ICER sensitivity analysis for preventing a fatal case, and was even more apparent if all vaccine-related costs reduced by half since the result became negative—denoting that the program became cost saving (Tables 5, 6).

Table 5. Incremental cost-effectiveness ratio for preventing an intubated case

Scenario	Number of cases	Grand cost in million USD*	ICER— USD*/case (95% CI)		
			Main analysis	Sensitivity analysis[a]	Sensitivity analysis[b]
Actual situation	34,517	1,944	45,646 (24,675–72,210)	35,952 (19,176–57,204)	21,412 (10,926–34,694)
No vaccination campaign	72,608 (59,122–101,658)	205 (167–287)			

Figures in brackets denote 95% confidence limit. Presumptive scenarios where total vaccination cost diminished to 80% (a) and to 50% (b).
**Based on 1 US dollar (USD) was equivalent to 35.47 Thai Baht (THB). ICER: incremental cost-effectiveness ratio. CI: confidence interval.*

Table 6. Incremental cost-effectiveness ratio for death aversion

Scenario	Number of cases	Grand cost in million USD*	ICER— USD*/case (95% CI)		
			Main analysis	Sensitivity analysis[a]	Sensitivity analysis[b]
Actual situation	30,648	2,786	23,938 (320–53,856)	15,901 (-4,240–41,414)	-475 (-13,530–16,062)
No vaccination campaign	64,470 (52,495–90,263)	1,976 (1,609–2,766)			

Figures in brackets denote 95% confidence limit. Presumptive scenarios where total vaccination cost diminished to 80% (a) and to 50% (b).
**Based on 1 US dollar (USD) was equivalent to 35.47 Thai Baht (THB). ICER: incremental cost-effectiveness ratio. CI: confidence interval.*

Discussion

As this study did not incorporate time-to-event data from the point of vaccination to the study period, the VE derived from this study might not precisely represent the exact amount of declination in VE over time. Nevertheless, the findings were consistent with a domestic study, demonstrating that the three-dose regimen exhibited superior effectiveness compared to the two-dose regimen.[9] Similarly, the two-dose regimen demonstrated higher effectiveness than the one-dose vaccination, albeit the two-dose effectiveness in this study was notably lower than the meta-analysis conducted by Zheng et al., which might be attributed to variations in vaccine regimens and the prevailing viral strains during the study period.[25] Consistent with other studies abroad, this study's findings indicate that a national vaccination campaign significantly helped reduce the number of severe illnesses by more than half.[26–28]

The reduction in severe illnesses also came along with savings in treatment costs and potential economic losses that would have occurred in the absence of vaccination.[22] When examining the breakdown of costs in the hypothetical scenario, this study found that approximately 80% of the total cost was attributed to productivity loss, while the remaining 20% was attributed to treatment expenses. Further analysis revealed that almost three quarters of the treatment cost was associated with elderly infections, whereas the GDP loss was largely influenced by those aged less than 60 years.[23]

These results suggest that if policymakers aim to reduce morbidity and mortality rates and focus on minimizing direct costs from the payer's perspective, the focus should be on the elderly population. However, from a macroeconomic standpoint, vaccinating individuals in the working age groups is more cost-effective.[28]

Compared with a scenario with no vaccination, the ICER analysis demonstrates that the Thai government invested approximately USD 45,646 to prevent one additional intubated case and USD 23,938 to prevent one additional death. Additionally, this study found that reducing the cost of vaccines and other related administration cost significantly improved the cost-effectiveness of the national vaccination campaign. Thus, policymakers should find ways to lower the vaccine related cost, either by enhancing bargaining power with the vaccine suppliers or by gradual shift from vaccine importation to investment on vaccine domestic supply.[29,30]

It should be noted that the ICER is not the only tool to determine cost-effectiveness and feasibility of implementing the vaccination campaign. It is advisable to consider integrating additional information, such as incorporating a willingness to pay threshold and budget impact analysis, to complement the ICER. These points also warrant further studies and offer a more comprehensive perspective for policy decision-making on budget allocation.[26]

The methodology of this study is marked by significant strengths, particularly in the utilization of routine nationwide service data. This approach stands out as a key advantage, allowing the findings to authentically mirror the real-world effectiveness of vaccines within the regular functioning of the health system.

Limitations

Several limitations should be acknowledged in interpreting the study findings. Firstly, the reliance on secondary data from diverse sources introduced inconsistencies in information collection, leading to excluded data on underlying diseases, occupation, and individual risk factors. To mitigate residual confounding, matching based on age, province, and specimen collection time was implemented, though potential confounding effects persist.

Secondly, the ICER analysis assumed fixed parameters without considering potential variations, such as viral mutations that may affect VE or changes in treatment costs due to shifts in national healthcare guidelines. Consequently, the estimated number of cases averted may not fully capture real-world epidemic dynamics.

Thirdly, while the study aimed to encompass a broad range of costs, certain items were not assessed, including the cost of GDP loss for adverse events following immunization, expenses for continuing care given long-term complications, and treatment costs for long COVID symptoms. These costs, along with those related to non-severe illness care, were beyond the study's scope.

Finally, the data, collected through a test-negative case-control design, might not perfectly align with a population-based case-control study due to underreporting of COVID-19 cases. This limitation is particularly relevant for asymptomatic or mildly symptomatic infection. Despite this, the study deemed the test-negative design a practical and valid choice, offering advantages in controlling biases related to initial symptom presentation and diagnostic suspicion.

Finally, the 95% CI yielded from the VE (and the ICER thereafter) was quite wide in value, this might be due to the small number of severe illness cases in different vaccine strata in each month. Thus, the interpretation of the results should be made with caution since the wide 95% CI meant non-negligible uncertainty of the estimates.

Conclusion

The COVID-19 vaccination campaign was effective in reducing the number of severe illness cases and fatalities. It also resulted in remarkable reduction in both treatment cost and GDP loss compared to a hypothetical scenario where vaccination campaign had not been in place. Besides, the vaccination policy can be even more cost-effective should the total vaccination cost be reduced. Further studies on willingness to pay threshold and budget impact analysis are of huge value for a more comprehensive policy decision making.

Recommendations

According to the vaccine effectiveness in this study, the booster dose policy still offers favorable merits in preventing severe illness. Therefore, it remains crucial to continually promote COVID-19 booster shot, especially among the elderly. Another important policy implication is that although the current vaccination policy can save money relative to no vaccination in place, it could be even more cost-effective in preventing severe illness cases if all related vaccination costs were reduced. Thus, cost bargaining, through bilateral or multilateral negotiations with the vaccine suppliers, and enhancing investment in domestic vaccine production, should be explored.

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Author Contributions

Conceptualization: RS and NN; Methodology RS, NN, and PP; Formal analysis: RS and PP; Writing-original draft: PP; Writing, review, and editing: PP and RS; Supervision: RS.

Declaration of Conflict of Interest

The authors declare no conflicts of interest.

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An Investigation of a SARS-CoV-2 Omicron Variant Cluster Linked to Nightclubs, Kalasin Province, Thailand, December 2021

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Abstract

In December 2021, an outbreak of the SARS-CoV-2 Omicron variant linked to two nightclubs was reported in Kalasin Province, Thailand. This outbreak investigation aimed to understand its epidemiological characteristics, identify sources of infection, assess vaccine effectiveness, and provide control measure recommendations. This study analyzed investigation reports, interviewed all confirmed/probable cases, engaged in active case findings, assessed vaccine effectiveness among high-risk contacts, and surveyed the nightclub environment. This study found 246 confirmed and 338 probable cases, with a median age of 29 years (quartile1–quartile3 25–38 years). Over 40% (271/584) of cases had received at least two doses of vaccination. No severe cases or deaths were reported. Index cases were a Thai couple who traveled from Belgium and visited a nightclub, where the disease spread to 75% (12/16) of nightclub workers before reaching communities. High-risk contacts who received a booster vaccination significantly reduced SARS-CoV-2 infection risk compared with unvaccinated. (vaccine effectiveness 87.5%, 95% confidence interval 59.5–96.1). One of the suspected nightclubs was air-conditioned, crowded, and lacked compliance with measures, which were potential factors contributing to the outbreak. This study strongly recommends that individuals receive booster doses of the SARS-CoV-2 vaccine. Nightclub owners should adhere to COVID-19 public health measures to prevent disease transmission to the communities.

Keywords: COVID-19, SARS-CoV-2 Omicron variants, COVID-19 vaccines, disease outbreaks

Background

Coronavirus disease 2019 (COVID-19), a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global health threat that mutates over time.[1] Some strains alter the transmissibility, virulence, and effectiveness of public health measures, defined as variants of concern (VOCs).[2] SARS-CoV-2 outbreaks emerged in Thailand in March 2020, and Thailand faced the first SARS-CoV-2 VOCs, Alpha variant, since December 2020.[3] By December 2021, almost all circulating VOCs were Delta.[4] The SARS-CoV-2 Omicron variant (B1.1.529) was detected in Africa in November 2021 and became the latest VOCs.[1,5] Evidence suggested the variant's potential to spread globally and overwhelm the healthcare system despite less severity.[1,5] While the reference method to detect the omicron variant is whole-genome sequencing (WGS), polymerase chain reactions (PCR)-based techniques, including single nucleotide polymorphism (SNP) genotyping and S-gene target failure (SGTF), were used as a proxy of Omicron variant detection.[5,6]

Transmissions of the Omicron variant have been reported in Thailand since 6 Dec 2021, in a man travelled from Spain.[7] The first locally transmitted Omicron cases were found on 20 December.[7] Nevertheless, no cluster of cases had been reported in Thailand.

On 23 Dec 2021, the Kalasin Provincial Public Health Office notified a group of Omicron variant cases linked to two nightclubs located in Mueang Kalasin District,

Kalasin Province. This investigation, conducted from 24 Dec 2021 to 7 Jan 2022, aimed to confirm the outbreak, characterize its epidemiological aspects, potential sources of infection, and the efficacy of vaccinations, and formulate suggestions for control measures.

Methods

Operational Definition

The patient under investigation for SARS-CoV-2 Omicron variant (Omicron-PUI) was any person with a positive reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 from 9 Dec 2021 to 7 Jan 2022, who were close contacts with confirmed/probable cases or had histories of visiting community areas that had been reported for COVID-19. The confirmed case was Omicron-PUI with a variant analysis result resembling Omicron variant from either SNP genotyping or WGS. The probable case was Omicron-PUI with a positive SGTF result by RT-PCR. Omicron-PUI with variant analysis indicated other variants than Omicron were excluded. The degree of separation from index cases for each case was classified. First-degree cases, second-degree cases and third-degree cases were those that had close contact with the index cases, first-degree and second-degree cases, respectively. Unknown-degree cases were cases without clearly linked to other cases. Individuals compatible with multiple degrees were placed in the degree closest to the index cases. Close contact was defined as any person who had contact with cases by either face-to-face contact within two meters for more than five minutes, in contact with secretions, or staying in the same closed space for at least 30 minutes. Close contacts who did not report wearing proper personal protective equipment were classified as high-risk contact (HRC), whereas those who did were classified as low-risk contact (LRC).

Descriptive Study

This study reviewed the COVID-19 situation in Kalasin Province, reviewed case investigations and laboratory reports of the index cases, interviews of the index cases via telephone, conducted source case investigation, contact tracing, and active case finding using methods complied with the Department of Disease Control (DDC) guidelines.[8] Active findings were conducted by announcing those suspected to be in close contact with the cases or had symptoms of fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, or ageusia, to get RT-PCR for SARS-CoV-2. This study interviewed all cases via telephone using investigation forms and in-depth interviews with all first-degree cases, including symptoms and onset. The incubation period was calculated for symptomatic cases with information on last exposure date, defined as the number of days between the last exposure and the onset of symptoms.

Laboratory Collection

For Omicron-PUI, nasopharyngeal swabs were collected and placed into a sterile transport tube containing 2–3 mL of the viral transport medium, packaged at 2–8 °C, and sent to Kalasin Hospital for RT-PCR with SGTF detection or affiliate laboratory for RT-PCR test. Some positive specimens were sent to confirm the presence of the Omicron variant at the Regional Medical Sciences Center 7 Khon Kaen by SNP genotyping technique or at the National Institute of Health by WGS technique. HRCs were tested for SARS-CoV-2 via RT-PCR up to three times: at the time HRCs were identified, day 7, and day 14 after the last contact with cases. If SARS-CoV-2 was detected, this study processed those specimens following the same procedures as for Omicron-PUI.

Environmental Study

Two nightclubs linked to the index cases were surveyed using direct observation and worker interviewing using a checklist developed from the COVID-Free Setting framework, a COVID-19 measures bundle from the Department of Health.[9] Actual customers and nightclub density, while index cases have been contacted, were estimated. The unit “per 4 square meters” was used in density calculation to compare with the physical distancing standard provided by the Department of Health.[9] Environmental swabs were collected by purposive sampling at high-touch areas and air conditioners. Specimens were packed the same as Omicron-PUI specimens and transferred to the National Institute of Health for SARS-CoV-2 PCR.

Analytic Study

A retrospective cohort study was conducted to calculate vaccine effectiveness (VE) against Omicron variant infection among HRCs who had visited Nightclub K. Interesting exposures were vaccination status, dose of vaccine, and vaccine formula received at least 14 days before the test date obtained from the Ministry of Public Health Immunization Center Database. Principal outcome was SARS-CoV-2 detection using RT-PCR within 14 days after the last contact with cases. Analysis was done using univariable logistic regression for vaccination status, vaccine formula, age group, and gender (reporting in odds ratio (OR) with 95% confidence interval (CI)) and multivariate logistic regression for vaccine doses and formula adjusted by age group and gender (reported as adjusted OR with 95% CI). VE was calculated using

1–adjusted OR from the multivariate analysis. The sample size was calculated using the World Health Organization formula.[10] Given the expected attack rate in the unvaccinated group at 50%, anticipated VE of 65.9%, type I error of 5%, and desired precision width of 30%, 124 participants per group were expected for the analysis.[11]

Ethics Consideration

This study kept the information about the participants and the outbreak confidential and complied with the ethical principles in the Declaration of Helsinki. This study was done following the routine mission of responding to a public health emergency, so ethical approval was exempted.

Results

Context and Situation in Kalasin Province

Kalasin Province is a province located in Northeastern Thailand with 975,790 population in mid-2021. In December 2021, around 52% of the population received at least two doses of COVID-19 vaccination, but only 10% received the booster. SAR-CoV-2 RT-PCR with SGTF detection was available in Kalasin Hospital's laboratory since October 2021. There were no confirmed cases of the Omicron variant before 16 Dec 2021.

Descriptive Study

This study identified 584 cases. The female-to-male ratio was 1.14:1. The median age was 29 years (interquartile range (IQR) 25–38 years). Five percent (31/584) of cases were elderly. Almost all cases lived in Kalasin Province, giving a provincial attack rate of 47 per 100,000 population. About 40 percent of identified cases had received at least two doses of COVID-19 vaccination, but only six percent had received booster doses (Table 1). This study identified 590 HRCs from 491 cases, and 15.8% (93/590) of HRCs became cases after follow-up. This study obtained clinical characteristics of 35.6% (208/584) of the cases. Around 60% (124/208) were symptomatic. The most common symptoms were cough (51.9%), sore throat (45.2%) and fever (34.1%), respectively. For symptomatic cases with known last exposure (n=38), the median incubation period was 4 days (IQR 3–5 days). There were no reports of fatal or severe cases requiring oxygen or intubation. All cases improved after mandatory 10 days hospitalization.

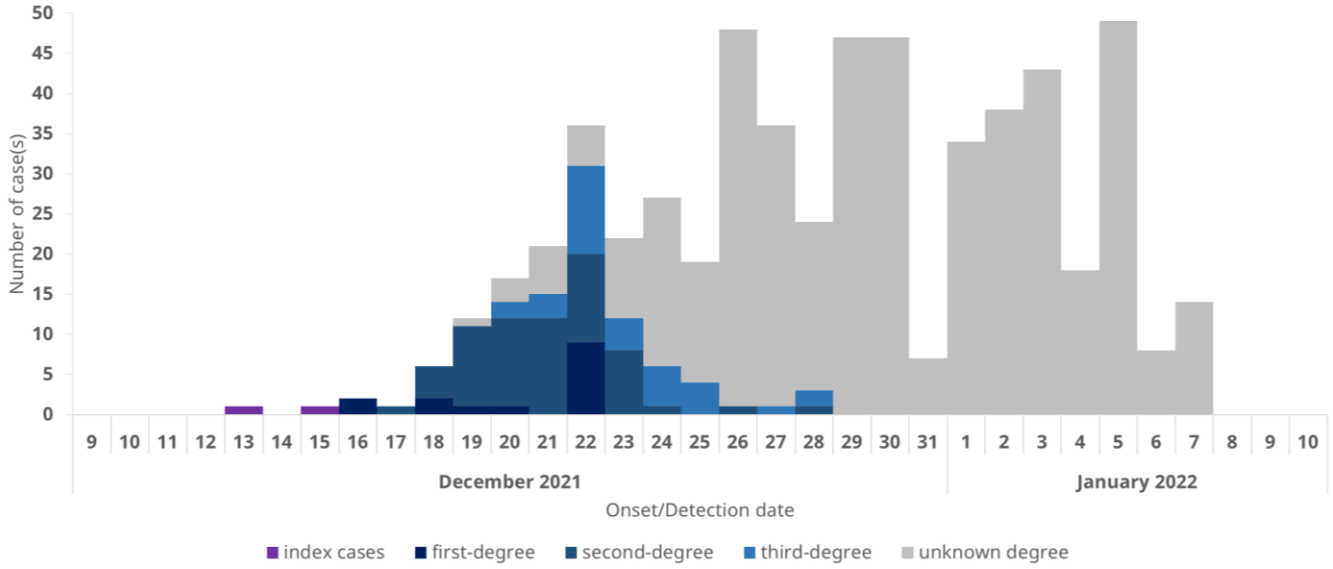
The index cases were a 47-year-old Thai couple who had received two doses of Comirnaty (BioNTech, Pfizer) vaccine. They worked at a nightclub in Belgium, denied close contact with people experiencing respiratory symptoms, and had a negative RT-PCR test for COVID-19 before traveled to Thailand via airplane. They arrived on 10 December and were tested again while quarantined in Bangkok Province. They were exempted from quarantine after negative testing on 11 December and took a plane to Khon Kaen Province before travelling by car with relatives to Kalasin Province. On 12 December, they dined with their family at Nightclub S and Nightclub K. They wore no masks and shared glasses with strangers while they were at Nightclub K. The index cases developed respiratory symptoms on 13 December and 16 December and were detected for SAR-CoV-2 with SGTF detection on 17 December. The specimens were sent for variant identification, which revealed the Omicron variant, sublineage BA.1 on 23 December. Source case investigation in the international airplane from Belgium to Bangkok Province and domestic airplane from Bangkok Province to Khon Kean Province revealed SARS-CoV-2 detection in four passengers, but no one had epidemiological linkage with the index cases.

Table 1. Epidemiological characteristics of confirmed and probable cases in the outbreak (n=584)

Factors	Number of cases	Percentage
Case type		
Confirmed case	246	42.1
Probable case	338	57.9
Gender		
Female	311	53.3
Male	273	46.7
Age (years)		
<10	55	9.4
10–19	105	18.0
20–29	197	33.7
30–39	90	15.4
40–49	64	11.0
50–59	42	7.2
60–69	19	3.3
≥70	12	2.0
Nationality		
Thai	457	78.3
Laos	23	3.9
American	1	0.2
Unidentified	103	17.6
Place of residence		
In Kalasin Province	455	77.9
Outside Kalasin Province	15	2.6
Unidentified	114	19.5
COVID-19 vaccination status		
Unvaccinated	94	16.1
1 dose vaccinated	21	3.6
2 doses vaccinated	234	40.1
3 doses vaccinated	31	5.3
4 doses vaccinated	6	1.0
Unidentified	198	33.9

Fifteen first-degree cases were discovered between 16–22 December (Figure 1,2). Most of them were Nightclub K workers. Nightclub K had a total of 16 workers including six musicians, seven waiters, and three cooks, who denied departing Kalasin Province since 1 December. Twelve of 16 workers were infected, including 100% (6/6) of musicians, 86% (6/7) of waiters, and no cook was infected. The first case in Nightclub K was a singer who developed symptoms on 16 December and tested positive for COVID-19 with antigen test kit but did not take sick leave. Usual behaviors included no mask-wearing, close contact with customers, sharing beverages with customers, and sharing meals with others. The remaining first-degree cases were two index cases' friends and one index cases' family member. The attack rate among the index cases' families was 14.3% (1/7).

Sixty second-degree cases were identified. Almost all had visited Nightclub K between 13–20 December including university students. Then, a suspicious epidemiological link between Nightclub K with 167 unknown-degree cases linked to Concert H, a large music festival held between 17 and 19 December with more than 300 participants, was detected since some musicians in Nightclub K and Concert H studied at the same university. Additionally, this study discovered 36 third-degree cases and 304 unknown-degree cases (Figure 1,2).



Dates were recorded by onset date for symptomatic cases or detected date for asymptomatic cases

Figure 1. Epidemic curve of confirmed/probable cases in the cluster by case classification, 9 Dec 2021–7 Jan 2022 (n=584)

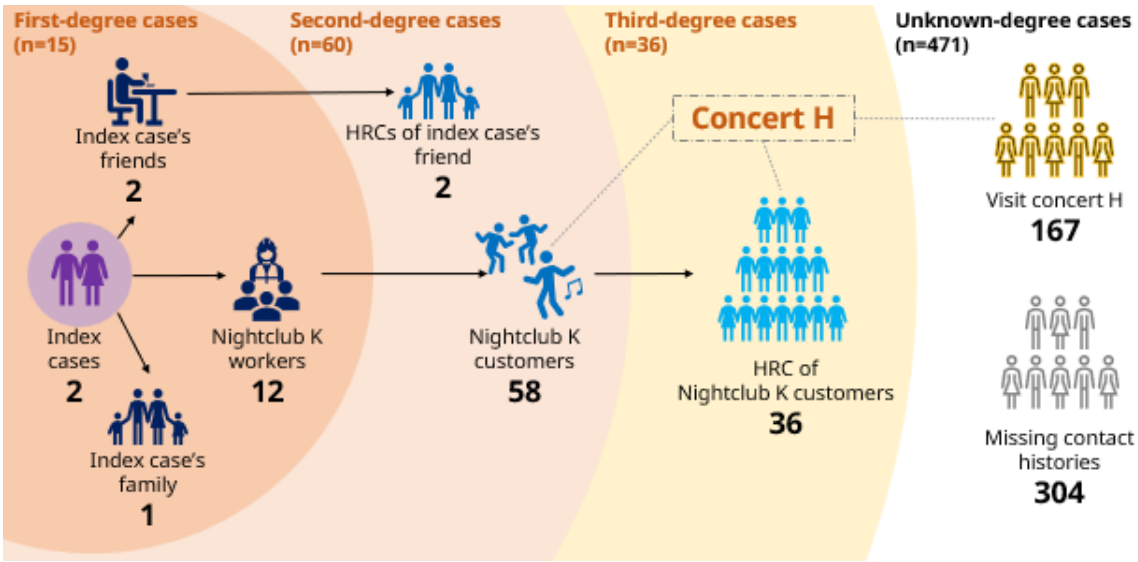


Figure 2. Epidemiological linkage of cases in the cluster by case classification, 9 Dec 2021–7 Jan 2022 (n=584)

Environmental Study

Nightclub K and S are air-conditioned nightclubs in Kalasin Province. Nightclub K has an area of 51.3 m^2 and can accommodate up to 90 people with estimated actual customers and densities of 90% and 6.32 persons/4 m^2, respectively. Although index cases spent 1.5 hours here, the attack rate among workers in Nightclub K was 75% (12/16). In contrast, Nightclub S has an area of 85.0 m^2 and can accommodate up to 40 people. The estimated actual customer and density were 20% and 0.16 persons/4 m^2, respectively. The index cases spent 2.5 hours in this nightclub, and no workers in Nightclub S became infected. Nightclub K had less compliance with COVID-19 measures compared to Nightclub S. Eighteen environmental specimens at Nightclub K were collected on 28 December, but none was positive for SARS-CoV-2.

Analytic Study

The analysis included 204 HRCs. From univariate analysis, vaccine dose, vaccine formula, age, and gender were associated with SARS-CoV-2 detection among HRCs (Table 2). Multivariate analysis showed that those receiving three or more doses of COVID-19 vaccination had less chance of SARS-CoV-2 detection compared to unvaccinated (VE 87.5%, 95% CI 59.5–96.1%, adjusted OR 0.12, 95% CI 0.04–0.40) while receiving one or two doses of COVID-19 vaccination showed no evidence of difference in SARS-CoV-2 detection compared to unvaccinated (adjusted OR 0.36, 95% CI 0.11–1.16 for one dose and adjusted OR 0.47, 95 % CI 0.19–1.16 for two doses). Multivariate analysis by vaccine formula revealed similar results among different formulas with the same number of doses (Table 3).

Table 2. Univariate analysis of detection of SARS-CoV-2 among HRCs within 14 days after the last contact with confirmed/probable cases (n=204)

Factor	Value	Attack rate (%)	Odds ratio	95% confidence interval	*P*-value
Dose received	≥3 (n=39)	18.0 (7/39)	0.12	0.07–0.65	0.03
	2 (n=110)	39.1 (43/110)	0.64	0.28–1.44	
	1 (n=25)	36.0 (9/25)	0.56	0.19–1.67	
	0 (n=30)	50.0 (15/30)	Reference		
Vaccine formula	SV+SV+AZ	15.3 (2/13)	0.12	0.02–0.65	0.01
	SV+SV+PZ	21.7 (5/23)	0.15	0.04–0.57	
	SV+AZ	41.9 (26/62)	0.50	0.19–1.30	
	PZ+PZ	28.0 (7/25)	0.34	0.20–3.17	
	SP+SP	53.9 (7/13)	0.80	0.10–1.13	
	Unvaccinated	50.0 (15/30)	Reference		
Age (years)	<18	14.3 (2/14)	0.27	0.06–1.23	0.11
	18–64	38.4 (71/185)	Reference	0.04–3.66	
	≥65	20.0 (1/5)	0.40		
Gender	Female	40.7 (46/113)	1.5	0.86–2.77	0.14
	Male	30.8 (28/91)	Reference		

SV: Sinovac. AZ: AstraZeneca. PZ: BioNTech/Pfizer. SP: Sinopharm.

Table 3. Multivariate analysis of detection of SARS-CoV-2 among HRCs within 14 days after the last contact with confirmed/probable cases by vaccine formula (n=204)

Vaccine dose	Vaccine formula	Number of vaccinees	Number of vaccinees detected with SARS-CoV-2	Vaccine-to-test interval median (IQR)	AOR (95% CI)	Estimate VE % (95% CI)
3 or more	**SV+SV+PZ**	23	5	140 (136–141)	0.15 (0.04–0.57)	84.6 (43.1–95.8)
	SV+SV+AZ	14	2	56 (41–102)	0.10 (0.02–0.58)	89.6 (42.4–98.1)
	Others*	3	0	16 (14–18)	NA	NA
2	**SV+AZ**	62	26	69.5 (48–103)	0.51 (0.19–1.33)	49.3 (0.0–80.7)
	PZ+PZ	25	7	39 (34–56)	0.34 (0.10–1.13)	65.8 (0.0–89.6)
	SP+SP	13	7	55 (26–73)	0.79 (0.20–3.16)	20.5 (0.0–80.0)
	Others†	9	3	35 (22–100)	0.42 (0.08–2.26)	57.7 (0.0–92.1)
1	**AZ**	10	2	38.5 (35–41)	0.16 (0.03–0.95)	83.7 (5.0–97.2)
	Others‡	15	7	24 (20–62)	0.57 (0.15–2.13)	42.7 (0.0–84.6)
Unvaccinated	**Unvaccinated**	30	15	-	Reference	-

*The odds ratio calculation was adjusted with age and gender. *Other 3 or more vaccination doses consisting of: SP+SP+PZ (n=1), SV+AZ+MN (n=1), SV+SV+PZ+PZ (n=1). †Other 2 vaccination doses consisting of: AZ+AZ (n=5), AZ+PZ (n=3), MN+MN (n=1). ‡Other 1 vaccination doses consisting of: PZ (n=8), SV (n=4), MN (n=3). AOR: adjusted odds ratio. CI: confidence interval. VE: vaccine effectiveness. NA: not applicable. SV: Sinovac. AZ: AstraZeneca. PZ: BioNTech/Pfizer. MN: Moderna.*

Discussion

This investigation confirmed the SARS-CoV-2 Omicron variant outbreak in Kalasin Province. SARS-CoV-2 (B.1.1.529, sublineage BA.1) was detected in the index cases, indicated the first Omicron variant cluster in Thailand. Readiness of SARS-CoV-2 with SGTF in a local laboratory supported omicron variant detection, which has different SGTF properties than the previously circulated variant.[4,6] With reference standard assays, this study confirmed the Omicron variant detection within one week, demonstrating the importance of laboratory network. SGTF detection might be useful in the areas where SARS-CoV-2's dominant VOCs do not show SGTF. Several studies have used SGTF as a surrogate indicator for Omicron variant in the early period of the outbreak.[12,13] However, SGTF is not specific to Omicron. Some variants, such as Alpha, may present SGTF, and Omicron BA.1, BA.4, and BA.5 linage may not present SGTF.[6]

The outbreak occurred among healthy, vaccinated adults, with a low percentage of vulnerable individuals. Two-thirds of cases had received at least 2 doses of the COVID-19 vaccination, highlighting the ability of Omicron variant to evade immunity.[14,15] The secondary attack rate among HRCs in this cluster was around 16% which was higher than the usual attack rate in COVID-19 outbreaks from 2020 to mid-2021, suggesting that Omicron variant is contagious among vaccinated individuals.[16] The incubation period among cases was four days, consistent with research indicating a shorter incubation period than other variants.[17] Most cases presented typical symptoms of COVID-19. No fatal or severe case was reported, aligning with studies showing milder symptoms and lower mortality than the previously dominant Delta and Beta variants.[12,13,18,19] This could be attributed to both the lower virulence of the Omicron variant and the impact of previous vaccination among those infected.

Four potential sources of infection were hypothesized initially: getting infection in Belgium, on the plane to Thailand, on the plane from Bangkok Province to Kalasin Province, and at the nightclub in Kalasin Province. This investigation found no evidence of other epidemiological-linked cases on both international and domestic airplanes. Moreover, the strain detected in index cases has never been identified in Kalasin Province. Therefore, the index cases were likely to bring the Omicron variant strain into the province. Although confirmation could not be done, this study mostly suspected that the index cases were in contact with the disease during their stay in Belgium which has reported Omicron variant cases since December 2021.[20]

Nightclub K had a favorable environment for disease spreading. It is an air-conditioned nightclub with high customer density (>1 person/4 m^2), facilitating disease spread towards workers. Evidence shows that SARS-CoV-2 could transmit through airborne transmission in enclosed spaces with insufficient ventilation.[21] The workers of Nightclub K also acted as carriers because of their behaviors of not taking sick leave and having low adherence to preventive measures, led to disease spreading into communities. Some of the Nightclub K customers were later involved with Concert H and a hundred cases were later found among people who attended the concert. Several studies have indicated COVID-19 outbreaks are common in dense gatherings, including nightclubs.[22–24]

High-risk contacts who received two doses of COVID-19 vaccination have shown insufficient effectiveness in protecting against Omicron variant, while those who have received a booster dose of vaccination have reduced infection, regardless of vaccine formula they received. Evidence indicated that COVID-19 booster dose vaccination improves the efficacy against SARS-CoV-2 infection, including the Omicron variant.[25,26]

Nightclub S, which adhered to COVID-19 measures, reduced COVID-19 spreading despite longer contact time of index cases. A comparison of two nightclubs with exposure to index cases demonstrated the effectiveness of COVID-19 public health measures, resulting in no infection in the nightclub that followed the measures. These measures include environmental and administrative actions such as limiting customers to no more than 1 person/4 m^2 and regular screening among workers.[9] Evidence shows the effectiveness of this public health measure bundle against COVID-19 spreading.[27]

Limitations

There were limitations in this study. First, the definite source of the infection could not be identified due to information missing, such as the index cases could not recall prior exposure in Belgium. Second, vaccine formulation among some identified cases could not be specified due to database limitations, which only account for vaccination dose received. Third, this study lacks other vaccine determinants in the vaccine effectiveness study, such as past COVID-19 infection, socioeconomic status, healthcare access, and personal protective practices. Furthermore, vaccine-to-test intervals, a surrogate indicator of immunity waning effect, were not included in the multivariable model in vaccine effectiveness analysis to keep the model parsimonious, so the vaccine effectiveness between different vaccine groups could not be compared directly.

As vaccine-to-test intervals among people who received three or more doses of vaccine tended to be slightly more than other groups, this study could underestimate vaccine effectiveness among those who received three or more doses of vaccine, compared to the effectiveness of other vaccine groups. Lastly, vaccinees in each vaccine formula group were limited. This led to low statistical power in vaccine effectiveness calculation. Nevertheless, this preliminary finding from the outbreak could be a starting point for large-scale study in vaccine effectiveness calculation.

Recommendations

Nightclubs and public spaces owners should follow COVID-19 public health measures. Public health authorities should provide adequate access to COVID-19 booster doses and implement COVID-19 measures in crowd-gathering places. People should receive COVID-19 booster doses and adhere to personal protective measures. Variant identification should be carried out alongside the outbreak investigation according to the DDC policy. National public health agencies should strengthen laboratory capacities to detect changes in VOCs, provide equitable access to COVID-19 vaccination, and conduct a nationwide study of vaccine effectiveness against emerging VOCs. Finally, Research on air ventilation in nightclubs and indoor spaces should be conducted.

Conclusion

This investigation confirmed the first SARS-CoV-2 Omicron variant cluster in Thailand, involving nightclubs in Kalasin Province, which may have been imported from a European country. The outbreak mainly affected healthy, vaccinated adults, with above half of the cases presenting symptoms, but none presenting severe illness or death. The outbreak was aggravated by crowded environments and the nightclub workers as carriers for transmission. Booster doses of vaccination have 87.5% effectiveness in reducing Omicron variant infection. This study suggests that crowd-gathering places' owners should follow COVID-19 public health measures to mitigate the spread of COVID-19.

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An Investigation of a Norovirus Outbreak Linked to Contaminated Vegetables in Mueang District, Chanthaburi Province, Thailand, December 2021–January 2022

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Abstract

A norovirus outbreak in Mueang District, Chanthaburi Province, was notified on 29 Dec 2021. This study's objectives were to describe epidemiological characteristics of the outbreak and identify possible sources of the ongoing outbreak. A descriptive study was performed by reviewing diarrhea cases and laboratory results from 1 Dec 2021 to 5 Jan 2022. Interviews were conducted with recent diarrheal cases who had onset during 3 to 5 Jan 2022. Polymerase chain reaction and genetic sequencing were used on patients and environmental specimens to identify genetic linkage. In the retrospective cohort analysis, a medical student cluster was investigated. A total of 675 diarrheal cases were found in Mueang District. Tha Chang Subdistrict had the highest morbidity rate at 0.95%. Out of 77 patient specimens, 30% (23/77) were confirmed norovirus. The median age of cases was 26 years old. Common symptoms included diarrhea (89%), nausea (67%), abdominal pain (67%), and fever (56%). No severe cases were reported. The interviews of recent diarrheal cases revealed that they visited four markets before symptom onset. Seventy percent (21/30) of the markets' vegetable samples tested positive for norovirus. However, the samples of tap/drinking water, ice, and seafood tested negative. Patient and vegetable genotypes were matched as GII.4[P7]. Contaminated vegetables were suspected sources of the outbreak. The recommendation for early case detection and pre-cool season preventive measures are ensuring adequate residual chlorine level, promoting handwashing, and washing vegetables before consumption.

Keywords: norovirus, outbreak, acute diarrhea, foodborne, Chanthaburi, Thailand

Introduction

Norovirus is the primary cause of acute gastroenteritis.[1] As of 2019, norovirus was classified into 10 genogroups (GI–GX) and 48 genotypes.[2] During 2015–2020, genotype GII.4 was the most common cause of norovirus illnesses worldwide and Thailand.[1,3,4] There is no specific antiviral medication for the virus. Norovirus can be detected in patients (stool, vomitus, and serum), food, water, and the environment by the polymerase chain reaction technique.

Globally, from 2008–2020, norovirus was estimated to be a cause of acute diarrhea in approximately 685 million cases annually, of which 200 million cases were among children under five. The overall detection rate

of norovirus was 18% among acute gastroenteritis patients.[1,5] Norovirus outbreaks are usually detected in healthcare facilities, schools, cruise ships, and restaurants.[6] Previous studies showed that leafy greens (such as lettuce), fresh fruits, and shellfish (such as oysters) were commonly identified as implicated foods for norovirus outbreaks.[7,8]

During 2015–2018, a surveillance conducted in Thailand for acute viral gastroenteritis revealed that the positive rate of norovirus was 12% among patients with acute gastroenteritis, with the predominance of norovirus GII.4.[4,7] Between 2017 and 2021, there were a total of nine norovirus outbreaks in Thailand. The outbreaks usually occurred during cool season, between November and February. Seventy-seven percent of those outbreaks occurred in school settings, while 11% were in prisons and 11% among travelers. The most commonly affected age group was children between 6–12 years old, followed by 13–18 years and more than 18 years.[9]

On 29 Dec 2021, the Department of Disease Control received a notification of the large number of acute diarrheal cases across Mueang District, Chanthaburi Province. This province is located on the eastern coast of Thailand, and consisted of 536,557 population and was divided into 10 districts. The number of cases were still higher than the 5-year median even though the local team had investigated for seven days. This study's objective was to describe epidemiological characteristics of the outbreak and identify possible source of the ongoing outbreak.

Methods

A descriptive study was conducted on diarrheal patients in Mueang District diagnosed with ICD-10 acute diarrhea and food poisoning at Hospital A, Private Hospital B, and Private Hospital C between 1 Dec 2021 and 5 Jan 2022. Data were gathered from two sources. The first source was the national communicable disease surveillance system (R506), for defined cases in Mueang District, Chanthaburi Province. This study compared cases during the study period with the past 5 years for trends. The second source was hospital data from the three Mueang District hospitals, where most patients in Mueang District went for treatment. Diarrheal cases were defined as patients from Mueang District diagnosed with ICD-10 acute diarrhea (codes A02.0, A04.0–A04.9, A08.0–A08.9, A09.0, A09.9) and food poisoning (codes A05.0, A05.2–A05.4, A05.8–A05.9). Viral gastrointestinal pathogen screening test and bacteria culture results from 1 Dec 2021, to 5 Jan 2022 were also reviewed.

To get information of food exposure among the recent diarrheal cases at the time of investigation, this study selected the diarrheal cases who had onset during 3–5 Jan 2022. The recent diarrheal case was identified as a patient who had visited any of the three hospitals who had symptoms onset between 3–5 Jan 2022 meeting at least one of the following clinical criteria: 1) experiencing diarrhea or vomiting at least once, or 2) having abdominal pain along with at least one of the following symptoms: fever, nausea or headache, and having a history of either residing in Mueang District or visiting within three days before the onset of symptoms. Phone interviews were done among the recent diarrheal cases to get history of food consumption and the sources of food.

This study obtained stool samples or rectal swabs from recent diarrheal cases admitted to the three hospitals. Laboratory testing involved real-time reverse-transcription polymerase chain reaction and sequencing of the norovirus gene, performed at the Center of Excellence in Clinical Virology (CECV). Seafood was collected from a Chanthaburi beach and a Mueang District market, both associated with recent cases. Regarding vegetables, this study acquired samples from four Mueang District markets, specifically selecting those suitable for raw consumption. This study also traced vegetables in Chanthaburi Province to a Pathum Thani market, selecting the varieties positive for norovirus in Chanthaburi Province. CECV analyzed both seafood and vegetables using the same method. This study gathered tap water samples from seven Mueang District locations, covering Mueang District communities. Furthermore, this study collected tap water and used water from three Mueang District markets, Chanthaburi Province, and a Pathum Thani market. Ice and pure water samples were taken from four large Mueang District ice factories and three small ice stores near the market and Chanthaburi Provincial Public Health Office. Water and ice samples underwent coliform bacteria testing, bacterial culture, and viral pathogen testing at Thai Red Cross Emerging Infectious Disease Health Science Centre, National Institute of Health, Department of Medical Sciences, and CECV.

This study conducted retrospective cohort only among the recent diarrheal cluster identified during the period of study to identify possible source of exposure. The cluster occurred among medical students who joined a workshop in hospital A between 23 and 25 Dec 2021. This study identified history of food consumption during 23–25 Dec 2021 by medical students and staff who joined the workshop by face-to-face interview.

Then the cases were defined as medical students and staffs with diarrheal symptoms as described previously. Relative risk and 95% confidence interval were calculated using univariate analysis. Fresh stool from medical students who met the case definition were sent for viral pathogen testing by real-time PCR method at the Thai Red Cross Emerging Infectious Disease Health Science Centre.

Results

The number of acute diarrhea cases during December 2021–January 2022 in Chanthaburi Province from R506 and ICD-10 code exceeded the 5-year median since 23 Dec 2021. The local team was aware of an abnormal event through social media on 28 Dec 2021 and immediately began investigation during 29–30 Dec 2021 (Figure 1). The result showed most cases were found in Mueang District. During the period of 16–29 Dec 2021, stool examination in 93 cases of acute diarrhea at private hospitals B and C revealed that 19.2% (5/26) of the cases were caused by norovirus, 6.8% (2/29) were rotavirus and 10.5% (4/38) were bacteria. A total of 675 cases were reported in Mueang District, and Tha Chang Subdistrict had the highest morbidity rate at 0.9% (186/19,482). The most affected age group was 5–14 years, followed by 0–4 years.

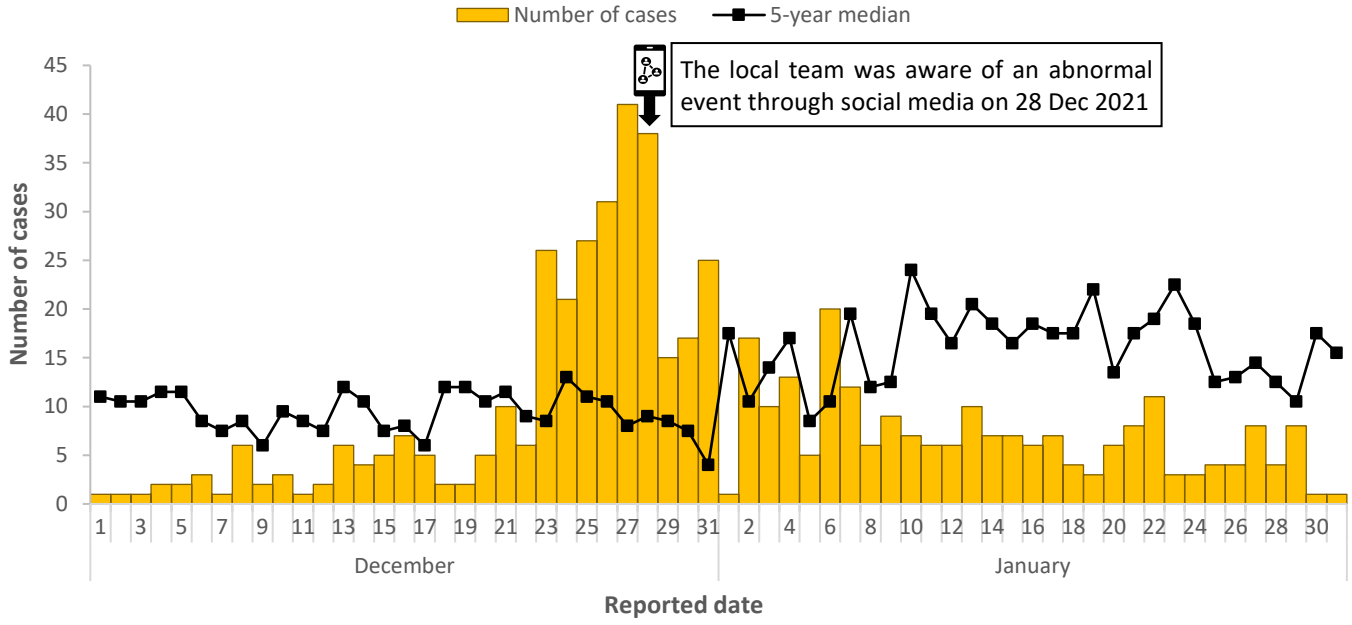

Figure 1. Number of acute diarrheal cases in Mueang District, Chanthaburi Province from R506 and ICD-10 code by reported date during December 2021–January 2022 compared with 5-year median (n=535)

As of 5 Jan 2022, the number of diarrhea cases in the district remained higher than the 5-year median. This study investigated 55 recent diarrheal cases visiting three hospitals in Mueang District, Chanthaburi Province during 3–5 Jan 2022. Male to female ratio was 1: 1.5, and median age (Q1, Q3) was 26 years (10, 35). Eighty-nine percent of the cases had diarrhea followed by nausea (67%), and abdominal pain (67%). There was no dead case, with 34% (19/55) of cases were inpatients while the rest were outpatients. The interviews revealed the food consumed by the cases was from sources around their homes and workplaces. Additionally, 43% of the cases reported a history of visiting four large markets in Mueang District within 3 days prior to the onset of acute diarrhea.

Retrospective Cohort Study in a Cluster

During the period of the investigation, one cluster of norovirus outbreak among medical students at Hospital A was detected. The cluster occurred following a workshop held between 23 and 25 Dec 2021, which was attended by 36 medical students and five staff. The overall attack rate was 46% (19/41) with four confirmed cases. All cases were medical students. Male to female ratio was 1: 1.1. The median age was 23 years old, and they were treated as outpatients. The most clinical symptoms were diarrhea (100%) followed by vomiting (57%) and nausea (47%). The first case had onset at 8:00 AM on 24 Dec 2021, and most cases had onset during 6:00 PM–12:00 AM on the same day (Figure 2). The incubation period for norovirus is between 12–48 hours. When comparing incubation period with the onset time of symptoms, it was suspected the exposure occurred between midday to midnight on 23 Dec 2021. There were four possible meals to be the source. The retrospective cohort showed no food item was a statistically significant risk factor (Table 1).

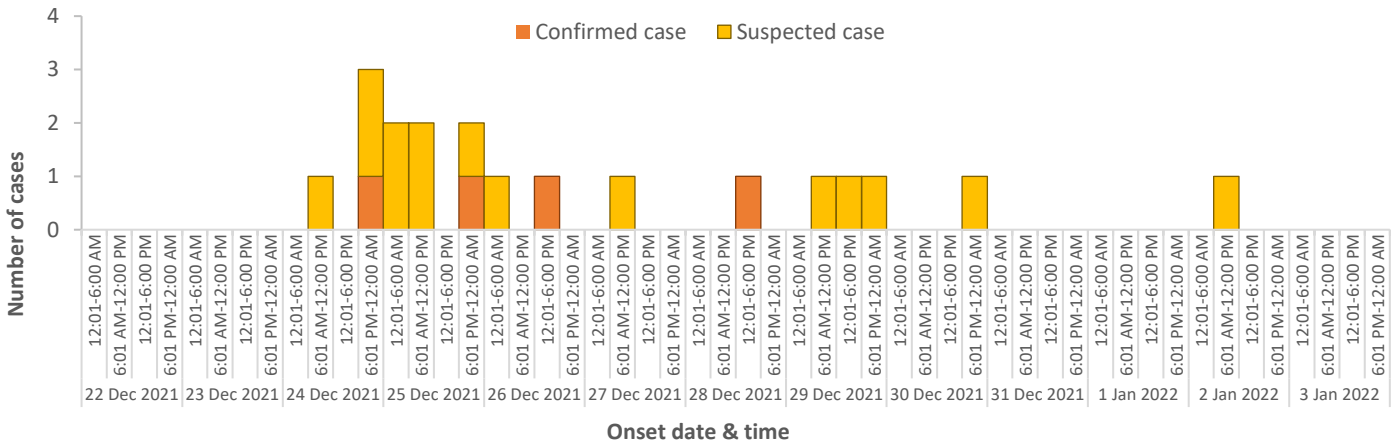

Figure 2. Epidemic curve of the suspected and confirmed cases in the medical student cluster during 23–25 Dec 2021 (n=19)

Table 1. Relative risk of four probable source meals and menus in the workshop in hospital A during 12 PM–12 AM on 23 Dec 2021

Meal	Exposed		Unexposed		Relative risk	95% confidence interval
	Case	Non-Case	Case	Non-Case		
Lunch	20	22	2	1	1.42	0.27–7.30
Bamboo lining soup	18	21	3	3	0.92	0.38–2.20
Crab roe chili	17	19	4	5	1.06	0.47–2.38
Vegetable	19	21	2	3	1.18	0.38–3.64
Fried chicken	18	18	3	6	1.5	0.56–3.99
Cooked rice	17	21	4	3	0.78	0.37–1.62
Lod chong with coconut milk	18	20	3	4	1.10	0.44–2.76
Afternoon break	20	22	2	1	1.42	0.27–7.30
Soft drink	18	22	3	2	0.75	0.33–1.65
Curry puff	17	22	4	2	0.65	0.33–1.27
Dinner	19	21	3	2	1.18	0.38–3.64
Spicy chicken soup	18	19	3	5	1.29	0.49–3.36
Roast pork	17	19	4	5	1.06	0.47–2.38
Minced shrimp omelet	17	19	4	5	1.06	0.47–2.38
Cooked rice	17	19	4	5	1.06	0.47–2.38
Orange	16	17	3	5	1.29	0.49–3.38
Night break	18	19	5	3	1.29	0.49–3.36
Orange juice	15	18	4	4	0.91	0.44–1.87
Bread	15	18	4	4	0.91	0.44–1.87

The food preparation process began at 6:00 AM, starting with the purchase of raw food and ice from Market E and Ice B factory. The food was prepared and cooked 2–4 hours before serving. The cooked food was packed in boxes 1–2 hours before serving and kept at room temperature before being served.

Laboratory Investigation

A total 77 stool specimens were examined, of which 30% (23/77) tested positive for norovirus. The analysis occurred in two phases: in December 2021, the local team detected norovirus in 10% (6/55) of the tested specimens. Additionally, the investigation team found increased positive norovirus to 77% (17/22) of samples from recent diarrheal cases visiting three hospitals during 3–5 Jan 2022 (Table 2). This study collected ice products and pure water from various ice factories. Most of the ice and pure water were found to contain coliform bacteria, and were tested positive for various bacteria such as *Bacillus cereus*, *Aeromonas* spp., from bacterial cultures. However, norovirus was not detected (Table 3). Seventy percent (21/30) of vegetable samples from the four markets were positive for norovirus. The other water and food samples in Mueang District, Chanthaburi Province were negative for norovirus, while tap water in Pathum Thani Province was positive.

Norovirus sequencing identified three genotypes from the recent patients. The predominant genotype identified in food samples was Norovirus GII.6[P7], and it was traced back to vegetables originating from Market F in Pathum Thani Province, which supplies products to Market D. Market D, is known as the major

fresh vegetable market in Mueang District. On 5 Jan 2022, this study found genotype GII.4[P7] in vegetables from market D and a patient from Tha Chang Subdistrict who had a history of travel around three subdistricts, although the patient did not report history of visiting to Market D.

Table 2. Laboratory result of food, water and ice samples related to the outbreak from rectal swab and fresh stool samples from patients in three hospitals during 3–5 Jan 2022

Hospital	Test	Result	Number of cases	Organism
Hospital A	Real-time PCR	Positive	12	Norovirus GII
		Negative	5	
Private hospital B	Real-time RT-PCR	Positive	4	Norovirus GII
		Negative	0	
Private hospital C	Real-time RT-PCR	Positive	1	Norovirus GII
		Negative	0	

PCR: polymerase chain reaction. RT-PCR: reverse-transcription polymerase chain reaction.

Table 3. Laboratory of food and ice samples related the outbreak during 29 Dec 2021–23 Feb 2022

Collected date	Samples	Source	Detected samples / total samples		
			Bacteria	Norovirus	Norovirus sequencing
Water and ice					
29 Dec 2021	Ice	Factory A, B, C, D	Coliform+ (2/4) *Bacillus cereus* (3/4)	0/4	-
8 Jan 2022	Ice	Factory A, B, E, F, G	-	0/4	-
17 Jan 2022	Ice	Factory A, B, C, D	*Aeromonas* spp., Biovar sobria (2/4)	0/4	-
	Pure water	Factory A, B, C, D	*Aeromonas* spp., Biovar sobria, *Bacillus cereus*, *Escherichia coli* (4/4)	0/4	
18 Jan 2022	Tap water	Market C, D, E	-	0/3	-
	Used water	Market C, D, E	-	0/3	-
23 Feb 2022	Tap water	Market F	-	1/1	GII.X[P7]
Seafood					
5 Jan 2022	Squid, shrimp	Market A	-	0/2	-
6 Jan 2022	Oyster, shrimp	Chao Lao Beach	-	0/5	-
Vegetables					
5 Jan 2022	Lettuce, Chinese cabbage, basil	Market D	-	2/3	GII.6[P7] GII.4[P7]
14 Jan 2022	Chinese cabbage, cabbage, morning glory, celery, basil, sweet basil, lettuce, tomato, radish, cucumber	Market D	-	9/11	GII.6[P25] GII.6[P7] GII.6[P31] GII.3[P7] GII.3[PX] GII.21[P31] GII.21[PX]
18 Jan 2022	Morning glory, lettuce, coriander, dill, Chinese cabbage	Market C	-	4/5	GII.X[P7] GII.X[PX] GII.6[P17]
	Morning glory, kale, bok choy, paco fern, dill	Market E	-	3/5	GII.17[P17] GII.4[P17] GII.6[P7]
23 Feb 2022	Lettuce, Chinese cabbage, kale, morning glory, coriander, basil	Market F	-	3/6	GII.X[P7] GII.X[P31]

Discussion

This study detected the diarrhea outbreak in Mueang District, Chanthaburi Province, from 23 Dec 2021 to 5 Jan 2022 due to a large number of diarrhea cases that exceeded the 5-year median, based on the communicable disease surveillance system. Norovirus was the most predominant pathogen of this outbreak. This outbreak occurred during cool season of Thailand similar to the previously reported global situations.[7] Norovirus can cause acute gastroenteritis in all age groups, but typically affects young children under five years of age.[1,10]

Several recent diarrheal cases have exposed large food markets in Mueang District. Since this study did not find positive norovirus from water or ice, whereas several vegetables specimens showed positive for the virus, this study suspected the source was likely to be food, especially vegetables. Vegetables are commonly reported as the source of norovirus infection including vegetables, salads, berries, and fruits.[1] This study detected norovirus contamination in various vegetables, such as Chinese cabbage, lettuce, cabbage, morning glory, and dill, obtained from four markets in Mueang District. Upon tracing back to the origins of the contaminated vegetables, norovirus was also detected in both the vegetables and tap water. However, the market authorities did not permit an investigation into the source of the contaminated tap water. This lack of access to explore the source could be linked to inadequate chlorine levels within the water system.[7] However, this study did not detect norovirus in shellfish and seafood, which were commonly identified as sources of other norovirus outbreaks. Thus, vegetables were highly possible to be one source of infection in this outbreak.

Although norovirus was detected from the human and environmental specimens, this study did not find a clear linkage between recent diarrheal cases and vegetables. However, it is possible that patients may have contracted norovirus from fresh vegetables consumed at restaurants they visited. Additionally, it was possible that the vegetables might have been contaminated with norovirus from contaminated water (tap water in market F) during cultivation or processing.

The norovirus outbreak among the medical student cluster was the only cluster captured by an event-based surveillance in the area. Although it had been 13 days since the onset, this study still found norovirus positive from stools. According to the epidemic curve, a point common source was most probable. The exposure time was suspected to be on 23 Dec 2022. However, this study did not find any food item that was a statistically significant risk factor causing sickness. The most suspected dish was fresh vegetable served in lunch boxes since this study found positive norovirus in vegetable samples in Market E later on.

Limitations

Due to the delayed investigation, this study did not have specimens from patients and vegetables during the early phase of the outbreak. Thus, this study could not conclude that these vegetables were also responsible as the only source of the outbreak during that period. Since this study's main objective was to control the ongoing outbreak, this study tried to find the source of infections by focusing on the recent cases visiting the major hospitals in the district and tried to identify common exposure among them. Memory bias could occur when this study asked about food exposure three days before the onset. Recall bias might occur among cases in the analytic study, although this study used the menu on each day of the workshop to help interviewees recognize food items they have eaten. This study could not get the specimen to test for norovirus from asymptomatic chefs, assistants and staff who prepared and served food in the workshop.

Recommendations

R506 should have an alert function for early warning when the number of cases is higher than the 5-year median, so that local epidemiologist could detect the outbreak and perform investigation early. Close cooperation with local public health organization and Provincial Waterworks Authority is required to ensure the quality of tap water, focusing on maintaining residual chlorine levels at the required standard. Risk communication for norovirus prevention should be done to the public before cool season by promoting hand hygiene, and cleaning vegetables with running water before eating or cooking.

Conclusion

There was a norovirus outbreak in Mueang District, Chanthaburi Province from 23 Dec 2021 to 6 Jan 2022. The majority of cases were aged below 15 years and lived in Tha Chang Subdistrict. There were no severe or fatal cases. This study investigation identified various genotypes of norovirus, but only GII.4[P7] was found to be matched between patients and vegetables. Although this study did not find any direct epidemiological linkage between the patient and the contaminated vegetables, this study identified leafy vegetables as potential sources of infection for the cases in early January 2022. This study did not find evidence of other potential sources of infection for the

entire outbreak. To prevent future outbreaks, this study recommends strengthening early detection of acute gastroenteritis cases, risk communication of diarrhea before and during cool season, especially avoiding eating fresh vegetables from unsafe sources, and washing vegetables thoroughly with running water before eating or cooking.

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Suggested Citation

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The Grammar of Science: How Many Participants Do I Need in My Survey?

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An adequate sample size is a prerequisite for any research study.[1] Sample size justification is required to be considered from both scientific and ethical points of view. A smaller sample size than required may result in "underpowered study" with questionable reliability or reproducibility, and not detecting results that are in fact important. A larger sample size than required consumes unnecessary resources and may also lead to questionable statistically significant result for a tiny different deviation even though it is not practically important.[1–3]

In this paper, we will focus on sample size calculation for a descriptive survey. Survey is generally a descriptive cross-sectional study design to describe certain phenomena in population of interest; (e.g., prevalence of back pain among office workers, mean depression score among cancer patients). However, survey can be an analytic cross-sectional study design with the specific objective to assess the association among variables or to compare a variable between groups (e.g., association between smoking and lung cancer, association between depress score and quality of life score).

Sample Size for Descriptive Survey

Main objective of a descriptive cross-sectional study is to "estimate" population characteristics, so-called "parameter". The classic formula for sample size calculation of a descriptive study depends on the types of parameter to be estimated, categorical data (prevalence, proportion, percentage) or continuous data (mean/variability).

For categorical data

$$n = z^2_{1-\frac{\alpha}{2}} \frac{p(1-p)}{d^2}$$

For continuous data

$$n = z^2_{1-\frac{\alpha}{2}} \frac{\sigma^2}{d^2}$$

There are three basic elements in both formula that are required.

Expected Value of the Parameter

In sample size calculation, you need to input the expected value of the parameter that you want to estimate. The expected value is a proportion (p) for categorical data or mean and standard deviation (μ, σ) for continuous data. This expected value is typically based on "priori information" which could be obtained from previously published studies, pilot study, or expert opinion.

Confidence Level / Interval (CI)

CI refers to the percentage of all possible samples that can be expected to include the true value of the population parameter that you attempt to estimate. CI is typically set up as 95% or higher. The CI relates to the value of the area under curve ($Z_{\alpha/2}$). When setting up CI=95%, the $Z_{\alpha/2}$=1.960; and when CI=99%, the $Z_{\alpha/2}$=2.576. The higher the CI, the larger $Z_{\alpha/2}$ and consequently the larger the sample size.

Precision or Margin of Error (d)

As different samples from the same population would give different estimates of the true value, thus the estimate of the true value is generally inferred with some margin of error or precision. The terms, "precision" and "margin of error", are opposite to one another. Margin of error expresses the maximum expected difference between the true population parameter and a sample estimate of that parameter.[4] Setting up the lower the margin of error would lead to the higher the precision (reliability) of the estimate. The higher precision (the lower margin of error), the larger sample size. It is a challenging issue to select the precision level which may be quite subjective, depending on the objective and nature of the survey.[1,5,6] The precision can be set up as "absolute precision" or

"relative precision". Absolute precision is simply set by specifying the exact value of the margin of error or the absolute uncertainty of the estimated parameter. For example, based on a study elsewhere the prevalence of tuberculosis (TB) is 20%; and in your survey, you simply set up 10% as the absolute margin of error, that means the you expect the prevalence is to be estimated with an uncertainty of 10% on either side of the estimate (between 10–30%). Relative precision is set corresponding to the priori information of the estimate. For example, based on a study elsewhere the prevalence of TB is 20% and you set up a relative margin of error for the current survey as 10% of the previous estimate (10% of 20%=2%), that means you expect the prevalence is to be estimated with an uncertainty of 2% on either side of the estimate (between 18–22%).

In a certain situation when samples are drawn from a finite (limited and small size) population, the formula for sample size calculation can be adjusted by taking into consideration the size of the population under survey.[6] For example, if you want to get a certain estimate form the 100 specimens archived in the hospital laboratory, the population size in this case is limited to only N=100 specimens, not the "population at large" or infinite population. The formulas for sample size of finite population are:

For categorical data

$$n = \frac{Np(1-p)z^2_{1-\frac{\alpha}{2}}}{d^2(N-1)+p(1-p)z^2_{1-\frac{\alpha}{2}}}$$

For continuous data

$$n = \frac{N\sigma^2 z^2_{1-\frac{\alpha}{2}}}{d^2(N-1)+\sigma^2 z^2_{1-\frac{\alpha}{2}}}$$

Non-responses in Survey

The calculated sample size is the minimum number that you should have at the end of the study in order to obtain the parameter estimate with the precision and CI that you proposed. However, when conducting a survey, you will unlikely get the responses back from all potential participants that you attempt to recruit, and responses from some participants may be incomplete. Such non-response is a potential source of bias. Securing a high response rate to a survey can be hard to control, particularly in a postal survey, but still difficult for a face-to-face or telephone interview.[7] The non-response rate is usually unknown and unpredictable; it may be based on previous experience or a pilot study.[3] It is suggested in literature that achievable and acceptable rate for a survey study should be around 75% for interviews and 65% for self-completion postal questionnaires.[7] If p is the proportion of non-responses, the number of sample size must be increased by a factor of (1 – p).

$$n_{adjusted} = n / (1 - p)$$

Sampling Techniques

Simple Random Sampling vs. Cluster Sampling

Sampling refers to the process of choosing samples from a total population. We can classify sampling methods into 2 types: probability vs. non-probability sampling.[4] Probability sampling includes methods that are based on two concepts: (1) equal probability of selection, everybody in the population has equal chance of being selected, and (2) proportionate to size, the proportions of the sample subgroups reflect the proportions within the population subgroups. Non-probability sampling is based on the concept of relevancy or representativeness of the samples to the population of interest. Survey sampling is usually based on probability sampling technique.[4] The goal of a probability sampling technique is to minimize the sampling error of the parameter to be estimated.[8]

Simple Random Sampling (SRS)

SRS is a probability sampling with equal probability of selection approach which can be done with or without replacement. Usually, the SRS is conducted without replacement because it is more convenient and gives more precise results.[8] The sample size formula presented above are for SRS survey. With a large enough sample size, SRS has high external validity as it represents the larger targeted population.[9,10] If you want to estimate the parameter of interest in different subgroups or strata (say by gender, age, geography, etc.), given using the same priori information and level of precision for all stratum, you can simply multiply the sample size calculated from SRS by the number of strata.[5]

Cluster Sampling (CS)

Sometimes it is too expensive to draw samples that spread out over a large geographic area. It may be much more practical and reduce costs to conduct a survey employing CS that the participants will be randomly selected within only the selected areas—so-called "clusters".[11] CS divides the population into clusters. A number of clusters are then selected randomly to represent the total population, and all eligible participants within the selected clusters are included in the survey. If not all, but some participants are randomly selected within the selected clusters, it is called multi-stage sampling technique.[8] Figure 1 presents the differences between simple random sampling and cluster sampling.

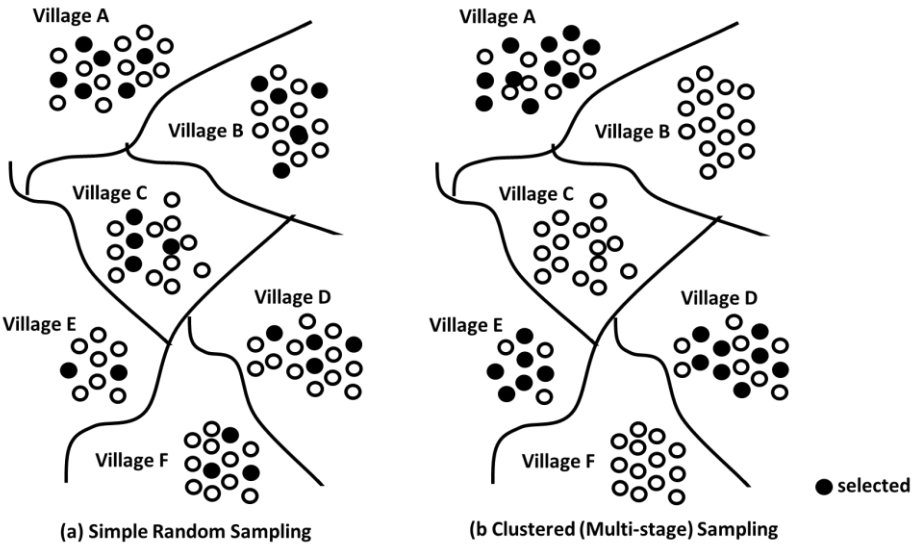
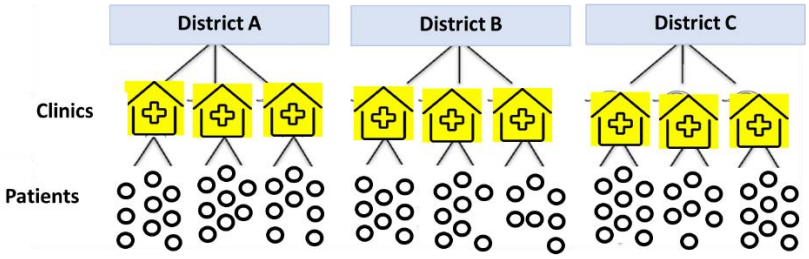


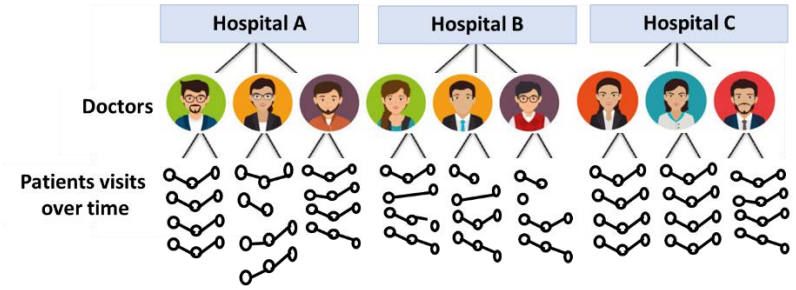
Figure 1. Simple random sampling vs. Cluster sampling

Effect of Clustered Samples in Cluster Sampling Survey

Clustered samples generally refer to surveyed participants who are physically grouped in geographical locations (villages, districts, provinces), but they may also refer to a group of participants within a shared relationship such as within a clinic/hospital. There might be more than one level of clustering. For example, a group of villagers is clustered within (i.e., get accessed to) a sub-district health facility, and a set of sub-district facilities are clustered in the same district, while different districts may possess different types of resources or surrounding conditions. Or, patients are seen by (clustered within) the same doctor, while doctors are working the same hospital, and different hospitals may have different resources and quality (Figure 2).



(a) patients clustered within a sub-district clinic which are clustered within a district



(b) patient visits (repeated measures) clustered within a doctor who are clustered within each hospital

Figure 2. Cluster levels

Cluster samples violate the SRS assumption of independence of observations as they reside in and share the same environment or settings. The observations within the same cluster may potentially be similar to one another than observations across clusters.[12] Similarities among participants in a cluster can reduce the variability of observations. This leads to a statistical concept called—the intra-cluster correlation (ICC), ρ *("rho")*—such that there might be variation across clusters more than variation within clusters. That is, ICC reflects a measure of the relatedness of clustered samples. It accounts for the relatedness of clustered samples by comparing the variation of observations (variance) within clusters (S^2_w) with the variance between

clusters (S^2_b).[11,12] Similar to the process of comparing the between and within group variances in analysis of variance (ANOVA), the ICC is calculated by dividing the between-cluster variation by the total variation of the variable to be estimated.[13,14]

$$ICC\ (\rho) = S^2_b / (S^2_b + S^2_w)$$

Like other correlations, ICC value ranges between 0 to 1. Figure 3 shows theoretical quantity where ICC=1 when all observations (Ys) within a cluster are identical (Figure 3(a)). ICC will be smaller when the variance within cluster S^2_w is much greater than the variance between clusters S^2_b. When there is no correlation of observations within a cluster, ICC=0 (Figure 3(b)).[11,14]

ID	Cluster	Y		
1	1	10	Mean within cluster =	10.00
2	1	10	Variance within Cluster =	0.00
3	1	10		
4	2	17	Mean within cluster =	17.00
5	2	17	Variance within Cluster =	0.00
6	2	17		
7	3	21	Mean within cluster =	21.00
8	3	21	Variance within Cluster =	0.00
9	3	21		
Mean Total =16.00			ICC = 1	
Variance Total =23.25				

(a) variances between clusters, no variances within clusters

ID	Cluster	Y		
1	1	10	Mean within cluster =	16.00
2	1	17	Variance within Cluster =	31.00
3	1	21		
4	2	10	Mean within cluster =	16.00
5	2	17	Variance within Cluster =	31.00
6	2	21		
7	3	10	Mean within cluster =	16.00
8	3	17	Variance within Cluster =	31.00
9	3	21		
Mean Total =16.00			ICC = 0	
Variance Total =23.25				

(b) no variances between clusters; variances within clusters

Figure 3. Intra-cluster correlation (ICC) with hypothetical scenarios

In other words, ICC tells you the degree of similarity between participants belonging to the same cluster; If it is 0, there is no evidence of clustering effects in the observations. If the ICC is approaching 1, then there is a clustering effect. Failure to take into consideration of ICC when designing CS survey might result in an under-powered study. ICC and cluster size (average number of observations to be sampled within a cluster) are thus used as part of "design effect" in sample size calculation for CS survey.[12] The difficulty is what should be the level of ICC to be input in the sample size calculation. We can calculate ICC by a post-hoc examination of the study results from previous studies that have used CS, but this has been rarely reported in the published works.[12] ICC generally varies corresponding to the parameters being estimated and the type of clustering, However, it was suggested in literature that ICC value are commonly set at ranges between 0.005–0.30.[12–14]

Design Effect in Descriptive Survey

Design effect (D) is a measure for the relative efficiency of the estimated parameter under a sampling technique employed in the survey. In other words, D is a constant used to correct for the effect (i.e., sampling error (SE)) of clustering and stratification on the estimated parameter.[15] In this case, the SE can be defined as the difference between study result and population value due to random selection of sample. It should be noted that SE is not the "bias" of the study because it can be predicted, calculated, and accounted for; and SE is influenced by sample size and sampling technique employed in the survey.[15] Thus, when taking into consideration of clustered observations, the D should be applied to adjust for the efficient sample size, particularly in CS survey.

$$n_{adjusted} = n \times D$$

In CS survey, you start with sample size calculation using the formula for SRS method and follow by accounting for the D.[16] The sample size will increase or decrease by D. When D=1, it means no effect of sample design on SE. If D >1 then sample design inflates the SE of the estimate while D <1 reduces the SE.[13] As suggested in literature, there are several ways in determining the design effect.[5,14,17]

Variance (Standard Error) Difference

D is defined as a ratio between the variance of the parameter to be estimated under CS method vs. the variance of the same estimate under SRS method. In this approach you need to have the known variances (S^2) which may be obtained from previous survey experiences. If not known, as a rule of thumb, D is typically set at 1.5, 2 or 2.5.

$$D = \frac{S^2 \text{ (Variance or Standard Error) of the designed sampling method}}{S^2 \text{ (Variance or Standard Error) of simple random sampling}}$$

Example

Adapted from a cross-sectional survey that was designed to determine prevalence of HIV among people who use drugs.[18] In the sample size calculation, the following elements were set: (1)

population size—the estimated people who used drugs (PWUD) in the study areas, N=13,000; (2) priori information—the estimated HIV prevalence of 3.5%, p=0.035, based on national report in recent years; (3) absolute margin error of 1.5%, d=0.015; (4) CI=95%. With the formula for sample size calculation for finite population SRS sampling survey, the sample size=553. For sample size adjustment, additional elements were set: (1) the design effect of variance difference, D=2.0, based on previous surveys, and (2) the expected non-response rate: 20%. The minimum sample size required in the survey=(553 x 2 /0.8)=1,383. According to the sampling plan, the total number of sample size was stratified by study sites in 21 locations, making it roughly 15% of the estimated PWUD in each site.

Variance Inflation Factor

In this approach, the design effect gives the increase in the variance arising from the clustering size (average cluster size, m) and the mean (μ) and standard deviation (sd) of the parameter to be estimated across clusters. The mean and sd may be based on previous studies/experiences. The coefficient of inflation variation is the ratio of the sd to the mean across all possible clusters, $\alpha=sd/\mu$. As the result, the D will be big if there are large clusters (big m), the clusters are very different (big α) and/or the parameter to be estimate is high (big μ, high prevalence).

$$D = 1 + m\alpha^2\mu$$

Example

Adapted from a cross-sectional survey that was designed to determine TB prevalence at national level.[19] In sample size calculation, the following elements were set: (1) priori information based on previous reports—the expected prevalence of TB=483/100,000, p=0.00483; (2) relative precision of 25%=0,00483 x 0.25, d=0.0012075; (3) CI=95%. With the formula for SRS sampling survey, the sample size=12,675. With the plan for cluster sampling, the design effect was based on variance inflation formula, $D = 1 + m\alpha^2\mu$. With the targeted 42 clusters across the country, the cluster size, m=12,675/42 ≈ 302. The sd or variation of TB prevalence across clusters was assumed to be ±40% of the average value, thus α ≈ 0.4. With the prevalence of TB, μ=0.00483. then $D = 1 + 302 \times 0.4^2 \times 0.00483=1.23$ (the design effect increased the variance by 23%), The sample size required for this survey was approximately 12,675 x 1.23=15,590.

Intraclass Correlation Approach

Another popular variance inflation factor, D is accounted for cluster size (average number of participants per cluster, m) and ICC (ρ).

$$D = 1 + (m-1)\,\rho$$

Example

Adapted from a cross-sectional study with the purpose to determine the use of physical restraints in nursing home.[20] The primary sampling unit of study were 103 nursing homes. In sample size calculation, the following elements were set: (1) priori information based on previous studies as well as consensus among 5 experts in the field—prevalence of physical restraints of 25%, p=0.25; (2) absolute margin of error of 6%, d=0.06; (3) CI=95%. With the formula for SRS sampling survey, the sample size=200. The sample size was adjusted for design effect by assuming: (1) ICC=0.08 according to the result from a similar study, and (2) mean cluster size (#participants/home)=68. The design effect, D= + (m−1) x ICC=1 + (68−1) x 0.08=6.36. With cluster design effect, the required sample size=6.36 x 200=1,272 residents. With cluster size of 68, overall 19 (1,272/68) out of 103 nursing homes were randomly selected to participate in the study.

Conclusion

To answer **"***How many participants do I need in my survey?"* or *"What should be my sample size?"* depends on your study objective, type of parameter, sampling technique, design effect, and non-response rate. Plus two more important issues that are not discussed here —the costs/resources (man & money) and logistics (management) to conduct your survey.

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