



การศึกษาข้อมูลผลของการเฝ้าระวังเชิงรุก การควบคุมและป้องกันการระบาดของโรค COVID-19 ในชุมชนชนบท อำเภอร่อนพิบูลย์ จังหวัดนครศรีธรรมราช

A retrospective study on the effectiveness of active surveillance, control and prevention of the outbreak of COVID-19 in rural communities, Ron Phibun District Nakhon Si Thammarat Province

ศิริสุนีย์ ดัญบุญยิกิจ¹, พนม สุขจันทร์², แทน สังข์ศรี^{2*}
Siritun Thunboonyakid¹, Phnom Sukchan², Tanes Sangsri^{3*}

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บทคัดย่อ

การเฝ้าระวังการระบาดของ Coronavirus disease 2019 (COVID-19) มีผลกระทบสำคัญต่อกระทรวงสาธารณสุข สังคมและเศรษฐกิจเป็นอย่างยิ่ง การศึกษานี้มีวัตถุประสงค์เพื่อวิเคราะห์มาตรการเชิงรุก และการควบคุมการระบาดของโรคโควิด-19 ในชุมชนชนบท อำเภอร่อนพิบูลย์ จังหวัดนครศรีธรรมราช โดยศึกษาผลของการใช้มาตรการควบคุมการระบาดทั้งหมดที่เกี่ยวข้องกับการระบาดของโรคโควิด-19 ตั้งแต่วันที่ 24 เมษายน ถึง 20 พฤษภาคม พ.ศ. 2564 จากการศึกษาพบผู้ป่วยโรคโควิด-19 ที่ได้รับการยืนยันทางห้องปฏิบัติการทั้งหมด 80 ราย ในอำเภอร่อนพิบูลย์ โดยใช้มาตรการเฝ้าระวังเชิงรุก พบผู้ติดเชื้อจำนวน 17 ราย (21.25%) จากการค้นหาเชิงรุก 33 ราย (41.25%) จากการติดตามผู้สัมผัสใกล้ชิด และ 30 ราย (37.5%) จากระบบเฝ้าระวัง โดยมีอายุมัธยฐาน คือ 39 ปี (Q1=19, Q3=51) ผลการวิเคราะห์พบว่ากลุ่มผู้ติดต่อในครัวเรือนและในงานพิธีอุปสมบทชาวพุทธของผู้ติดเชื้อที่ได้รับการยืนยันมีความเสี่ยงในการติดเชื้อ SARS-CoV-2 มากกว่าการติดต่อในชุมชน การศึกษานี้ชี้ให้เห็นว่าการใช้มาตรการเชิงรุก เช่น การค้นหาผู้ติดเชื้อเชิงรุก การเฝ้าระวังเชิงรุก และการร่วมมือของหน่วยงาน

¹โรงพยาบาลร่อนพิบูลย์

¹Ron Phibun hospital

²คณะแพทยศาสตร์ มหาวิทยาลัยราชวิถีวาระนคินทร์

²Faculty of Medicine, Princess of Naradhiwas University

*Corresponding Author: tanes.s@pnu.ac.th



รัฐและเอกชนทุกภาคส่วนสามารถควบคุมการระบาดของ COVID-19 ในชุมชนชนบทได้อย่างมีประสิทธิผล ข้อเสนอแนะจากการวิจัยเป็นประโยชน์อย่างค้านสามารถสูงในการใช้มาตรการเชิงรุกโดยการค้นหาผู้ติดเชื้อในทันที การเฝ้าระวังเชิงรุกเพื่อควบคุมการระบาดของโรค COVID-19 และเมื่อมีการระบาดของโรคอุบัติใหม่ในบริบทที่คล้ายคลึงกัน

คำสำคัญ: การระบาดของ COVID-19 การเฝ้าระวังเชิงรุก การสื่อสารแบบไข้แมงมุม การค้นหาผู้ติดเชื้อเชิงรุก การควบคุมและการป้องกัน

Abstract

The spread of Coronavirus disease 2019 (COVID-19) has had a significant impact on public health, medical, social, and economic systems. This study aimed to analyze the utilized multiple interventions and control measures for the outbreak of COVID-19 in the rural community, Ron Phibun district, Nakhon Si Thammarat Province. A descriptive study was conducted to review all laboratory-confirmed COVID-19 case investigation reports and identify active measures from April 24 to May 20, 2021. A total of 80 laboratory-confirmed COVID-19 cases were identified in the Ron Phibun district; 80 cases were detected via active surveillance measures, with 17 (21.25%) identified through active case finding, 33 (41.25%) through close contact tracing, and 30 (37.5%) through the surveillance system. The median age of 80 cases was 39 years (Q1=19, Q3=51). The analytic result showed that the group of household contacts and Buddhist ordination ceremony of the confirmed cases had a higher risk of SARS-CoV-2 infection than community contacts. This study indicated that prevention and mitigation of a super-spreading event require decisions that are based first and foremost on quickly recognizing and comprehending these events, especially in healthcare settings, identifying and mitigating high-risk settings, and strict adherence to active measures. Suggestions based on research findings to inform public health policies should be strengthened timely implementation of nonpharmaceutical interventions could all help in the prevention and control of the COVID-19 outbreak, and when future infectious disease outbreaks in a similar context.

Keywords: COVID-19 outbreak, active surveillance, spider-web-communication, active case finding, control and prevention



Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a new coronavirus disease 2019 (COVID-19) in late 2019, which the World Health Organization declared a pandemic on March 11, 2020 (WHO, 2020). On January 13, 2020, Thailand became the first country outside of China to detect a case of COVID-19, and the Thai Ministry of Public Health reported the first imported case of SARS-CoV-2 infection (WHO, 2021) (a). The situation in Thailand in numbers was 32 cases of COVID-19 started in a boxing stadium and drinking haunts in Bangkok on March 15, 2020, and quickly spread throughout the country. According to COVID-19 data from April 9-13, 2021, infections were discovered in more Provinces, owing primarily to the super-spreading event from entertainment venues, which resulted in a spread to family members. On April 13, 2021, incidents linked to entertainment venues accounted for 26.5% of confirmed cases in Bangkok, Chon Buri and Prachuap Khiri Khan Provinces followed by close contacts in Bangkok, Nakhon Ratchasima, Samut Prakan, and Prachuap Khiri Khan Provinces (CDC, 2021) (b)

The Ministry of Public Health of Thailand announced a policy requiring people to follow preventive measures such as distancing, mask-wearing, hand washing, temperature testing when visiting various risk areas, seeking to avoid travel to vulnerable areas, and monitoring their symptoms after visiting the risk areas (CDC, 2021) (a) However, people were not restricted to travelling from Bangkok (the outbreak center) to their hometown, consequently spreading the disease throughout the upcountry which includes Ron Phibun district, Nakhon Si Thammarat Province. As of April 24, 2021, an imported COVID-19 case (index case) was detected, that tested positive for SARS-CoV-2 with real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Since the beginning of 2021, Ron Phibun district, a small city in southern Thailand comprising 6 subdistricts and a population of approximately 82,401, has faced a significant risk of the COVID-19 outbreak. Ron Phibun hospital is primary care with 30 beds available. If super-spreading events occur, the hospital may not afford crowded patients. Compliant defensive measures of the Ministry of Public Health of Thailand (Klompas, 2020) may not work for COVID-19 control and prevention in rural communities (Abdullahi et al., 2020). Therefore, Ron Phibun hospital together with local governments and District public health set up countermeasures for mitigating and controlling the spread of COVID-19 in the



context of rural communities, including active case finding, contact tracing, and an active surveillance system that could control the outbreak of COVID-19 in the areas within 2 weeks.

In this study, we described the COVID-19 countermeasures and epidemiologic characteristics in Ron Phibun district from April 24 to May 20, 2021. The rate of confirmed cases and effective control measures during the study period were analyzed to consider the associations of multiple public health interventions.

Materials and methods

Ethics approval

This study was approved by the Ethical Review Committee of Nakhon Si Thammarat Provincial Public Health Office (IRB number NSTPH 036/2564). All procedures were carried out following the applicable guidelines and regulations.

Data sources

A retrospective study on COVID-19 countermeasures was conducted in Ron Phibun district of Na Khon Si Thammarat Province. Data of all RT-PCR positive SARS-CoV-2 confirmed cases in Ron Phibun district as of April 24 - May 20, 2021, including sex, age, exposure date and diagnosis date was collected from Ron Phibun hospital. The case investigation was carried out following the criteria of Thailand's Ministry of Public Health's National Novel Coronavirus Pneumonia Prevention and Control Program (CDC, 2021) (B). The multiple interventions and management, including outbreak investigation and management, active surveillance measures and epidemiologic characteristics were described below:

Outbreak investigation and management

The outbreak investigation of COVID-19 was performed according to the guideline of the Ministry of public health in Thailand (CDC, 2021) (B). Our team was one of the investigation teams that determined the outbreak's magnitude, epidemiologic characteristics, the source of infection and control measures. The active measures included active case finding, close contact tracing, and a surveillance system. Active case finding was implemented in the community outbreak linked to



village number 4 of Sao Thong subdistrict, village numbers 4 and 5 of Khuan Phang subdistrict and any location that had been linked to these clusters. The index cases and RT-PCR-confirmed COVID-19 cases were transferred by Special COVID-19 Operation Team (SCOT) to cohort wards including Thasala hospital, Maharaj hospital Nakhon Si Thammarat, Thungsong hospital, Sichon hospital and Pakpanang hospital. The outbreak was analyzed and presented as geographical epidemiology. The map of geographical distributions of confirmed COVID-19 cases was plotted by using R version 4.1.1 (<https://www.r-project.org>).

Case definition and case finding

A person who contacts within 1 meter of the confirmed case without effective protection, such as living or working with the patients, healthcare officers, household members, or other persons who have close contact during the patient's diagnosis, therapies and/or passengers who traveled with the patients, were considered to be in high-risk contact. A low-risk contact was defined as someone who had a close relationship with a patient and was less likely to contract the virus from that patient. This category includes close contact who do not meet the criteria for high-risk close contact. The contacts of each case were tracked down by epidemiological investigators. In this study, the type of contact was divided into 3 groups, including the Buddhist ordination ceremony; where the super-spreading event of the COVID-19 disease occurs, Household contacts; where the COVID-19 disease spread to family members and community contacts; where the COVID-19 disease spreads in the communities.

Active surveillance measure

Active surveillance was implemented for the COVID-19 disease according to the Thailand guideline for outbreak investigation and surveillance of COVID-19 (CDC, 2021) (b). On April 24, 2021, the first report of the COVID-19 case was identified in Ron Phibun hospital. The patient had a history of visiting the Thonglor area, in Bangkok, Thailand, where the high-risk cluster occurred. On April 27, 2021, the provincial communicable disease control panel for COVID-19 began the active surveillance of COVID-19 in the subdistricts of Sao Thong and Khuan Phang areas which were identified as risk areas. In addition, any new arrivals in these risk areas were screened at every village



entrance, including village number 4 in Sao Thong subdistrict and villages number 4 and 5 in Khuan Phang subdistrict. All officers collaborate as a spider-web-commination, including Ron Phibun hospital, Ron Phibun District Public Health Office, village leaders, village health volunteers, subdistrict health promotion hospital, local government and police. Potentially exposed populations were isolated at home for 14 days, receiving treatment from village health volunteers and the village headman and being monitored daily by health workers for illness or respiratory symptoms. The person who developed any related symptoms during the quarantine period was transferred to an acute respiratory infection clinic by the SCOT.

Measures for control and prevention

Close contacts and potential exposure populations were quarantined at home. Village lockdown was implemented in village number 4 of Sao Thong subdistrict and villages number 4 and 5 of Khuan Phang subdistrict that had been linked to these clusters from April 30, 2021, to May 15, 2021. Visitors arriving in Ron Phibun district were screened and reported to subdistrict health promotion hospital, Ron Phibun hospital, and Ron Phibun District Public Health Office, where they were added to a list and quarantined for 14 days. At-home quarantine was observed by village health volunteers. Traveller lists were reported to district public health office daily. The measures for COVID-19 disease control were cooperated by the local politicians and also the governor who decided to announce the policy of the community lockdown (Figure 1).

Statistical analysis

The data from the surveillance system was analyzed from April 24, 2021, to May 20, 2021. Analyses included geographic epidemiology, case characteristics, age distribution and sex ratio. Statistical analysis was performed using R version 4.1 (<https://www.r-project.org>) and GraphPad Prism 6.0 software (GraphPad Inc.). Logistic regression was used to conduct both univariate and multivariate analyses, which were then presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI). A statistically significant difference was considered at P value < 0.05 .

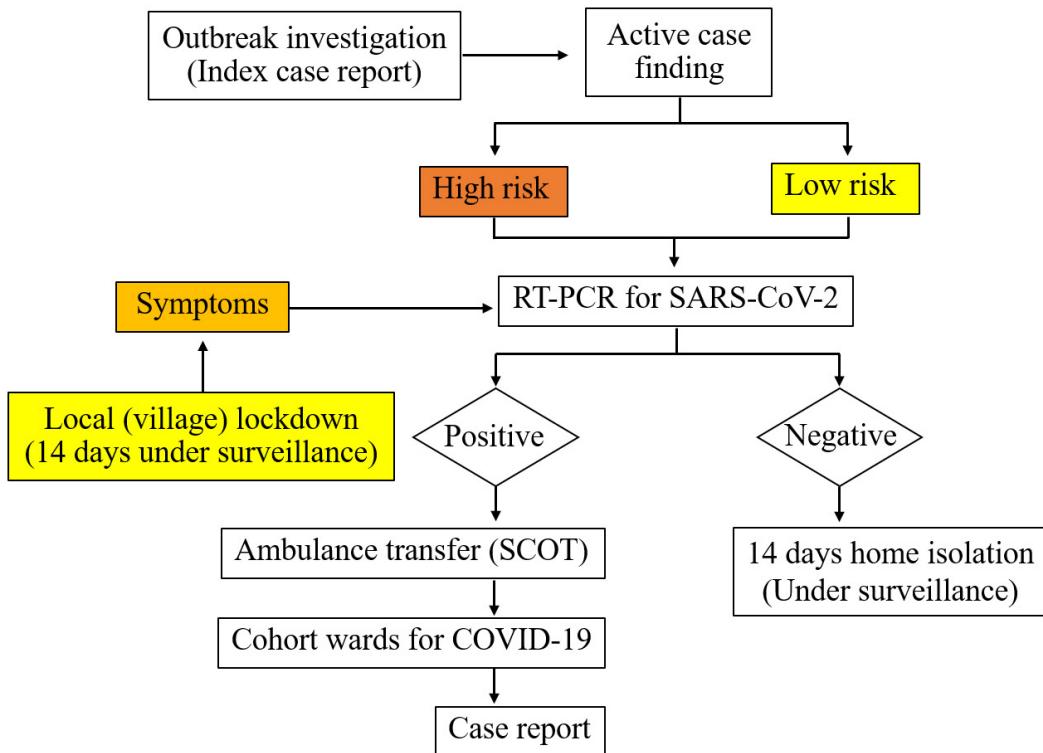


Figure 1 The measures for COVID-19 outbreak control and prevention in local transmission villages, Ron Phibun district, Nakhon Si Thammarat Province, April 27 - May 20, 2021

Results and discussion

Descriptive result

Ron Phibun district is located in the south of Thailand. About 82,401 people live in 6 subdistricts. The first case of COVID-19 in Ron Phibun district was detected on April 24, 2021. A total of 50 laboratory-confirmed cases were identified from active case findings and contact tracing which was 5.88% of the overall attack rate. Of the 50 cases, 17 cases were identified from active case finding and 33 were close contact tracing. Specific attack rates among community contact, household contact and Buddhist ordination ceremony were 1.87%, 5.13% and 13.82%, respectively. They were all hospitalized for at least 14 days and received supportive care at the cohort ward, a COVID-19-specific isolation ward under infectious control (Table 1).



Table 1 Specific attack rate of confirmed COVID-19 cases during active case finding and contact tracing of active local transmission villages in Ron Phibun district, Nakhon Si Thammarat Province, Thailand, April 27-29, 2021

	Characters	The number of persons examined	Positive by	The attack
			RT-PCR	rate (%)
Gender	Male	410	28	6.83
	Female	439	22	5.01
Age groups (year)	≤ 19	172	12	6.98
	20-29	87	6	6.90
	30-39	120	6	5.00
	40-49	144	10	6.94
	50-59	181	8	4.42
	≤ 60	145	8	5.52
Case source	Active case finding	768	17	2.21
	Contact tracing process (Examined at the hospital)	81	33	40.74
Type of contacts	Buddhist ordination ceremony	275	38	13.82
	Household contacts	535	10	1.87
	Community contacts	39	2	5.13

Factors associated with COVID-19 from active case finding and contact tracing

The risk factors for COVID-19 transmission were not significantly different by age or gender. After controlling for covariates in the multivariable analysis, the group of Buddhist ordination ceremony contacts (adjusted OR 2.62, 95% CI 1.19-5.76) of the confirmed case was a higher risk of SARS-CoV-2 infection than community contacts, while household contacts (adjusted OR 3.12, 95% CI 0.84-11.57) of the confirmed case had a lower risk of SARS-CoV-2 infection than community contacts (Table 2).



Table 2. Logistic regression analysis of risk factors associated with COVID-19 in Ron Phibun district, Nakhon Si Thammarat Province, Thailand, April 24- May 20, 2021

Factors	COVID-19		p-value ^a	p-value ^b
	Crude OR	Adjusted OR		
	(95% CI)	(95% CI)		
Gender				
Female (Ref)	-	-	-	-
Male	1.28 (0.72, 2.29)	1.20 (0.67, 2.17)	0.5274	
Age (years)				
≤19 (Ref)	-	-	-	-
20-29	0.95 (0.31, 2.67)	0.95 (0.32, 2.85)	0.9348	
30-39	0.65 (0.22, 1.91)	0.67 (0.23, 1.99)	0.4747	
40-49	1.23 (0.53, 2.85)	1.24 (0.53, 2.90)	0.6196	
50-59	0.73 (0.29, 1.77)	0.83 (0.33, 2.05)	0.6855	
≥60	0.69 (0.26, 1.79)	0.72 (0.27, 1.91)	0.5081	
Type of contacts				
Community contacts (Ref)	-	-	-	-
Buddhist ordination ceremony	2.75 (1.50, 5.02)	2.62 (1.19, 5.76)	0.0161	
Household contacts	3.15 (0.87, 11.42)	3.12 (0.84, 11.57)	0.0884	
Log-likelihood				
AIC	-179.00			
AIC= Akaike information criterion				

^aWald's test, ^bLR-test

Tracing of the index case and the source of transmission

The first (index) case was a 51-year-old man with COVID-19 who had a history of visiting nightclubs at Thonglor in the capital Bangkok where the second wave of COVID-19 outbreak occurred “Thonglor cluster”. The index case travelled to village number 5 of Khuan Phang subdistrict, Ron Phibun district, Nakhon Si Thammarat Province to participate in the party of Buddhist ordination



ceremony on April 20, 2021. The index case was diagnosed with SARS-CoV-2 infection on April 24, 2021. The spread occurred during this event.

The geographic distribution of confirmed cases of the surveillance system in Ron Phibun district from April 24 to May 20, 2021, was shown in Figure 2. The outbreak began in village number 5 of Khuan Phang subdistrict and spread across 4 subdistricts including Sao Thong, Hin Tok, Chuan Chum and Ron Phibun. Interestingly, there was no case of COVID-19 transmission in Khuan Koei after multiple interventions (Figure 2A). The active transmission villages were distributed from the index case in the Buddhist ordination ceremony, village number 5 of Khuan Phang subdistrict. Following interventions, the number of reported cases began to stabilize and rapidly decline (Figure 2B). The 80 confirmed cases at the end of May 20 included two cases of cough, a case of fatigue, a case of rhinorrhea, a case of sore throat, a case of cough and fatigue, two cases of fever and cough, a case of fever and diarrhoea, a case of fever, cough, and fatigue, four cases of fever, cough, and rhinorrhea, a case of fever, cough, and sore throat, a case of cough, sore throat, and diarrhoea, and 64 cases with no symptoms. The median age was 39 years (Q1=19, Q3=51).

The effectiveness of countermeasures

Early detection and immediate implementation of control measures such as community surveillance were successful to contain the number of cases in Ron Phibun district. Active surveillance and management, combined with the quarantine of high- and low-risk contacts, was an effective strategy for preventing infection that was successfully employed in Singapore and South Korea (Lai et al., 2020; Liu et al., 2021; Wong, Leo, & Tan, 2020; Zhou et al., 2021). This study suggested how important active measures were in mitigating the COVID-19 outbreak in rural communities.

Discussion

In this study, after the implementation of multifaceted public health measures, including active case finding, close contact tracing, surveillance system and village lockdown along with public health procedures, the number of COVID-19 cases was diminished and the outbreak was improved and controlled in rural communities, Ron Phibun district, Nakhon Si Thammarat Province, Thailand.



The daily case report reached a peak on April 28 and excellently decreased after early interventions were taken, intending to interrupt sustained COVID-19 transmission outside Ron Phibun district. This result suggests that active case finding and village lockdown can effectively reduce the number of cases and must be employed after the detection of the first case of COVID-19 in the community (Islam et al., 2020; Lai et al., 2020; Wong et al., 2020). In addition, a local lockdown may not interrupt the occupations of the majority population as well as a country lockdown.

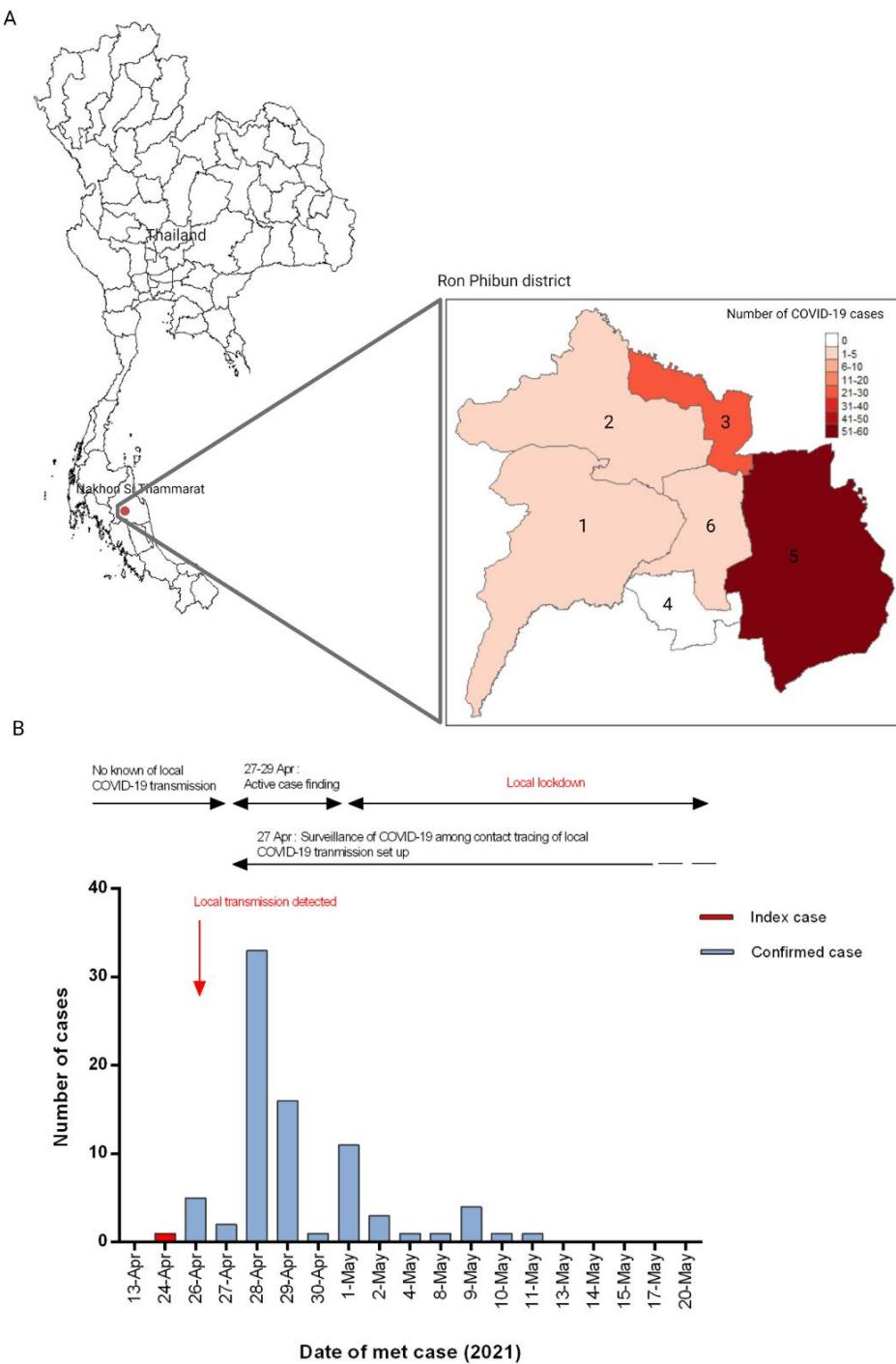


Figure 2 The geographic distribution of COVID-19 cases in Ron Phibun district and calendar date from April 13 to May 20, 2021. A shows the geographic distribution of COVID-19 cases in each subdistrict (n= 80) at which 1, Ron Phibun; 2, Hin Tok; 3, Sao Thong; 4, Khuan Koei; 5, Khuan Phang and 6, Khuan Chum subdistricts, respectively. B shows the daily number of cases in 6



subdistricts, April 13 - May 20, 2021. The graph was created with R version 4.1 (<https://www.r-project.org>) and merged by BioRender.com.

There is no case of COVID-19 in Khuan Koei subdistrict during the period of intervention suggesting that active case finding are more effective strategies to discontinue the outbreak of COVID-19 than only travel restrictions (Lai et al., 2020; Liu et al., 2021). Among the 50 confirmed COVID-19 cases of active surveillance show that males are at higher risk of infection rate than females (attack rate, 6.83% vs 5.01%), according to a previous report from China (Wang et al., 2020) mentioned that men may have more risk behaviors than women, such as coffeehouse forums (very popular in local communities). The logistic-regression analysis of multivariate shows that the Buddhist ordination ceremony; the center of the active local transmission villages shows a significantly higher risk than community contact, however, household contacts are the highest risk of SARS-CoV-2 infection, which suggests the increasing awareness of transmissibility of COVID-19 through family members (Xu et al., 2020; Zhou et al., 2021). All age groups are not significantly different in terms of susceptibility to COVID-19 infection; however, it appears that middle-aged groups are more susceptible than older. The transmission rate is associated with middle age, male sex, and household contacts. The prevalence of symptoms in men (62.50%) is higher than in women (37.50%), where no symptom cases are 53.2% of men and 46.8% of women, respectively, which is consistent with a previous report from China indicating that men are more susceptible to COVID-19 than women (Guan et al., 2020; Yang et al., 2020). However, the logistic-regression analysis of only people who attended the Buddhist ordination ceremony shows that males and females are equally susceptible to COVID-19 infection (Crude OR 1.02, 95% CI 0.47-2.25). The findings of this study could be useful in current efforts to combat the global COVID-19 pandemic, especially in a similar context of communities.

Following the implementations, we consistently observe a rapid reduction in the number of cases in all regions. This remarkable declining trend begins immediately after the detection of the first case in late April in Khuan Phang subdistrict and is presumably attributable to increasing population awareness and the effect of active measures. After May 1, the lockdown allowed the case number to fall the outbreak distinctly and mitigate the active local transmission of COVID-19 in all subdistricts as previously found in other countries such as Italy, Singapore and China (Goh et al., 2006; Guzzetta



et al., 2021; Lai et al., 2020). COVID-19 emerged in Ron Phibun district with a cluster similar to that described in the capital Bangkok, and with other clusters around the cities of Bangkok, including Samut Sakhon and Samut Prakan Provinces (WHO, 2021) (a). Interestingly, this study indicates that 80% (64/80) are asymptomatic persons which might explain the rapid ongoing active transmission village and also indicates a rapid person-to-person transmission of COVID-19 occurs in a population density and family members.

Thailand's preventive measures for the COVID-19 transmission are D-M-H-T-T; Distancing, Mask-wearing, Hand-washing, Temperature check and Thai Chana application, respectively, have been used nationwide (WHO, 2021) (c). The government decree was issued on a national scale, including the suspension of congress and large meetings, restaurants, schools/ universities that teach online, and all activities that lead to mass gatherings. Universal prevention in Thailand was applied in January 2021 (WHO, 2021) (c). People are requested to scan "Thai Chana" applications when they need to travel to other places. An effective vaccine is the most protective measure against COVID-19 but now is not the best way to control the transmission. The evolution of viruses that have been mutated to new variants affects the efficacy of vaccines to protect against infection or mortality (Bian et al., 2021). According to the findings of this study, policymakers should implement a local lockdown to reduce the relative risk and attack rate, in addition, active measures are the most effective to limit the transmission of COVID-19 during super-spreading events occurred together with vaccination. Due to the efficacy of the vaccine that could not protect against variants of SARS-CoV-2 infection (Bian et al., 2021; Lopez et al., 2021) we believe that controlling potentially infected populations, including high-risk close contacts and populations from high-risk areas, as well as cooperation between local and public health officers as a spider-web communication, could be considered for COVID-19 control and that the successful approach in Ron Phibun district could serve as a model.

This study has two limitations. First, we did not have the population of potential exposure population data who came to test nasopharyngeal swabs for SARS-CoV-2 in the hospital due to the urgent situation. Second, since data was extracted from the infectious disease reporting system, other epidemiological and clinical characteristics were unavailable, such as time to admission, time to discharge, medical treatment, and vital status.



Recommendations

The investigation of the disease by the patient's family may not be completed, because there are often many activities that the patient cannot disclose. After all, it will harm their image or even break a law, so an inquiry from a community member or a community leader, such as the village headman, is required. This is not a punishment or a stigma; it is solely for disease control and will not be disclosed regarding the patient's timeline. To establish a clear policy, it is necessary to rely on the cooperation of the Ministry of Interior. Because of the problems encountered during the lockdown, the responsibility will fall primarily on the village headman and officers to manage the villagers during the control measures, which also include those who are unable to provide food to villagers during village lockdown, as well as remedies for the impact of a lack of income in the occupation. We have recommendations for the implementation of active measures for super-spreading event prevention which depends on quickly recognizing and understanding this event as the following: (1) early detection is essential for mitigation and the decision for policymakers to immediately employ a local lockdown and active surveillance, (2) the cooperation like spider-web communication should be deployed when a newly characteristic emerging disease is similar to SARS-CoV-2 infection, (3) Effective vaccine is needed to distribute the whole country to reduce the admission of the patient in the hospital and/ or mortality and also the booster shot for higher and longer protection. It would be of interest to future research to investigate the impact of COVID-19 infection on both physical and mental health in the long term as well as the impact on society and the economy.

Conclusions

In this study, we summarized the effectiveness of policies and provided a reference point at the beginning of the epidemic, when active control measures such as active case finding, active surveillance, local restricted traffic and even local lockdown in rural communities could effectively reduce the chance of a super-spreading event. When there is neither a viable medicine nor a vaccine, vigorous nonpharmaceutical interventions could all help in the prevention and control of the COVID-19 outbreak.



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Conflict of interest

The authors declare no potential conflict of interest in this study.

Author contributions

S.T. and T.S. conceptualized and designed the experiments. S.T. conducted most of the experiments. P.S analyzed and managed some data. All authors participated in the writing and final editing of the manuscript.

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