Preplanned Studies

The Associated Factors of SARS-CoV-2 Reinfection by Omicron Variant — Guangdong Province, China, December 2022 to January 2023

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Summary

What is already known about this topic?

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection by variants is being reported commonly and has caused waves of epidemic in many countries. Because of dynamic zero policy, the SARS-CoV-2 reinfection was less reported in China.

What is added by this report?

SARS-CoV-2 reinfections were observed in Guangdong Province between December 2022 and January 2023. This study estimated that the reinfection incidence was 50.0% for the original strain primary infections, 35.2% for the Alpha or Delta variants, and 18.4% for the Omicron variant; The reinfection incidence within 3-6 months after primary infection by Omicron variant was 4.0%. Besides, 96.2% reinfection cases were symptomatic while only 7.7% sought medical attention.

What are the implications for public health practice?

These findings suggest a reduced likelihood of an Omicron-driven epidemic resurgence in the short term but emphasize the importance of maintaining vigilant surveillance of emerging SARS-CoV-2 variants and conducting population-based antibody level surveys to inform response preparedness.

Between December 2022 and January 2023, coronavirus disease 2019 (COVID-19) became widespread in China (*1*). This study aimed to preliminarily determine the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection during this epidemic period and identify its associated factors. A telephone survey was conducted in January 2023, focusing on patients in Guangdong, a province in southern China, who had recovered from COVID-19 after initial confirmation beginning in 2020. The study included 368 participants, aged 1–80 years.

The overall SARS-CoV-2 reinfection incidence was found to be 28.3% [95% confidence interval (*CI*): 23.7%, 33.2%]. Univariate analysis revealed that the reinfection incidence for primary cases involving the Omicron variant was significantly lower than that for primary cases involving pre-Omicron strains (χ^2=23.94, P<0.001). Additionally, the study indicated that while the majority of reinfection cases developed symptoms, only a small proportion required medical attention. These findings may contribute to a better understanding of the risk associated with subsequent epidemics and inform improved response preparedness.

In this study, SARS-CoV-2 reinfection was defined as an infection occurring more than 90 days after the onset of the primary infection or after the collection of the first positive specimen. Following the criteria established by the US CDC (*2*) and the 10th edition of the Chinese Diagnosis and Treatment Protocol, SARS-CoV-2 reinfections were categorized as either probable or confirmed cases.

Probable cases were defined as those without a positive SARS-CoV-2 nucleic acid or antigen test result but who met at least one of the following two conditions since December 2022: 1) an acute onset or worsening of cough or loss of sense of smell/taste or 2) an acute onset or worsening of at least two of the following symptoms or signs: fever, fatigue, nasal congestion, runny nose, sore throat, myalgia, diarrhea, or conjunctivitis.

Confirmed cases were identified as those who tested positive for SARS-CoV-2 nucleic acid or antigen, irrespective of symptoms, according to self-reporting and laboratory record review.

The predominant strains of SARS-CoV-2 causing local outbreaks in Guangdong shifted from the original strain in 2020 to the Alpha and Delta variants in 2021, and the Omicron variant in 2022. This study included

local primary infection cases of COVID-19 reported between January 2020 and August 2022 in Guangzhou and Shenzhen. A total of 3,331 local recovered COVID-19 patients were sampled from cases reported in Guangzhou and Shenzhen during that time (856 in 2020, 181 in 2021, and 2,294 in 2022). The cases were selected using a systematic sampling method based on the primary infection strains.

Data on demographic characteristics, vaccination history, COVID-19-related symptoms, and laboratory test results for both primary infection and reinfection with SARS-CoV-2 were obtained through telephone surveys and the National Notifiable Disease Reporting System. The incidence of SARS-CoV-2 reinfection was calculated using the sum of confirmed and probable cases. A chi-square test was employed for univariate analysis, and logistic regression was performed separately to explore the factors influencing reinfection for individuals with primary infections caused by different strains.

All statistical analyses were carried out using R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria), and all statistical tests were two-sided with an α value of 0.05.

In this study, a total of 368 case participants were investigated, consisting of 183 males and 185 females ranging in age from 1 to 85 years old. The participants were categorized based on the type of SARS-CoV-2 infection: 68 individuals with the original strain, 88 with either the Alpha or Delta variants, and 212 with the Omicron variant. Vaccination status was also recorded, with 103 participants having completed the primary SARS-CoV-2 vaccination series and 189 having received a booster dose. The demographic and characteristic details are presented in Table 1.

A total of 104 cases were identified as SARS-CoV-2 reinfections, comprising 70 confirmed cases and 34 probable cases. The overall incidence of SARS-CoV-2 reinfection was estimated to be 28.3% (95% *CI*: 23.7%, 33.2%). When categorized by the primary infection strain, the reinfection incidences were 50.0% (95% *CI*: 37.6%, 62.4%) for the original strain, 35.2% (95% *CI*: 25.3%, 46.1%) for the Alpha or Delta variants, and 18.4% (95% *CI*: 13.4%, 24.3%) for the Omicron variant. Notably, the reinfection incidence for cases with primary Omicron variant infection was significantly lower than that for cases with primary pre-Omicron strain infections (χ^2=23.94, P<0.001). Among the 104 reinfection cases, 96.2% were symptomatic. The most common symptoms included cough (72.0%), fever (57.0%), sore throat (47.0%), and fatigue (39.0%). Only 8 (7.7%) reinfection cases sought medical attention.

Reinfections were observed during December 2022 and January 2023, with intervals between infections ranging from 3.7 to 35.5 months. For participants initially infected with the Alpha or Delta variant, all reinfections occurred more than 12 months later. Among the 212 participants infected with the Omicron variant, one case experienced reinfection within the 3 to 6 months timeframe, while 38 cases had reinfections occurring beyond 6 months following the primary infection. Additional details regarding reinfection cases are presented in Table 2.

Logistic regression analysis revealed no significant associations between gender, age, clinical manifestations of primary infection, or vaccination history and reinfection incidence. However, for cases with primary infection involving the Omicron variant, logistic regression indicated that being a medical worker and the time interval since the last infection were significant risk factors, with odds ratios (*OR*s) of 9.13 (95% *CI*: 2.70, 30.90) and 9.66 (95% *CI*: 1.12, 83.60), respectively. The results of the multivariate analysis for reinfection risk factors are presented in Table 3.

DISCUSSION

This investigation examined the SARS-CoV-2 reinfection rates and associated factors in Guangdong Province, China. All reinfections were identified during the initial wave of widespread community transmission beginning in December 2022. The findings revealed that the reinfection incidence among individuals primarily exposed to the Omicron variant was significantly lower than that of individuals exposed to pre-Omicron strains. Additionally, our study demonstrated that the majority of reinfection cases were symptomatic, but only a small percentage necessitated medical intervention.

In this study, we observed a low risk of reinfection within 3 to 6 months following primary infection by the Omicron variant. Prior research has indicated that neutralizing antibody titers in COVID-19 patients remain stable for at least 3 months post-infection (*3*–*5*). The rapid development of herd immunity across the general population of Guangdong Province can be attributed to the widespread COVID-19 outbreak from December 2022 to January 2023.

Additionally, our survey revealed a significant increase in SARS-CoV-2 reinfection incidence more

TABLE 1. Characteristics of participants according to primary infection strain of SARS-CoV-2 (*n*=368).

Characteristic	Wild type infection		Alpha/Delta infection		Omicron infection		Total	
	n	%	*n*	%	*n*	%	*n*	%
Gender								
Male	36	52.9	45	51.1	102	48.1	183	49.7
Female	32	47.1	43	48.9	110	51.9	185	50.3
Age, years								
0–17	7	10.3	14	15.9	18	8.5	39	10.6
18–59	49	72.1	51	58.0	183	86.3	283	76.9
≥60	12	17.6	23	26.1	11	5.2	46	12.5
Occupation								
Medical worker	4	5.9	3	3.4	20	9.4	27	7.3
Other	64	94.1	85	96.6	192	90.6	341	92.7
Clinical manifestation of primary infection								
Asymptomatic	13	19.1	14	15.9	47	22.2	74	20.1
Symptomatic	55	80.9	74	84.1	165	77.8	294	79.9
SARS-CoV-2 vaccination status								
Unvaccinated	0	0	4	4.5	4	1.9	8	2.2
Incomplete	7	10.3	9	10.2	9	4.2	25	6.8
Complete	12	17.6	39	44.3	52	24.5	103	28.0
Booster	34	50.0	34	38.6	121	57.1	189	51.4
No detail	15	22.1	2	2.3	26	12.3	43	11.7
Interval since last vaccination*								
Unvaccinated	0	0.0	4	4.7	4	2.2	8	2.5
<12 months	26	49.1	74	86.0	50	26.9	150	46.2
≥12 months	27	50.9	8	9.3	132	71.0	167	51.4
Reinfection status								
Non-reinfection	34	50.0	57	64.8	173	81.6	264	71.7
Reinfection	34	50.0	31	35.2	39	18.4	104	28.3
Probable case	7	10.3	6	6.8	21	9.9	34	9.2
Confirmed case	27	39.7	25	28.4	18	8.5	70	19.0

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
* Only 325 respondents had access to detailed vaccination information.

than 6 months after an initial Omicron infection. It is anticipated that epidemic levels will remain low for the next 3 to 6 months. However, as immunity declines over time, the risk of COVID-19 resurgence may increase.

Viral mutation serves as another cause for reinfection, as it can render previously established acquired immunity ineffective against new variants. Reinfections with SARS-CoV-2 original strain, Alpha, Beta, Delta, and Omicron variants have been observed in numerous countries, leading to ongoing epidemic waves. Numerous studies have demonstrated that individuals previously infected with pre-Omicron strains exhibited a higher risk of reinfection by the Omicron variant (*6*). The univariate analyses in this study revealed that the reinfection incidence following primary infections by the original strain or by the Alpha or Delta variant was significantly higher than the reinfection incidence following the primary infection by the Omicron variant.

China's dynamic COVID-zero strategy has effectively maintained low morbidity and mortality rates in the country for the past three years. However, it remains challenging to independently discern the effects of variants and time elapsed since the initial infection on SARS-CoV-2 reinfection. The SARS-

TABLE 2. Univariate analysis on the associated factors of SARS-CoV-2 reinfection, according to primary infection strain (n=368).

Factor	Wild type infection, n (%) (N=68)						Alpha/Delta infection, n (%) (N=88)						Omicron infection, n (%) (N=212)					
	Reinfection cases			Non-reinfection cases	χ^2	P	Reinfection cases			Non-reinfection cases	χ^2	P	Reinfection cases			Non-reinfection cases	χ^2	P
	Confirmed case	Probable case	Sub-total				Confirmed case	Probable case	Sub-total				Confirmed case	Probable case	Sub-total			
Gender																		
Male	11 (30.6)	4 (11.1)	15 (41.7)	21 (58.3)	2.13	0.145	14 (31.1)	2 (4.4)	16 (35.6)	29 (64.4)	0.01	0.947	9 (8.8)	13 (12.7)	22 (21.6)	80 (78.4)	1.32	0.251
Female	16 (50.0)	3 (9.4)	19 (59.4)	13 (40.6)			11 (25.6)	4 (9.3)	15 (34.9)	28 (65.1)			9 (8.2)	8 (7.3)	17 (15.5)	93 (84.5)		
Age, years																		
0–17	0 (0)	1 (14.3)	1 (14.3)	6 (85.7)			4 (28.6)	0 (0)	4 (28.6)	10 (71.4)			1 (5.6)	2 (11.1)	3 (16.7)	15 (83.3)		
18–59	25 (51.0)	5 (10.2)	30 (61.2)	19 (38.8)	9.04	0.011	17 (33.3)	5 (9.8)	22 (43.1)	29 (56.9)	3.50	0.173	16 (8.7)	19 (10.4)	35 (19.1)	148 (80.9)	0.74	0.692
≥60	2 (16.7)	1 (8.3)	3 (25.0)	9 (75.0)			4 (17.4)	1 (4.3)	5 (21.7)	18 (78.3)			1 (9.1)	0 (0)	1 (9.1)	10 (90.9)		
Occupation																		
Medical worker	4 (100.0)	0 (0)	4 (100.0)	0 (0)	2.39	0.122	1 (33.3)	0 (0)	1 (33.3)	2 (66.7)	0.30	0.586	5 (25.0)	4 (20.0)	9 (45.0)	11 (55.0)	8.55	0.004
Other	23 (35.9)	7 (10.9)	30 (46.9)	34 (53.1)			24 (28.2)	6 (7.1)	30 (35.3)	55 (64.7)			13 (6.8)	17 (8.9)	30 (15.6)	162 (84.4)		
Clinical manifestation of primary infection																		
Asymptomatic	6 (46.2)	2 (15.4)	8 (61.5)	5 (38.5)	0.86	0.355	6 (42.9)	2 (14.3)	8 (57.1)	6 (42.9)	2.46	0.117	2 (4.3)	6 (12.8)	8 (17.0)	39 (83.0)	0.08	0.783
Symptomatic	21 (38.2)	5 (9.1)	26 (47.3)	29 (52.7)			19 (25.7)	4 (5.4)	23 (31.1)	51 (68.9)			16 (9.7)	15 (9.1)	31 (18.8)	134 (81.2)		
Interval since last infection*																		
3 to 6 months	0 (0)	0 (0)	0 (0)	0 (0)	–	–	0 (0)	0 (0)	0 (0)	0 (0)	–	–	0 (0)	1 (4.0)	1 (4.0)	24 (96.0)	2.90	0.089
>6 months	27 (39.7)	7 (10.3)	34 (50.0)	34 (50.0)			25 (28.4)	6 (6.8)	31 (35.2)	57 (64.8)			18 (9.6)	20 (10.7)	38 (20.3)	149 (79.7)		
Interval since last vaccination†																		
Unvaccinated	0 (0)	0 (0)	0 (0)	0 (0)			1 (25.0)	0 (0)	1 (25.0)	3 (75.0)			0 (0)	1 (25.0)	1 (25.0)	3 (75.0)		
<12 months	11 (42.3)	2 (7.7)	13 (50.0)	13 (50.0)	0.02	0.893	23 (31.1)	5 (6.8)	28 (37.8)	46 (62.2)	2.22	0.329	4 (8.0)	6 (12.0)	10 (20.0)	40 (80.0)	0.06	0.972
≥12 months	9 (33.3)	4 (14.8)	13 (48.1)	14 (51.9)			1 (12.5)	0 (0)	1 (12.5)	7 (87.5)			14 (10.6)	13 (9.8)	27 (20.5)	105 (79.5)		

Note: "–" means not applicable.
Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
* The interval between non-cases is the time from the first infection to the investigation date.
† Only 325 respondents had access to detailed vaccination information.

TABLE 3. Logistic regression analysis on the associated factors of SARS-CoV-2 reinfection, according to primary infection strain (*n*=325).

Factors	Wild type		Alpha/Delta		Omicron	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
Gender						
Female	Ref		Ref		Ref	
Male	0.61 (0.17, 2.16)	0.442	1.02 (0.37, 2.81)	0.968	2.32 (1.00, 5.35)	0.049
Age, years						
0–17	Ref		Ref		Ref	
18–59	6.71 (0.59, 76.04)	0.124	2.38 (0.50, 11.41)	0.277	1.69 (0.35, 8.17)	0.513
≥60	2.01 (0.14, 29.25)	0.610	0.61 (0.11, 3.49)	0.582	0.36 (0.03, 4.76)	0.436
Occupation						
Other	Ref		Ref		Ref	
Medical worker	Inf (0.68, Inf)	0.999	0.81 (0.06, 10.71)	0.870	9.13 (2.70, 30.90)	0.000
Clinical severity of first infection						
Asymptomatic	Ref		Ref		Ref	
Symptomatic	0.29 (0.05, 1.62)	0.158	0.29 (0.07, 1.18)	0.083	1.25 (0.48, 3.26)	0.654
SARS-CoV-2 vaccination status						
Incomplete	Ref		Ref		Ref	
Complete	1.53 (0.17, 13.86)	0.705	0.22 (0.04, 1.12)	0.073	0.87 (0.14, 5.29)	0.876
Booster	1.06 (0.15, 7.39)	0.951	0.19 (0.03, 1.11)	0.066	0.49 (0.08, 2.88)	0.426
Interval since last vaccination						
Nonvaccinated	–	–	Ref		Ref	
<12 months	Ref		12.46 (0.68, 228.72)	0.089	0.42 (0.02, 9.40)	0.586
≥12 months	1.15 (0.32, 4.08)	0.835	2.10 (0.06, 77.31)	0.688	0.29 (0.01, 6.64)	0.439
Interval since last infection						
3 to 6 months	–	–	–	–	Ref	
>6 months	–	–	–	–	9.66 (1.12, 83.60)	0.039

Note: "–" means not applicable; Ref means reference group.
Abbreviation: *OR*=odds ratio; *CI*=confidence interval; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

CoV-2 Omicron variant was imported into Guangdong in December 2021 and became the dominant strain in 2022. Notably, the primary infections' dominant variants shifted from Omicron BA.1 and BA.2 in early 2022 to BA.5 and BF.7 towards the end of the year. The analysis suggests that the risk of reinfection by different Omicron subvariants remains low but significantly increases after six months.

This study found that healthcare workers experienced a higher reinfection incidence than other populations, suggesting that increased professional exposure during epidemic periods may be a contributing factor (*7*).

In the present study, the majority of reinfection cases presented with symptoms; however, only a minority necessitated medical intervention, and no critical cases were detected. The findings suggest that protection conferred by a prior infection may contribute to a reduced incidence of severe illness upon reinfection, irrespective of the viral variants or the time elapsed since the previous infection. This observation is in alignment with the outcomes of other research studies (*8*–*9*). Although the study did not identify a significant association between vaccination and reinfection, prior research indicates that hybrid immunity — stemming from both a previous infection and a recent booster vaccination — offers the most effective defense against symptomatic Omicron infections (*10*).

This study has several limitations that warrant consideration. First, the study was conducted using a telephone survey, which might have introduced non-response bias compared to a face-to-face survey.

Nevertheless, we compared the demographic characteristics of the participants and the non-respondent group, finding no statistically significant differences between them. This suggests that the study maintains adequate population representation.

Second, information regarding reinfection-associated symptoms and case classification was obtained via self-report; thus, the potential underestimation of reinfection incidence may be a concern. Asymptomatic reinfections are less likely to result in laboratory testing or clinical visits and could lead to an underestimation of the actual occurrence of reinfections.

Additionally, due to the relatively limited scale of COVID-19 cases in Guangdong in the past three years, the re-exposure risk among previously infected individuals remained artificially controlled prior to adjustments in epidemic prevention policies. Consequently, nearly all exposures were concentrated in December 2022, making it challenging to differentiate reinfections based on time intervals and the influence of distinct viral variants within this investigation.

Future research should focus on conducting large-scale studies with extended follow-up periods to further elucidate the dynamics of SARS-CoV-2 reinfection.

The results of this study may enhance the assessment of potential epidemic risks and bolster response preparedness. Our findings indicate that, for at least the next three months, the likelihood of an epidemic resurgence driven by the Omicron variant in Guangdong is relatively low. Nevertheless, it remains crucial to maintain vigilant surveillance of emerging SARS-CoV-2 variants and to conduct routine population-based antibody level surveys.

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