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Patient Reporting of Preventive Practices and Experiences of Suspected Adverse Drug and Vaccine Events During and After the COVID-19 Pandemic

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Abstract

This study aimed to compare patients' preventive practices during and after the COVID-19 pandemic, to investigate patient-reported suspected adverse events (SAEs) of drugs and vaccines used for COVID-19 and their associated factors, and to identify their barriers regarding COVID-19 prevention and treatment. A cross-sectional survey was conducted at a secondary care hospital using systematic random sampling of outpatients with prior COVID-19. A total of 400 valid questionnaires were analyzed. The preventive practices declined significantly in post-pandemic period ($P < 0.001$). A total of 110 respondents (27.5%) reported SAEs of COVID-19 vaccines, with fever (84.5%), fatigue (44.5%) being the most common events. Additionally, 19 respondents (4.8%) reported SAEs of anti-COVID-19 drugs, mainly andrographis (47.4%) and favipiravir (42.1%). The common SAEs related to drugs included nausea or vomiting (31.6%), itching (26.3%), and rash (26.3%). Most SAEs were mild, but 59.1% of vaccine-related and 57.9% of anti-COVID drugs-related SAEs were unreported to healthcare professionals (HCPs). The use of self-medication was associated with a higher rate of SAEs (OR 2.206, $p = 0.003$). Concern regarding vaccine safety was the primary barrier to prevention during both phases (61.0% vs. 52.8%; $P = 0.002$). These findings highlight a need for proactive monitoring by HCPs and an accessible patient reporting system, particularly for self-medicating patients.

1. Introduction

Coronavirus disease 2019 (COVID-19) presents with a wide clinical spectrum, ranging from mild respiratory symptoms to severe pneumonia [1]. Although the World Health Organization (WHO) has declared the end of the public health emergency of international concern [1, 2], the virus continues to undergo rapid and ongoing mutation [3]. Consequently, predicting precise epidemiological patterns remains challenging, and the risk of emerging infection persists [4]. In the post-pandemic or endemic phase of COVID-19, there has been a drop in public compliance with preventive practices in several contexts [5, 6].

Approval for most COVID-19 vaccines and antivirals was granted under Emergency Use Authorizations (EUA). Safety monitoring after approval of the product is also important in this transition. COVID-19 vaccines and antiviral medicines were developed quickly during an emergency response; the safety information from real-world data will also rely on parts of surveillance systems that can identify events that happen outside of clinical trials. Therefore, post-marketing surveillance is required [7, 8].

In Thailand, the current Spontaneous Reporting System (SRS) relies primarily on healthcare professionals (HCPs). However, this system has major limitations, notably under-reporting [9, 10] and a tendency to prioritize reports of serious adverse events [11]. Consequently, some of the symptoms experienced by the patients may not be reported to the official pharmacovigilance pathway if they are not communicated to HCPs.

Patient self-reporting is essential, as it enables individuals to report all perceived abnormalities and provides a more accurate estimate of adverse event frequency, particularly for symptoms affecting daily

life [12]. This approach offers a comprehensive view of the real-world experience. Moreover, patient reporting facilitates the identification of new adverse event signals that may not be previously reported by HCPs [9, 10, 13]. Previous studies have demonstrated the value of patient self-reporting. A study indicated a 53% incidence of AEs among nirmatrelvir/ritonavir users, with dysgeusia (metallic taste) and nausea most frequently reported [14]. Furthermore, patient-reported data have been useful in highlighting barriers to vaccination and service access, such as safety anxiety and mistrust in the public health system [15].

Thailand implemented a public health policy during the COVID-19 crisis by integrating the herbal medicine Andrographis into its national treatment guidelines for mild COVID-19. Although its inclusion in the National List of Essential Medicines facilitated broad access through hospitals and community pharmacies, while its familiarity and availability also supported self-medication. Andrographis therefore occupies an important boundary between formal public health policy, community access, and informal patient use. Products moving across these settings may be used widely and inconsistently monitored, especially when patients manage symptoms on their own or do not report SAEs to HCPs.

Although vaccines, antivirals and herbal medicines are still used today and in the post-pandemic phase, there is little evidence regarding adverse event suspected by patients and reporting rates among outpatients. Moreover, preventive practices and perceived barriers to COVID-19 prevention and treatment may provide important context for understanding patient safety experiences. Therefore, this study aimed to compare patients' preventive practices during and after pandemic stages (defined by Thailand's declaration of COVID-19 as an endemic disease), to investigate patient-reported suspected adverse events (SAEs) of drugs and vaccines used for COVID-19 and their associated factors, and to identify barriers regarding COVID-19 prevention and treatment during both periods.

2. Methods

2.1 Study design and setting

This study was a cross-sectional survey using self-administered online and paper-based questionnaires. Data were collected between August and October 2024 among outpatients aged 18 years or older who had prior COVID-19 infection. The study was conducted at Sawangdandin Crown Prince Hospital, a 320-bed secondary care hospital located in northeastern Thailand. The reporting of this observational study followed the strengthening the reporting of observational studies in epidemiology (STROBE) checklist [16] ,which is provided as a supplementary file.

2.2 Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Khon Kaen University Ethics Committee for Human Research (Approval No. HE611559, dated 1 December 2023). Verbal informed consent was obtained from all participants prior to study participation.

2.3 Participants and sample size

Eligible participants were outpatients aged 18 years and older who reported a previous COVID-19 infection and were able to complete the questionnaire in Thai. Participants were asked whether they had had a COVID-19. infection; if they answered “yes”, they could complete the questionnaire. To be included in the final analysis, participants were required to complete at least 70% of the items in Sections 2, 3, and 4 of the questionnaires.

The sample size was determined with Yamane's formula based on 174,004 outpatients during 6 months of the reference period, and a 5% margin of error, which yielded a sample size of 400 respondents. This calculation was done to estimate proportions in the survey. Those associations which were explored in regression were considered exploratory. Participants were selected by systematic sampling, and only fully completed, valid questionnaires were analyzed. Participants were excluded if they could not read Thai, were unable to communicate with the researchers, did not provide voluntary consent, had previously completed a related questionnaire or submitted incomplete or late responses. Participants were asked to complete the questionnaire independently. For visually impaired participants, assistance from a relative was permitted only to record the participant’s responses, provided that the participant agreed.

2.4 Questionnaire development and testing

The questionnaire was developed for this study. Three HCP experts in the field (one physician and two hospital pharmacists) were asked to assess content validity using the index of consistency (IOC) [17], with all developed questionnaire items achieving an IOC score exceeding 0.5 at the value of 0.95. The questionnaire was then piloted with 10 outpatients from another hospital with similar characteristics to the target population. The questionnaire was appropriately modified following the suggestions from the experts and pilot study. The final questionnaire consisted of the four sections.

Section 1: Participants’ demographic data, including sex, age, education level, occupation, underlying diseases, number of current medications, history of drug allergies, timing and number of COVID-19 infection, Long COVID symptoms, vaccination or antiviral treatment history, self-medication with herbs or dietary supplements, and patient-reported SAEs after COVID-19 vaccination or anti-COVID drugs.

Section 2: Closed questions were used with checklists exploring practice activities related to COVID-19 prevention and control during and post-outbreak stage, using 6 items with “always,” “sometimes,” and “never” response options. A score of 1 was given for “always” and 0 for “sometimes” and “never” responses.

Section 3: This section consisted of 15 open-ended and closed-ended questions designed to assess patient participation in safety monitoring. The items were categorized into two areas: patient-reported SAEs after COVID-19 vaccination (7 items) and anti-COVID drugs (8 items).

Section 4: A 19-item checklist of closed-ended questions was used to address problems and barriers related to COVID-19 prevention and treatment during both the outbreak and post-pandemic periods. Respondents could select multiple options.

2.5 Data collection

Data collection was conducted at the General Practice Department, the Non-Communicable Diseases (NCD) Clinic and the After-hours Clinic, as well as among participants waiting at the Outpatient and NCD Pharmacies. Participants were provided with a one-page invitation letter containing a QR code for electronic submission (via Google Form) or were offered a paper-based questionnaire, depending on their convenience. Offering both online and paper formats was intended to improve accessibility for participants with different levels of digital access. Distribution followed a systematic sampling method with an interval of 4. A random starting number between 1 and 4 was generated using Microsoft Excel, and every fourth outpatient was subsequently selected. In the event of a refusal, the next available person was approached as a replacement. This process continued until 400 complete and valid questionnaires were obtained for statistical analysis.

2.6 Data analysis

All questionnaire responses were analyzed using IBM SPSS Statistics for Windows version 22.0. Descriptive statistics were computed as frequencies and percentages for categorical variables. COVID-19 prevention practices were assessed using 6 items, with scores from 0 to 6. A score below 5 indicated a practice level below 80%, while 5 or above indicated 80% or higher. Pearson's chi-squared test was used to compare subgroups for categorical data, while the McNemar chi-squared test was utilized to evaluate practices and barriers to COVID-19 prevention and treatment during the outbreak and post-outbreak stages within the same populations. For nonparametric continuous variables, the Mann-Whitney U or Kruskal-Wallis tests were used to assess the comparisons. Factors associated with patient-reported SAEs after COVID-19 vaccination or anti-COVID-19 drugs were analyzed using binary logistic regression. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1 Response rate and demographic data

A total of 478 questionnaires were distributed to outpatients with a history of COVID-19 infection by using systematic random sampling, yielding 400 valid responses (83.68%). The majority of respondents were female (68.3%) with a mean age of 43.76 ± 14.52 years. Most participants (71.8%) had an education level below the undergraduate degree, and 24.3% were employed as farmers. Regarding COVID-19 history, 84.0% of respondents reported being infected once. Specifically, 60.0% of these infections occurred during the pandemic, 30% during the post-pandemic period, and 10% respondents reported infections across both phases. Nearly half of respondents reported Long COVID symptoms (49.8%). Most respondents had received two or more doses of a COVID-19 vaccine (96.5%). (Table 1)

[Insert Table 1]

3.2 Practices relating to COVID-19 preventive measure during and post the COVID-19 outbreak

Overall, for all six activities, the proportion of respondents who reported performing them “always” significantly declined in the post-outbreak period compared to the outbreak period ($P < 0.05$). The activity most frequently performed “always” in both periods was self-isolation when COVID-19 infection was suspected (outbreak 89.8% vs post-outbreak 58.0%; $P < 0.001$), followed by using an antigen test kit (ATK) when infection was suspected (outbreak 88.5% vs post-outbreak 57.3%; $P < 0.001$). Conversely, maintaining social distance in crowded places was observed to be the least practiced activity in both periods (outbreak 73.5% vs. post-outbreak 32.5%; $P < 0.001$) (Table 2).

[Insert Table 2]

3.3 Patient-reported SAEs of COVID-19 vaccines and anti-COVID drugs.

Overall, 110 respondents (27.5%) reported at least one SAEs of COVID-19 vaccines. Sinovac was the most commonly administered vaccine (n = 275, 68.8%); 41 recipients reported SAEs, representing the lowest incidence (14.9%). In contrast, the highest incidence of SAEs was observed among recipients of the AstraZeneca vaccine (56/245, 22.9%), followed by Pfizer (44/206, 21.4%) and Moderna (5/27, 18.5%). Among those reporting adverse events, the three most common SAEs were fever (n = 93, 84.5%), fatigue (n = 49, 44.5%) and pain at the injection site (n = 29, 26.4%) (Table 3). The majority of respondents classified the severity of their vaccine-related adverse events as mild (n=68, 61.8%). The most frequently reported management strategy was self-treatment (n=68, 62.4%), followed by immediate consultation with a doctor (n=26, 23.6%) and taking no action (n=17, 15.5%), respectively. The majority of respondents did not inform HCPs after experiencing vaccine-related adverse events (n = 65, 59.1%).

A total of 19 respondents (4.8%) reported one or more SAEs of anti-COVID drugs.Andrographis (n=9, 47.4%) was the highest proportion of reports of drugs-related SAEs followed by favipiravir (n=8, 42.1%). The highest self-reported SAEs incidence among anti-COVID drugs users was observed for favipiravir (8/94, 8.5%), followed by Andrographis (9/243, 3.7%) and molnupiravir (2/93, 2.2%).Among Andrographis users who reported SAEs, the most common symptoms were dizziness (n=4, 44.4%), nausea or vomiting (n = 3, 33.3%), itching (n = 3, 33.3%), and diarrhea (n = 3, 33.3%).Of the favipiravir users who reported SAEs, the most frequent symptoms were palpitations (n = 4, 50.0%), dizziness (n = 3, 37.5%), and blurred vision (n = 3, 37.5%). Among molnupiravir users who reported SAEs, the most common symptoms included nausea/vomiting. (n = 1, 50.0%), rash (n = 1, 50.0%), and itching (n = 1,

50.0%). Overall, the most common suspected symptoms of anti-COVID-19 drugs were nausea/vomiting (n = 6, 31.6%), followed by itching (n = 5, 26.3%) and rash (n = 5, 26.3%) (Table 3).

Regarding participants' perceived confidence that their symptoms were related to anti-COVID drugs , most reported moderate confidence (n = 11, 57.9%), followed by high confidence (n = 6, 31.6%) and very high confidence (n = 2, 10.5%), respectively, with most classifying the severity as mild (n = 12, 63.2%) and moderate (n = 7, 36.8%). Regarding the management of these adverse events, the most common approach was taking no action (n = 9, 47.4%), followed by self-treatment (n = 7, 36.8%) and immediate consultation with a doctor (n = 3, 15.8%), respectively. Notably, the majority of respondents did not inform HCPs about their antiviral-related adverse events (n = 11, 57.9%).

[Insert Table 3]

3.4 Factors related to patient reported SAEs of COVID-19 vaccines or anti-COVID drugs (univariate analysis)

Univariate analysis revealed that sex (p=0.020), highest educational level (p=0.049), occupation (p = 0.007), Andrographis users (p = 0.032), and self-administration with herbs or dietary supplements during the COVID-19 pandemic (p < 0.001) were statistically significant factors related to the patient-reported SAEs of COVID-19 vaccines or anti-COVID drugs. (Table 4)

[Insert Table 4]

3.5 Factors associated with patient-reported SAEs of COVID-19 vaccines or anti-COVID drugs (multiple logistic regression analysis)

Variables with a p-value of less than 0.25 were included in the multiple logistic regression analysis. The results identified that a history of self-medication with herbs or dietary supplements during the COVID-19 pandemic was significantly associated with patient-reported adverse events. Patients who self-medicated with these products experienced a higher incidence of reporting SAEs compared to non-users (aOR 2.206; 95% CI: 1.317–3.696; P = 0.003). (Table 5)

[Insert Table 5]

3.6 Patients' perspectives on barriers to COVID-19 prevention and care: pandemic and post-pandemic

Comparing the pandemic and post-pandemic periods, the overall prevalence of problems related to COVID-19 prevention and treatment declined significantly ($P < 0.05$). Specifically, insufficient COVID-19 screening and surveillance systems decreased from 41.2% to 30.7% ($P < 0.001$).

Regarding the reliability of information sources, issues concerning information about the COVID-19 disease and prevention guidelines significantly decreased (56.0% during the pandemic vs. 39.8% post-pandemic; $P < 0.001$ and 44.3% during the pandemic vs. 36.3% post-pandemic; $P = 0.005$, respectively). Conversely, issues regarding the reliability of information on drugs or supplements for COVID-19 prevention remained the most prevalent problem in the post-pandemic period, showing a slight, non-significant increase (40.3% during the pandemic vs. 41.5% post-pandemic; $P = 0.712$).

Vaccine-related issues were the most frequently reported barriers in both periods. Anxiety regarding vaccine safety was the leading concern (61.0% during the pandemic vs. 52.8% post-pandemic; p=0.002), followed by concerns about vaccine efficacy (59.1% during the pandemic vs. 52.4% post-pandemic; p=0.014).In contrast, barriers related to the inconvenience of receiving multiple booster doses increased significantly in the post-pandemic period (16.8% during the pandemic vs. 24.0% post-pandemic; $P = 0.001$).

Finally, regarding treatment, barriers such as medication insufficiency and delayed access to anti-COVID drugs also decreased significantly during the post-pandemic phase (47.3% vs. 37.8%; $P < 0.001$ and 42.3% vs. 35.8%; $P = 0.019$, respectively). (Table 6)

[Insert Table 6]

4. Discussion

Out of 478 distributed questionnaires, 400 valid responses were received, resulting in a response rate of 83.68%. This was broadly similar to a previous study, which reported a response rate of 84.3% [18]. The significant decline in preventive practices after the pandemic period is consistent with previous studies showing relaxation of COVID-19 preventive behaviors as public risk perception decreases [5, 6] In this study, all six assessed preventive practices declined significantly after the pandemic period. Rather than interpreting this finding only as a prevention problem, it should also be viewed as part of a broader normalization of COVID-19 risk. As COVID-19 becomes perceived as less urgent, patients may be less likely to attend to, seek care for, or report mild and transient symptoms after vaccination or treatment. This is important in the context of passive pharmacovigilance which depends in part on symptoms experienced by patients being reported to HCPs.

A total of 110 respondents (27.5%) reported experiencing adverse events following COVID-19 vaccination. The majority of these cases were classified as mild (61.8%), consistent with previous studies [19]. Furthermore, self-treatment was identified as the most common management strategy, aligning with prior finding that approximately half of AEs required no medical intervention (39.7%-56.6%) and around half necessitated medical symptomatic treatment (42.5%-50.2%) [20]. Similarly, an

observational study found that 95% of the adverse effects reported after either an inactivated or mRNA vaccine were mild, requiring no or home-based treatment [21].

The most commonly reported adverse events included fever, fatigue, and pain at the injection site. Notably, fever and injection site pain are well-documented vaccine-related reactions consistent with findings from several previous studies [22, 23]. A number of adverse events were likely reported by AstraZeneca recipients. (n = 56, 50.9%). Our results were in line with those of other studies; for example, a study found that adverse events following immunization (AEFI) occurred more frequently with the AstraZeneca vaccine compared to the Pfizer-BioNTech vaccine [24]. A previous study showed the frequency of side effects has been reported to be higher in the recipients of the Oxford-AstraZeneca vaccine (52.6%) than in those who have received the Pfizer-BioNTech (4.8%) or the Sinopharm vaccine (42.6%) [25].Conversely, Sinovac showed the lowest incidence of adverse events (n = 41, 14.9%), followed by Sinopharm (n = 4, 15.4%). This aligns with a prior study [22], which indicated that the Sinopharm and Sinovac vaccines (21%–28%) were associated with the fewest adverse events. This finding was consistent with the results of multiple previous studies reporting that inactivated vaccines induced fewer side effects than either adenoviral vector-based or mRNA-based vaccines [26].

In this study, the most frequently reported SAEs of favipiravir were palpitations (n = 4, 21.1%), followed by dizziness and blurred vision (n = 3, 15.8% each). These findings contrast with a previous study [27], which reported primarily gastrointestinal symptoms such as loss of appetite (2%) and nausea/vomiting (1.5%). Furthermore, our results diverge from the WHO database [28], where the most common adverse events included elevated liver enzymes (23.66%), nausea/vomiting (13.98%), increased heart rate (9.68%), diarrhea (7.52%), and QT prolongation (5.37%). These divergent results could be attributed to recall bias, exacerbated by the brief five-day treatment course, which may hinder the recall of mild symptoms. Additionally, the lack of routine liver function monitoring during the treatment period likely contributed to these differences. Because some adverse reactions, such as elevated liver enzymes and hyperuricemia, are often asymptomatic or subclinical, laboratory verification is essential for diagnosing these conditions and assessing their causality.

Our findings reveal the safety profile of Andrographis. Although the incidence rate of adverse events (3.7%) was lower than that of Favipiravir (8.5%), Andrographis accounted for the largest proportion (47.4%) of all anti-COVID drug-related safety reports in this study. The predominant reported symptoms included gastrointestinal disturbances (nausea, vomiting, diarrhea) and dizziness, which are consistent with previous pharmacological studies [29, 30].

Self-medication with herbs or dietary supplements during the COVID-19 pandemic reported a significantly higher proportion of patient-reported SAEs compared to non-users (aOR 2.206; 95% CI: 1.317–3.696; p = 0.003). It may be attributed to tendency toward polypharmacy for prevention or treatment during the pandemic, which likely increased the risk of adverse events [31, 32]. Self-medication may lead to polypharmacy, incorrect diagnosis, adverse effects, drug interactions [33], medication errors and overdoses [34]. These complications can make it difficult for patients to identify

the true cause of their abnormal symptoms. This confusion can lead to overreporting of adverse events, a finding consistent with evidence from previous studies [35]. The major factors associated with self-medication were fear, anxiety, and perception regarding COVID-19 [36]. This heightened concern about experienced symptoms was associated with more frequent Adverse Drug Reactions (ADRs) reports [11, 37]. However, this association is may not an indication of the causal relationship between self-medication and adverse events. It could alternatively be related to a combination of factors and reduced contact with HCPs who could verify, document or manage SAEs.

This study found that SAEs of COVID-19 vaccines and anti-COVID drugs were not rare among outpatients who had previously received the vaccine and treatment. Over 57% the participants who had SAEs after vaccination or anti-COVID drugs did not inform HCPs. Therefore, enhancing the accuracy of patient-reported adverse events requires HCPs to re-evaluate and verify suspected adverse reactions. This validation process is essential to maintain high-quality data, particularly during public health emergencies. Furthermore, educating patients about potential adverse effects will improve report quality and strengthen the overall efficiency of pharmacovigilance systems [11]. SRS alone is inadequate for managing COVID-19 in its endemic phase. Community based active surveillance protocol is recommended with proactive follow-up, particularly for the patients using self-medication with herbs or dietary supplements. HCPs should challenge the assumption of medications or vaccine safety by actively screening for adverse effects. Moreover, educating patients, at the point of dispensing, on what to monitor and how to report is essential to restoring the integrity of national pharmacovigilance databases.

Consistent with previous studies [38, 39], this study identified anxiety regarding vaccine safety and efficacy as the primary barrier. Additionally, varying vaccine profiles caused confusion among patients regarding vaccine selection. Although extensive research confirms the high safety and efficacy of COVID-19 vaccines [40, 41], public concern persisted. To address this, HCPs should provide evidence-based information and ensure continuous safety monitoring to foster confidence in vaccine acceptance.

Strengths of this study included the involvement of patients in reporting of SAEs, monitoring both vaccines and drugs used for COVID-19 prevention and treatment, and demonstrating the incidence of patient reported SAEs in real practice. These can lead to potential screening of adverse drug and vaccine events in the hospitals. However, this study has some limitations. Data were collected using self-administered questionnaires, recall bias might occur. Causality was not clinically verified; patient-reported SAEs lacked HCPs assessment using objective parameters or formal algorithms. Therefore, these findings represent 'patient-reported suspected symptoms' and reflect the perceived burden of harm rather than clinically confirmed ADRs. Moreover, the single-center design may limit the generalizability of the findings. Future research should incorporate medical record reviews by HCP assessment and multi-center active surveillance to enhance reliability.

5. Conclusion

The findings of this study highlight that patient-reported SAEs of COVID-19 vaccines and anti-COVID-19 drugs remain relevant in post-pandemic outpatient care. Many SAEs are not reported to HCPs, especially those involving mild or self-managed symptoms. Patients who self-medicate with herbs or dietary supplements have higher odds of reporting SAEs. The use of Andrographis is an important monitoring concern because it is used in both formal and informal care settings in Thailand. Traditional, passive SRS are inadequate for detecting real-world AEs in people who use health products (e.g., COVID-19 vaccines, herbal products, and antivirals). To strengthen pharmacovigilance, health policies need to integrate active surveillance protocols into the formal pharmacovigilance system. HCPs can improve patient safety and support the integrity of post-marketing medication and vaccine surveillance by conducting proactive monitoring and educating patients at the point of service.

Abbreviations

COVID-19	Coronavirus Disease 2019;
SAEs	Suspected Adverse Events;
WHO	World Health Organization;
EUA	Emergency Use Authorizations;
CI	Confidence Interval;
aOR	Adjusted Odds Ratio;
SRS	Spontaneous Reporting System;
HCPs	healthcare professionals;
IOC	Index of Consistency;
NCD	Non-Communicable Diseases;
AEFI	Adverse Events Following Immunization;
ADRs	Adverse Drug Reactions;

Declarations

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions statement

Sasina Kaiyarat: Methodology, Investigation, Formal analysis, Writing - original draft preparation**.**

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Anthony R. Cox: Writing - review and editing, Validation**. Narumol Jarernsiripornkul:** Conceptualization, Investigation, Formal analysis, Writing - review and editing, Funding acquisition, Supervision, Validation. All authors read and approved the final manuscript.

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Additional Information

Competing interest: All authors declare that they have no conflict of interest.

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Tables

Tables 1 to 6 are available in the supplementary files section

Supplementary Files

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