CORONAVIRUS DISEASE-2019 CHARACTERISTICS AMONG THAI ADULTS REINFECTED WITH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2

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Abstract. Some severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) omicron subvariants may be resistant to vaccines and/or infection-induced immunity increasing the risk for reinfection. In this study, we aimed to determine coronavirus disease-2019 (COVID-19) severity, need for hospitalization, symptoms and time to reinfection with SARS-CoV-2 among previously infected Thai adults in order to inform efforts to control COVID-19 in Thailand. The study subjects were Thais aged >18 years, currently living in Thailand who had two previous COVID-19 infections at least 90 days apart confirmed by either an antigen test or COVID-19 real-time polymerase chain reaction testing, where the reinfection was presumed to be an omicron variant based on the most prominent strain of COVID-19 occurring at the time of reinfection. Study subjects were recruited via advertisements on the social media applications Line and Facebook. Each subject was asked to complete an online questionnaire asking about demographic data, dates of COVID-19 infections, time from the initial infection to reinfection, severity of infection, hospitalizations and symptoms during both infections. The minimum number of subjects determined to be needed for the study was 220. The study was conducted during 12-31 January 2023. A total of 201 subjects were included in the study, 59.7% female. The mean (±standard deviation (SD)) age of study subjects was 44.3 (±11.4) (range: 20-81) years. The symptoms significantly more common in the first infection than the second infection were: anosmia (36.8% *vs* 13.9%) (p<0.001), dyspnea (36.3% *vs* 18.9%) (p<0.001) and myalgia (60.2% *vs* 43.8%) (=<0.001), respectively. The hospitalization rate was significantly higher during the first infection than the second infection (14.9% *vs* 3.5%; crude odds ratio (cOR) = 6.25; 95% confidence interval (CI): 2.16-24.71; p<0.001). The average time from first infection to reinfection was 263 (range: 96-725)

days. In summary, anosmia, dyspnea, myalgia, and hospitalizations were more common during first than the second COVID-19 infection among study subjects and the time between infections averaged 9 months. We conclude, as COVID-19 immunity decreases over time, there is a need for a booster, possibly updated, vaccine to reduce the risk for reinfection.

Keywords: COVID-19; SARS-CoV-2; reinfection; Omicron variant; clinical severity

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INTRODUCTION

In March 2020, the World Health Organization (WHO) declared the coronavirus disease-2019 (COVID-19) to be a worldwide pandemic (WHO, 2020). COVID-19 is an infectious disease caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Since the onset of the pandemic, there have been over 769 million cases and 6.9 million deaths worldwide (WHO, 2023). As of May 2023, 4.7 million cases and 34,100 deaths due to COVID-19 were reported from Thailand (WHO Thailand, 2023). Omicron variants of SARS-CoV-2 have mutated to be resistant to vaccine- and infection-induced immunity (Zhou *et al*, 2023; Huo *et al*, 2023). A previous study reported the Omicron BA.4/5 subvariant was neutralized less effectively by BA.1 convalescent plasma than the Omicron BA.1 subvariant, since the BA.4/5 subvariant contains mutated amino acid sequences on the receptor binding sites which differ from the BA.1 variant sequence (Zhou *et al*, 2023).

In August 2020, the first case of COVID-19 reinfection was documented in Hong Kong (Parry, 2020). COVID-19 reinfection is defined as a person being infected with COVID-19 again after an interval of at least 90 days (Akinbami *et al*, 2022). A previous study from Nevada, USA, found the incidence rate of COVID-19 reinfection in March 2020 to be 2.7% and in March 2022 to be 11% after the onset of the omicron wave (Ruff *et al*, 2022).

Individuals previously infected with the non-omicron variant were found to have lower hospitalization

rates on reinfection with the omicron variant (Mensah *et al*, 2022). However, there is limited data regarding the severity of COVID-19 on reinfection.

In this study, we aimed to determine COVID-19 severity, need for hospitalization, symptoms and time to reinfection due to COVID-19 among Thai adults in order to inform efforts to control COVID-19 in Thailand.

MATERIALS AND METHODS

Study design and study subjects

We conducted a cross-sectional study using an online link to a Google Forms questionnaire. Subjects were recruited using social media sites Facebook and Line and given the link to the questionnaire. The link was active during 12-31 January 2023.

The inclusion criteria for study subjects were being Thai aged ≥18 years, residing in Thailand and having had at least two previous COVID-19 infections >90 days apart. The exclusion criteria for study subjects were not completing the questionnaire and having two infections less than 90 days apart.

The minimum number of study subjects calculated to be needed for this study was 220.

A COVID-19 infection was defined as having a positive test for COVID-19 using either a rapid antigen test kit or a real-time polymerase chain reaction (PCR) but obtained from patient history only.

Each subject was asked to complete the online questionnaire which asked about subject sex, age, comorbidities, occupation, COVID-19 vaccination history (number of doses, types and dates of vaccination) and COVID-19 infection history (dates of infections, interval between first and second infections), COVID-19 disease symptoms (fever, runny nose, cough, sore throat, sputum, shaking chills, headache, hoarseness, anosmia, dyspnea, myalgia, fatigue, pneumonia, chest pain, anxiety, gastrointestinal symptoms) and severity of infection reported by the subject. The level of severity was defined as mild (no effect on daily activities), moderate (some limitation of daily activities) and severe (unable to perform daily activities).

The Thai Ministry of Public Health conducts limited surveys of the COVID-19 variants being transmitted in Thailand. When the prevalence of the variant reached 80%, we assumed the study subject

to be infected with that variant based on when they became infected and the predominant COVID-19 variant spreading at that time as previously reported (Aiewsakun *et al*, 2023; Puenpa *et al*, 2023; Puenpa *et al*, 2024). The predominant variant spreading prior to January 2022 was the non-omicron variant and from January 2022 onward was the omicron variant. Therefore, study subjects infected prior to January 2022 were presumed to be infected with the non-omicron variant and from January 2022 and onward were presumed to be infected with the omicron variant.

We compared clinical symptoms of all subjects between the first and second infections. We also compared clinical symptoms of subjects whose first infection was presumed to be a non-omicron variant and second infection presumed to be an omicron subvariant.

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 29 (SPSS Inc, Chicago, IL). The Pearson's chi-square test was used to compare categorical data, such as sex and history of underlying comorbidities. The Mann-Whitney U test was used to compare groups using nonparametric analysis. The risk difference (RD) and 95% confidence intervals (CI) for clinical symptoms of subjects were used to determine significant clinical symptom differences between their first and second infections. Statistical significance was presumed when the 95% CI did not include 0. Crude odds ratios (cOR) and 95% CI for paired samples were calculated using McNemar's test. cOR and 95% CI for independent samples were calculated using the Chi-square test. A p-value <0.05 was considered statistically significant. Figures were generated using GraphPad Prism, version 9.0 (GraphPad Software, San Diego, CA) and RStudio with R statistical software version 4.2.0 (RStudio, Boston, MA).

Ethical approval

This study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB number: 750/65). Informed consent was obtained from each study subject prior to inclusion in the study.

RESULTS

Demographic data

A total of 201 subjects were included in the study, 120 (59.7%) females. Thirty-two subjects (15.9%) were healthcare workers. The mean

(±SD) age of subjects was 44.3 (± 11.4) (range: 20-81) years. 199 subjects (99.0%) had received at least two doses of a COVID-19 vaccine and 180 (89.5%) had received a third dose.

After dividing the participants based on presumed variants causing infection, 65 subjects (32.3%) were presumed to have a been infected with a non-omicron variant during their first infection and 136 (67.7%) were presumed to have been infected with an omicron variant during their first infection. All subjects were presumed to have been infected with the omicron variant during their second COVID-19 infection. There were no significant differences in sex, age or history of comorbidities between subjects presumed to have been infected with non-omicron variant during the first infection versus subjects presumed to be infected with the omicron variant during the first infection (Table 1). Reinfections peaked during January 2023 (Fig 1).

The average time interval between the first and second infections was 263 (range: 96-725) days. This interval was >180 days in 139 subjects (69.2%).

Comparison of symptoms and complications during the first and second infections

The symptoms with significantly different incidences between the first and second infections were: fever (71.6% *vs* 58.7%, p=0.003), sore throat (73.6% *vs* 64.2%, p=0.029), shaking chills (32.3% *vs* 20.9%, p=0.002), anosmia (36.8% *vs* 13.9%, p<0.001), dyspnea (36.3% *vs* 18.9%, p<0.001), myalgia (60.2% *vs* 43.8%, p<0.001), fatigue (64.2% *vs* 52.7%, p=0.003), chest pain (15.4% *vs* 6.5%, p<0.001),

Table 1

Demographics and selected characteristics of study subjects by SARS-CoV-2 variant type

Characteristic	Pre-Omicron (N = 65)	Omicron (N = 136)	Total (N =201)
Mean age ± SD in years	45.4 ± 11.3	43.8 ± 11.4	44.3 ± 11.4
Sex, *n* (%)			
Male	30 (46.2)	50 (36.8)	80 (39.8)
Female	35 (53.8)	86 (63.2)	121 (60.2)

Table 1 (cont)

Characteristic	Pre-Omicron (N = 65)	Omicron (N = 136)	Total (N =201)
Underlying disease, *n* (%)			
Hypertension	11 (16.9)	19 (14.0)	30 (14.9)
Diabetes Mellitus	3 (4.6)	8 (5.9)	11 (5.5)
Cardiovascular diseases	2 (3.1)	3 (2.2)	5 (2.5)
Obesity	7 (4.1)	5 (3.7)	7 (3.5)
Dyslipidemia	13 (20.0)	15 (11.0)	28 (13.9)
Allergy	9 (13.8)	16 (11.8)	25 (12.4)
Asthma	1 (1.5)	2 (1.5)	3 (1.5)
Thyroid	1 (1.5)	4 (2.9)	5 (2.5)
Cancer	1 (1.5)	0 (0.0)	1 (0.5)
Other (gout, COPD and others)	8 (12.3)	5 (3.7)	13 (6.5)
Interval between two infections in days (range)	375 (97-725)	209 (96-396)	263 (96-725)
Interval between the two infections, *n* (%)			
0-180 days	6 (9.2)	56 (41.2)	62 (30.8)
>180 days	59 (90.8)	80 (58.8)	139 (69.2)
Number of COVID-19 vaccine doses, *n* (%)			
0	0	1 (0.7)	1 (0.5)
1	1 (1.5)	0 (0.0)	1 (0.5)
2	8 (12.3)	11 (8.1)	19 (9.5)
3	24 (36.9)	44 (32.4)	68 (33.8)
4	24 (36.9)	58 (42.6)	82 (40.8)
5	7 (10.8)	21 (15.4)	28 (13.9)
≥6	1 (1.5)	1 (0.7)	2 (1.0)

COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease-2019; SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2; SD: standard deviation

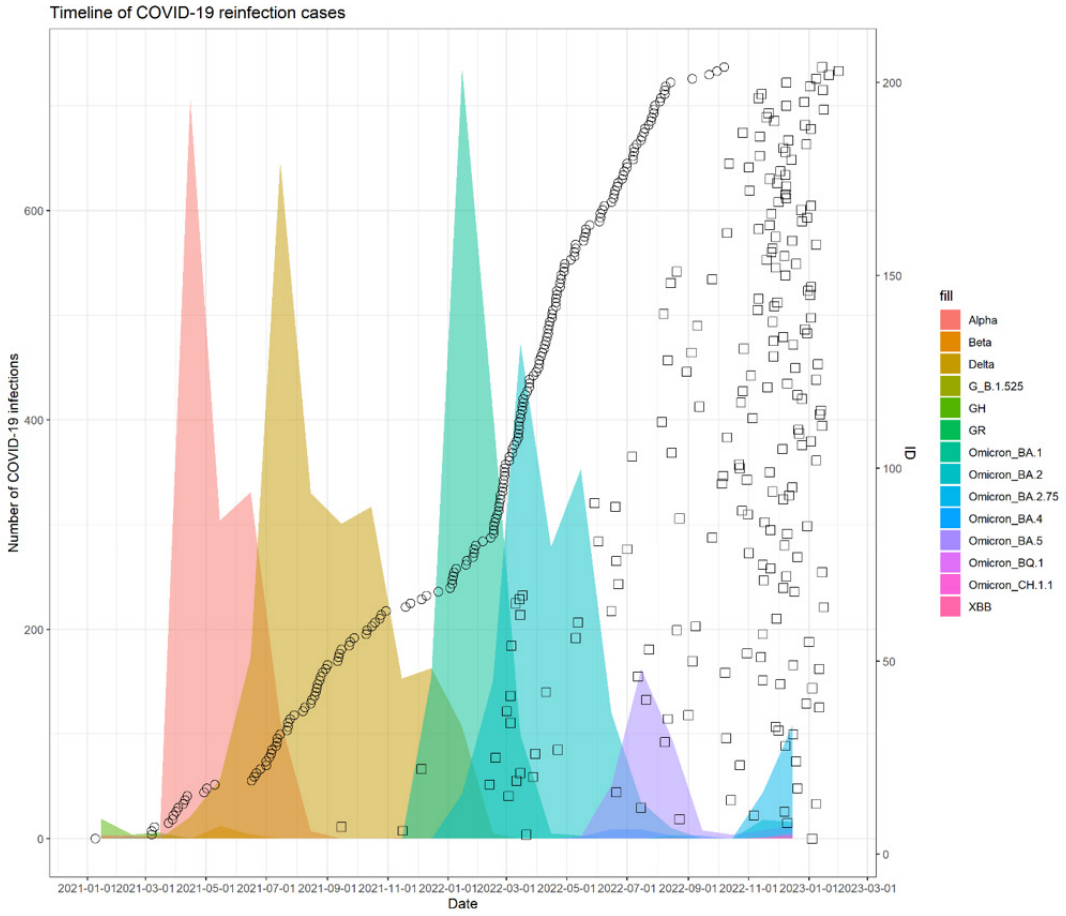

Fig 1 - Number of COVID-19 infections by SARS-CoV-2 variant type over time

Note: The circles denote the first infections, and the squares denote second infections. The various colors show the proportions of reported SARS-CoV-2 variants and subvariants found among surveys in Thailand (Puenpa *et al*, 2023; Puenpa *et al*, 2024).

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

anxiety (37.3% *vs* 20.4%, $p<0.001$), and gastrointestinal disturbances (23.9% *vs* 13.4%, $p=0.002$). The incidence of pneumonia was significantly more common during the first than the second infection (8.5% *vs* 3.0%, $p=0.007$), respectively (Figs 2, 3A and Table 2). The symptoms without

significant difference between the first and second infections were: rhinorrhea, cough, sputum production, headache, hoarseness and rash. The hospitalization rate was significantly higher during the first infection than the second infection (14.9% *vs* 3.5%, $p<0.001$) (Table 3).

Table 2

Incidences of clinical manifestations among subjects during the first and second COVID-19 infections

Clinical manifestation	Incidences (N =201)		*p*-value
	First infection *n* (%)	Second infection *n* (%)	
Fever	144 (71.6)	118 (58.7)	0.003
Runny nose	147 (73.1)	152 (75.6)	0.568
Cough	154 (76.6)	148 (73.6)	0.512
Sore throat	148 (73.6)	129 (64.2)	0.029
Sputum	140 (69.7)	126 (62.7)	0.130
Shaking chills	65 (32.3)	42 (20.9)	0.002
Headache	113 (56.2)	97 (48.3)	0.082
Hoarseness	87 (43.3)	79 (39.3)	0.350
Anosmia	74 (36.8)	28 (13.9)	<0.001
Dyspnea	73 (36.3)	38 (18.9)	<0.001
Myalgia	121 (60.2)	88 (43.8)	<0.001
Fatigue	129 (64.2)	106 (52.7)	0.003
Pneumonia	17 (8.5)	6 (3.0)	0.007
Chest pain	31 (15.4)	13 (6.5)	<0.001
Anxiety	75 (37.3)	41 (20.4)	<0.001
Gastrointestinal symptoms	48 (23.9)	27 (13.4)	0.002
Rash	25 (12.4)	17 (8.5)	0.108

COVID-19: coronavirus disease 2019

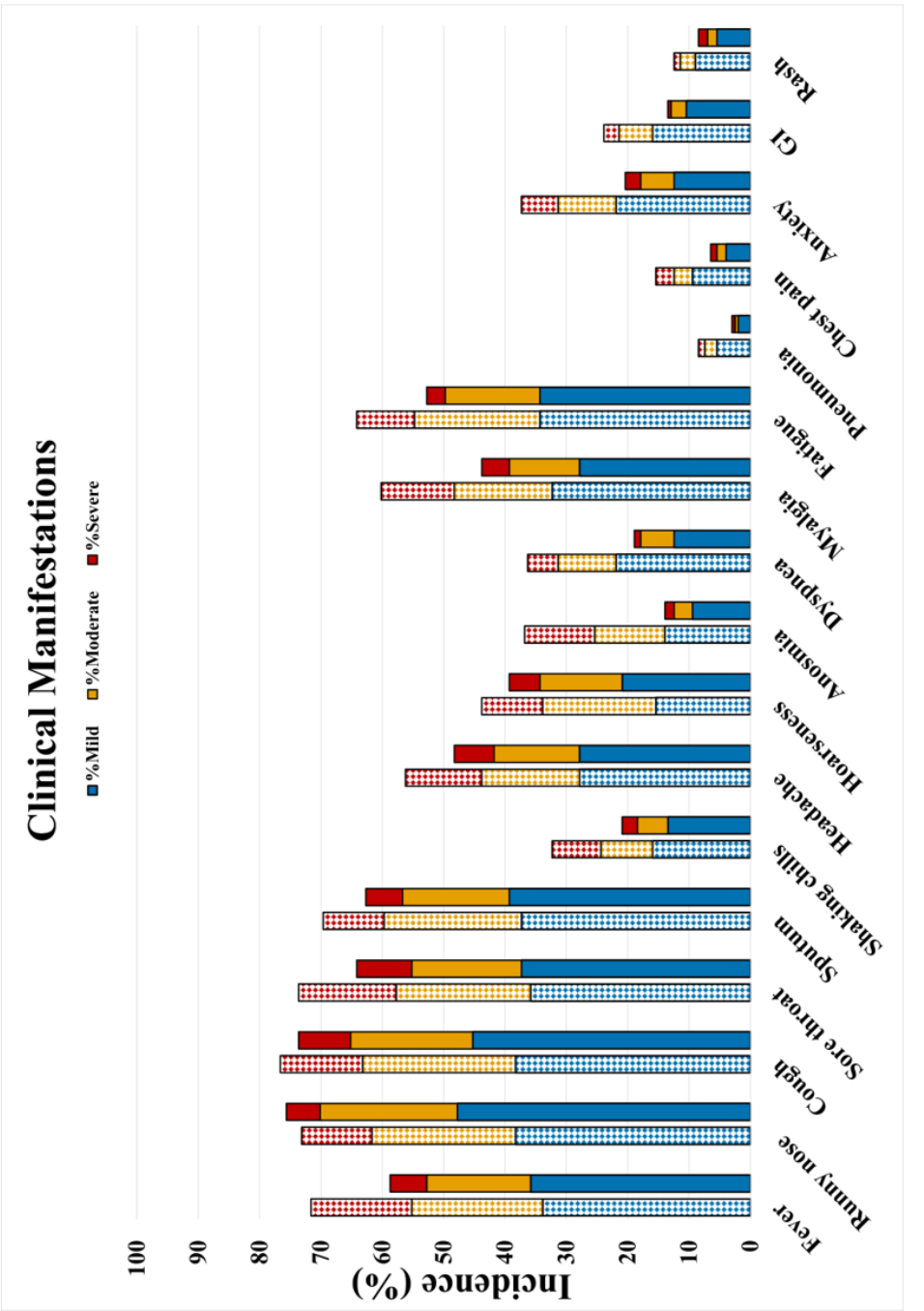

Fig 2 - Disease severity by symptom during the first (dot fill) and second (solid fill) COVID-19 infections
COVID-19: coronavirus disease-2019; GI: gastrointestinal symptoms

Comparison of symptoms and complications by presumed COVID-19 variant type.

The incidence of anosmia was significantly more common among subjects presumed to be infected with the non-omicron variant than an omicron variant during the first infection (56.9% *vs* 27.2%, $p<0.001$), respectively. The incidences of cough and sore throat were significantly less common among subjects presumed to be infected with the non-omicron variant than the omicron variant during the first infection (67.7% *vs* 80.9%, $p=0.039$; 58.5% *vs* 80.9%, $p<0.001$, respectively). The hospitalization rate was significantly more common among subjects presumed to be infected with the non-omicron variant than the omicron variant during the first infection (32.3% *vs* 6.6%, $p<0.001$) (Fig 3B and Table 3).

The incidences of the following symptoms were significantly more common among subjects presumed to be infected with the non-omicron variant then the omicron variant with the first infection: anosmia (56.9% *vs* 9.2%, $p<0.001$), dyspnea (46.2% *vs* 18.5%, $p<0.001$), chest pain (18.5% *vs* 4.6%, $p=0.022$), myalgia (64.6% *vs* 43.1%, $p=0.013$), fatigue (70.8% *vs*

Table 3

Comparison of hospitalization rates during first and second COVID-19 infections

Hospitalization	Frequency *n* (%)	cOR (95% CI)	*p*-value
By infection number			
First infection (N = 201)	30 (14.9)	6.25 (2.16-24.71)	<0.001[a]
Reinfection (N = 201)	7 (3.5)	Reference	
By variant type causing first infection			
Presumed non-omicron (N = 65)	21 (32.3)	6.76 (2.87-15.87)	<0.001[b]
Presumed omicron (N =136)	9 (6.6)	Reference	

[a]crude odds ratio (cOR) calculated based on paired samples using the McNemar's test; [b]crude odds ratio (cOR) calculated based on independent samples using the chi-square test

CI: confidence interval; COVID-19: coronavirus disease 2019

47.7%, p=0.004), anxiety (46.2% *vs* 24.6%, p=0.003) and GI disturbances (30.8% *vs* 10.8%, p=0.004). The incidence of pneumonia was significantly more common among subjects during their first infection, presumed to be infected with non-omicron variant, than during the second infection, presumed to be infected with the omicron variant (13.9% *vs* 1.5%, p=0.021) (Fig 4A).

The incidences of the following symptoms were significantly more common among subjects during their first infection, presumed to be infected with the omicron variant, than the second infection, presumed to be infected with the omicron variant: sore throat (80.9% *vs* 63.9%, p<0.001), sputum production (72.8% *vs* 59.6%, p=0.009), anosmia (27.2% *vs* 16.2%, p=0.011), dyspnea (31.6% *vs* 19.1%, p<0.001, fever (70.6% *vs* 57.4%, p=0.013), shaking chills (29.4% *vs* 19.1%, p=0.013), myalgia (58.1% *vs* 44.1%, p=0.003) and anxiety (33.1% *vs* 18.4%, p<0.001) (Fig 4B).

DISCUSSION

In this study, we compared the frequencies of clinical characteristics among subjects infected with COVID-19 twice at least 90 days apart. The frequencies of these clinical characteristics were less common during the second infection than the first infection, similar to the findings reported in a previous study from Iran (Sotodeh Ghorbani *et al*, 2022). A meta-analysis from China, found almost half of all SARS-CoV-2 reinfection cases were asymptomatic and those with symptoms had only mild symptoms (Deng *et al*, 2023).

In our study, the average length of time between the first and second infections was 263 days, about 8½ months. A previous study from Brazil, reported an average interval of about 14 months (Guedes *et al*, 2023). In our study, although COVID-19 immunity decreased over time, the disease severity and hospitalization rate were both significantly lower during the second than the first infection. In our study, the hospitalization rate with the first infection was significantly higher than with the second infection, similar to the findings of a study from Vietnam (Nguyen *et al*, 2023). A study from the US reported a 90% reduction in hospitalizations and death with the second compared to the first infection (COVID-19 Forecasting Team, 2023).

In our study, subjects with COVID-19 caused by an omicron variant were significantly more likely to have cough and sore throat and significantly less likely to have anosmia than those with

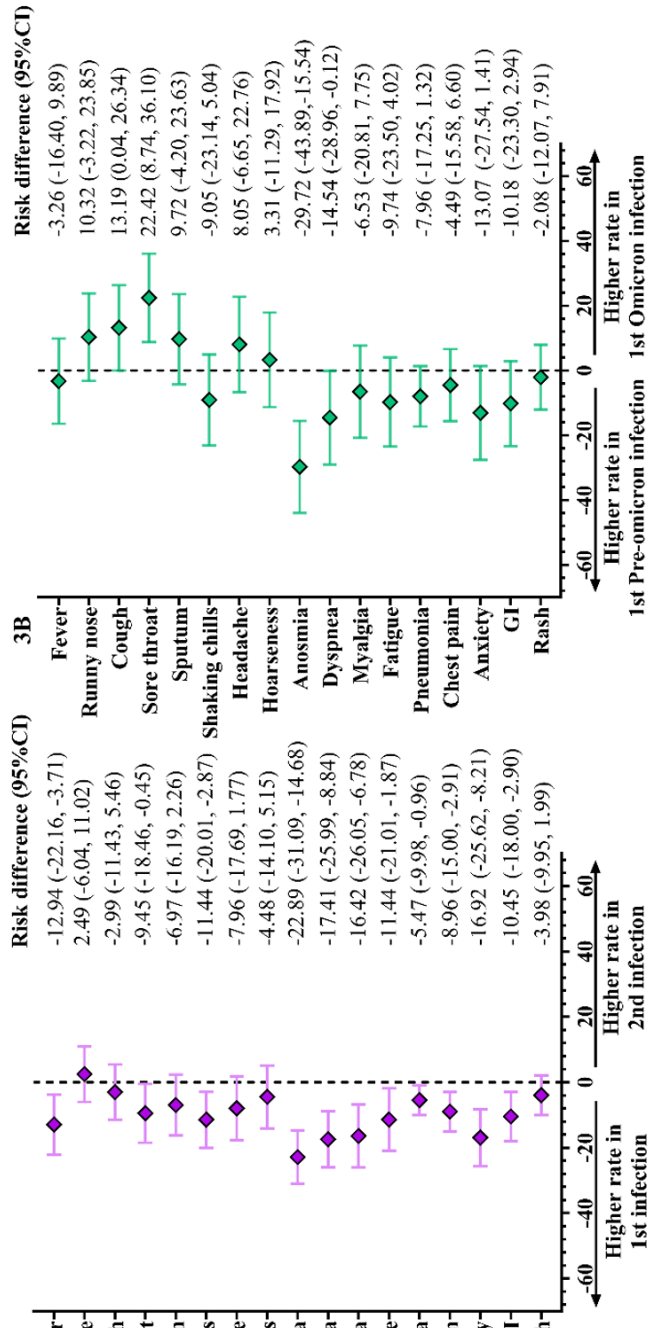

Fig 3 - Frequencies of clinical manifestations

Note: (3A) Frequencies of clinical manifestations during first and second infections; (3B) frequencies of clinical manifestations during the first infection presumed to be caused by a non-omicron variant and first infection presumed to be caused by an omicron variant.

CI: confidence interval; GI: gastrointestinal symptoms

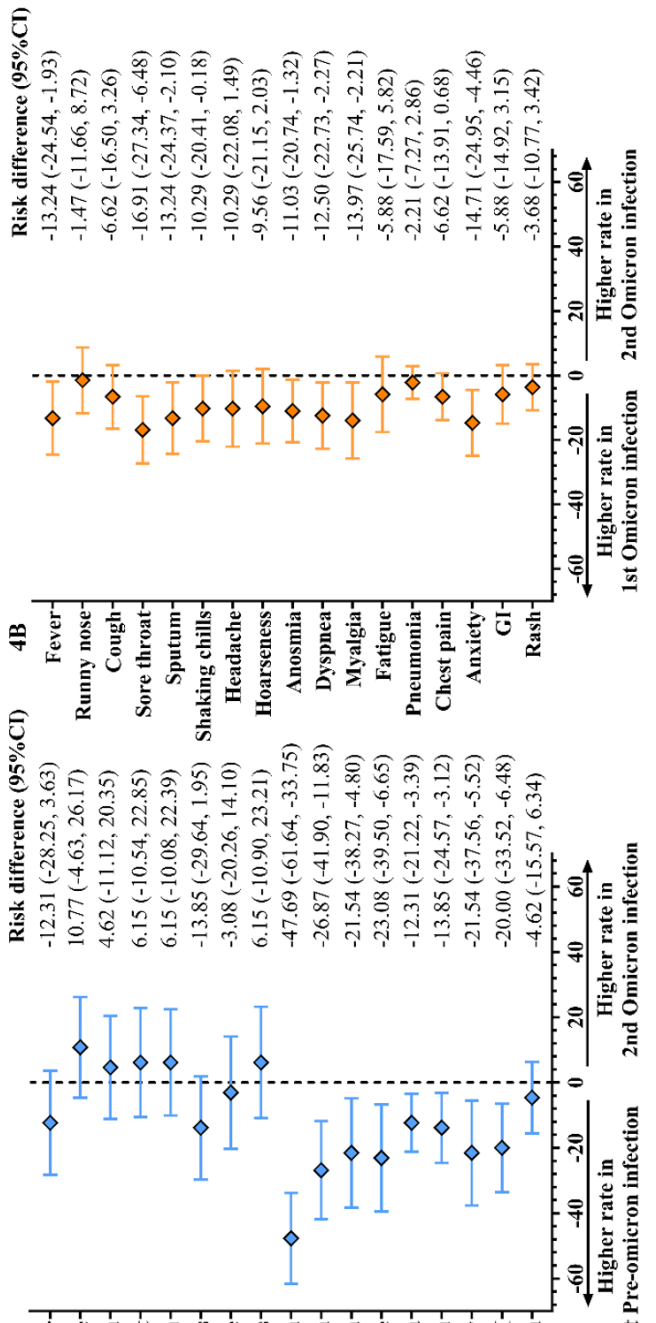

Fig 4 - Frequencies of clinical manifestations

Note: (4A) frequencies of clinical manifestations during first infection presumed to be caused by a non-omicron variant and second infection presumed to be caused by an omicron variant; (4B) frequencies of clinical manifestations during first infection presumed to be caused by an omicron variant and second infection presumed to be caused by an omicron variant.

CI: confidence interval; GI: gastrointestinal symptoms

a non-omicron variant, similar to the findings in a study from Mexico (Peña Rodríguez *et al*, 2023). In our study, the hospitalization rate with the first infection among study subjects was significantly lower among those with COVID-19 due to the omicron variant than the non-omicron variant. Several previous studies also reported lower hospitalization rates among those with COVID-19 due to an omicron variant than due to other variants (Esper *et al*, 2023; Zhang *et al*, 2022).

A major problem with our study was that the entire history was obtained from the patient and no studies to confirm accuracy were performed and may have been affected by subject recall bias. Another problem with our study is the variants were assumed based on the most common circulating variant rather than based on detection of the actual variant type. Another problem was that we did not determine sub-variant types which could have influenced our study results. A further problem was that we were unable to determine results by age group due to the small study population. Age adjusted results may have influenced our study conclusions, providing more useful data for policy making decisions.

In summary, the clinical characteristics with the second infection, presumed to be caused by the omicron variant, were generally less severe than those of the first infection and the hospitalization rate was lower with the second than the first infection. The average interval between the first and second infections averaged 8-9 months. In conclusion, it may be necessary to give a booster, preferably updated vaccine to reduce the rate of COVID-19 reinfection.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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