JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Analysis of re-infection cases and influencing factors post first severe COVID-19 wave in Jiangsu Province, China

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Abstract

Introduction: This study aimed to assess COVID-19 re-infection rates among individuals previously infected between 2020 and November 2022, particularly during the first wave of high-intensity transmission, and to identify the risk factors associated with re-infection in Jiangsu Province, China.

Methodology: Epidemiological investigations were conducted through telephone interviews and face-to-face visits in February and March 2023. Statistical analyses included the Chi-square or Fisher's exact test for categorical data, Student's *t*-test for numerical data, Poisson regression for influencing factors, and Kaplan–Meier for cumulative re-infection risk.

Results: Among 12,910 individuals surveyed, 957 (7.4%) cases of re-infection were identified. Re-infection rates varied significantly by initial infection period: 42.5% in January–February 2020, 15.5% in July–August 2021, 6.7% in March–April 2022, and 1.1% in September–October 2022. Females and individuals aged 18–50 years were more susceptible to re-infection. A reduced risk of re-infection was observed in those who received four vaccine doses, with a relative risk of 0.25 ($p = 0.019$).

Conclusions: For populations prone to COVID-19 re-infections, particularly females and young adults aged 18–50 years, receiving four or more vaccine doses effectively reduces the likelihood of repeated infections. These findings emphasize the need to prioritize vaccination and protect high-risk groups in COVID-19 prevention efforts.

Key words: COVID-19; re-infection; influencing re-infection factors; on-site epidemiological investigation.

J Infect Dev Ctries 2024; 18(9.1):S92-S100. doi:10.3855/jidc.20031

(Received 23 February 2024 – Accepted 15 May 2024)

Introduction

Since the emergence of the COVID-19 pandemic at the end of 2019, numerous waves of outbreaks have resulted in over 760 million confirmed cases and more than 6.9 million deaths globally as of May 2023 [1]. Understanding the phenomenon of SARS-CoV-2 re-infection has become crucial in addressing these ongoing challenges. Global research has highlighted the rates of re-infection and the associated factors [2,3], indicating that re-infection with COVID-19 is possible [4], and may be influenced by factors such as age, immune response, and the duration of protective antibodies after the initial infection [5]. However, due to variability in prevention and control strategies, as well as differences in vaccine types and deployment across populations, the applicability of these findings to the Chinese context remains uncertain.

In Jiangsu Province, China, from December 2019 to November 2022, stringent COVID-19 prevention and control measures largely contained the epidemic, with only sporadic local outbreaks and imported cases. However, the situation changed significantly following the implementation of the "Ten Measures for Epidemic Prevention and Control" on December 7, 2022, leading

to the province's first wave of widespread transmission among the general populace. During this period, some individuals previously infected with SARS-CoV-2 experienced re-infections. In response, an in-depth epidemiological investigation was conducted in February and March 2023 to assess the extent of re-infections, analyze associated characteristics, and inform future vaccination strategies.

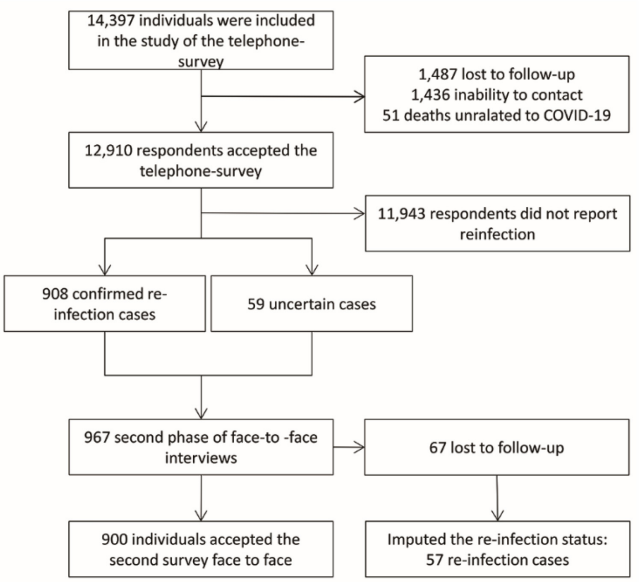
Methodology

Study design and inclusion criteria

The survey was conducted from February to March 2023.The epidemiological investigation was carried out in two phases. In the first phase, telephone interviews were conducted to preliminarily determine whether participants had experienced re-infection with SARS-CoV-2. In the second phase, face-to-face interviews were conducted to gather detailed information from individuals identified as having experienced re-infection.

Phase 1: Telephone interviews. Basic information of individuals previously diagnosed with COVID-19, including age, gender, current address, phone number, and diagnosis date, was extracted from the "Surveillance and Report Management" module of the "China Information System for Disease Control and Prevention". Selection criteria included reports dated between January 1, 2020, and November 30, 2022. The investigation targeted all individuals diagnosed with COVID-19 within Jiangsu Province, categorized by reporting region. During these interviews, participants were asked specific questions to assess their re-infection status. COVID-19 re-infection was determined based on the following criteria as of the survey date: (1) A positive SARS-CoV-2 nucleic acid test; (2) A positive SARS-CoV-2 antigen test; (3) Presented with symptoms related to COVID-19 infection (such as fever, cough, or other symptoms) combined with an epidemiological history of exposure to COVID-19 cases.

Figure 1. The process of participants' involvement in the two-stage survey and data processing.



Phase 2: Face-to-face interviews. In the second phase, face-to-face interviews were conducted with individuals identified as potentially having experienced re-infection. These interviews focused on collecting information related to the occurrence of re-infection, disease severity, major treatments, outcomes, and underlying medical conditions. The content of the face-to-face interviews was designed to provide comprehensive data on re-infection cases, facilitating a better understanding of the characteristics and outcomes associated with re-infection in the study population.

Study population and dataset

The survey included a total of 14,397 individuals diagnosed with COVID-19 between January 1, 2020, and November 30, 2022. In the first phase of telephone interviews, all 14,397 cases were targeted, and 12,910 cases were successfully interviewed, resulting in a follow-up rate of 89.67%. The primary reason for the 1487 cases lost to follow-up was the inability to contact the participants via telephone or other means. Among those lost to follow-up, 51 deaths (0.35% of the participants) were reported, all of which were determined to be unrelated to COVID-19 infection.

Among the 12,910 participants surveyed during the first phase of telephone interviews, 908 individuals (7.03%) reported experiencing re-infection, while 11,943 did not. Additionally, 59 participants were uncertain about their re-infection status. As a result, a total of 967 individuals, comprising 908 confirmed re-infection cases and 59 uncertain cases, proceeded to the second phase of face-to-face interviews. Ultimately, 900 individuals were successfully interviewed in the second phase, with 67 cases lost to follow-up. To address the potential underestimation of the re-infection rate due to these lost cases, the re-infection status was imputed. The imputation logic was as follows: if the "investigation conclusion" in the telephone survey indicated re-infection, it was classified as a re-infection case. If the "investigation conclusion" was uncertain, participants were asked, "Have you experienced COVID-19 again after the initial infection?" If the response was "yes", it was also classified as a re-infection case (Figure 1).

Table 1. Overall demographics of re-infection.

Group	N	Re-infection cases (%)	*p*
Gender			
Male	7,372	468 (6.35%)	< 0.001
Female	5,538	489 (8.83%)	
Age group (years)			
0–18	2,131	91 (4.27%)	
18–35	3,687	352 (9.55%)	
35–50	3,258	261 (8.01%)	< 0.001
50–60	2,256	153 (6.78%)	
60+	1,578	100 (6.34%)	

In the analysis of factors influencing re-infection, variables such as age, gender, initial infection time, and vaccination status were considered potential factors affecting the occurrence of re-infection. Observations included in the analysis were required to have complete data for all time points. Consequently, 73 observations with missing time points were excluded from the analysis, resulting in a total of 12,837 observations being included in the final analysis.

Data collection and statistical analysis

Following the completion of the paper-based epidemiological survey questionnaires, a database was established using EpiData version 3.1. A dedicated data verification team performed data validation and cleaning.

Categorical data were compared using the chi-square test or Fisher's exact test. For statistically significant differences, pairwise comparisons were conducted using the Bonferroni correction method. Numerical data were analyzed using Student's *t*-test. Given the variation in observation periods among participants, incidence density was utilized to measure the level of re-infection. The underlying influencing factors of re-infection were estimated using a Poisson regression model. The duration from the time of initial infection to either the time of subsequent infection or the survey time was included as an offset variable in the model. The Kaplan–Meier method (K–P curve analysis) was employed to assess changes in cumulative risk of subsequent infection over time across different populations. Hypothesis testing was conducted with a two-sided alpha value of 0.05. All analyses were performed using R software, version 4.3.0.

Ethical considerations

The survey protocol and informed consent form were approved by the ethics committee of the Jiangsu Provincial Center for Disease Control and Prevention (approval number JSJK2023-B009-02) on 24 February 2023. Written informed consent was obtained from each participant before enrollment. Prior to the formal implementation of the study, participants were informed about the study through oral promotion and distribution of notices, and were invited to participate voluntarily. During the study period, the participants were required to visit designated locations at specified times. Trained and qualified research personnel provided detailed explanations of the study. After confirming that participants fully understood the contents of the informed consent form, they were asked to sign the form to indicate their informed consent to participate in the study.

Results

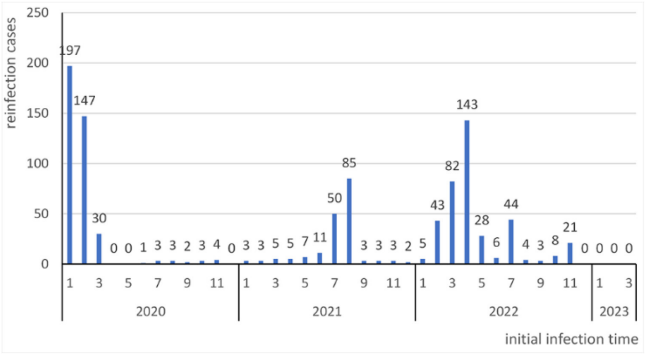
Overall re-infection scenario

Based on the imputed data, 957 re-infections cases were identified, accounting for 7.41% of the 12,910 respondents in the telephone survey. Among the 7,372 males, 468 re-infections were recorded (6.35%), while among the 5,538 females, 489 re-infections occurred (8.83%). The difference in re-infection rates between genders was statistically significant ($p < 0.001$) (Table 1).

The average age of individuals who experienced re-infection was 42 years, ranging from 1 to 83 years and a 95% confidence interval for the age of 38.5–45.2 years. The re-infection rates across different age groups were as follows: 4.29% (91/2,131) for the 0–18 years age group, 8.33% (766/9,201) for the 18–60 years age group (with 352/3,687 in the 18–35 age group, 261/3,258 in the 35–50 age group, and 153/2,256 in the 50–60 age group), and 6.34% (100/1,578) for the 60+ years group (Table 1). The differences in re-infection rates among these age groups were statistically significant ($p < 0.001$). Pairwise comparisons indicated that the re-infection rate in the 0–18 years age group was significantly lower than in the other two age groups. However, no significant differences in re-infection rates were observed between the other age groups.

Among the 957 re-infection cases, the majority (705 individuals, accounting for 73.66% of all re-infections) occurred during the period of high-intensity

Figure 2. Distribution of the time of initial infection among re-infected cases (n=957).



transmission in late December 2022. The initial infection times of the 957 re-infection cases were primarily concentrated in four periods: January–February 2020, July–August 2021, March–April 2022, and September–October 2022. In the January–February 2020 period, 809 individuals experienced initial infection, with 344 subsequently re-infected, resulting in a re-infection rate of 42.5%. During July–August 2021, 870 individuals were initially infected, and 135 experienced re-infection, corresponding to a re-infection rate of 15.5%. In the March–April 2022 period, 3,340 individuals were initially infected, with 225 re-infections (6.7%). In the September–October 2022 period, 1,002 individuals were initially infected, with 11 re-infections (1.1%) (Figure 2). The overall differences in re-infection rates among these four time periods were statistically significant ($p < 0.001$), with pairwise comparisons between each period also showing statistically significant differences ($p < 0.001$).

Analysis of factors influencing COVID-19 re-infection

Time-dependent risk assessment with K–P curve analysis

K–P curve analysis was employed to evaluate the variation in re-infection risk over time among different age groups, genders, initial viral strains, and immunization backgrounds among the surveyed participants after their first infection. The survival risk curves indicated that the cumulative risk of re-infection increased progressively following the initial infection across gender groups. After 1,000 days since the initial infection, the cumulative re-infection risk exceeded 75%, with females consistently showing a higher risk of re-infection compared to males (Figure 3A). The cumulative re-infection risk also showed an upward trend over time across different age groups, with individuals aged 18–60 exhibiting a consistently higher risk compared to those below 18 and above 60 years old. For the 18–35 age group, the cumulative re-infection risk exceeded 1 after 1,000 days, indicating that more than one re-infection event occurred on average for this group within that period (Figure 3B). Additionally, the cumulative re-infection risk varied among individuals infected with different viral strains, with the population initially infected with the Omicron variant showing the lowest re-infection rate, while those infected with the original Wuhan strain exhibited the highest re-infection risk. The results were strongly influenced by the initial infection period, reflecting the correlation between viral strain type and the timing of the initial infection (Figure 3C).

Figure 3. Impact of age, gender, and initial infection strain type on the time-dependent risk of re-infection.

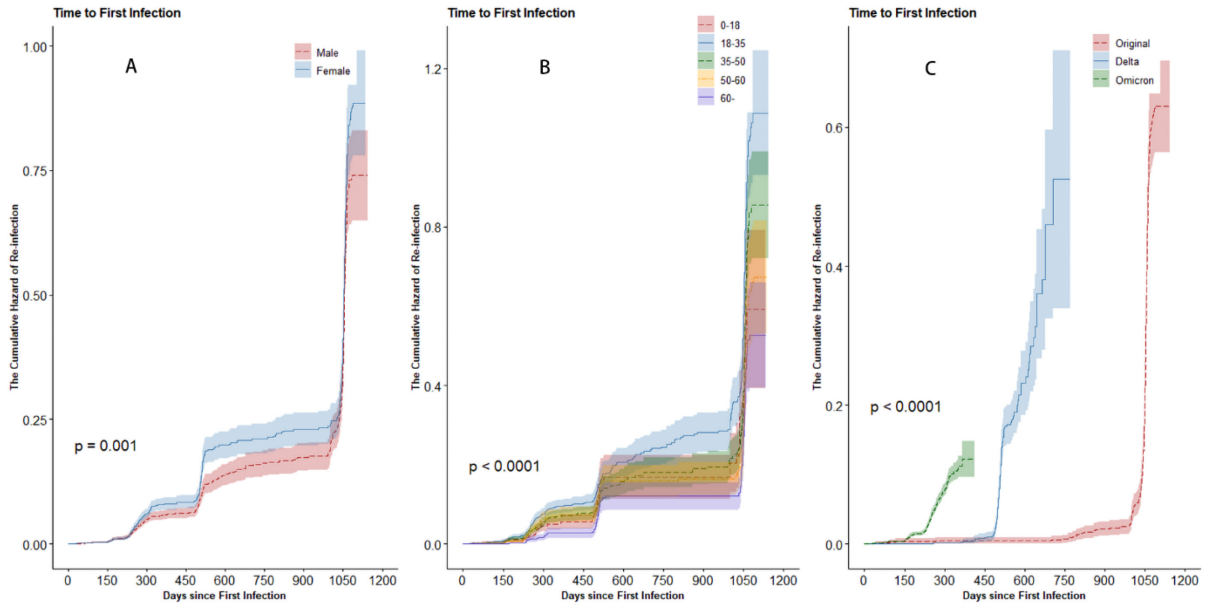


Table 2. Incidence density and results of univariate Poisson regression analysis.

Group	N	Re-infection cases (%)	Observation period (yrs.)	Incidence density (cases/1000 person/yrs.)	Incidence rate ratio	*p*
Gender						
Male	7339	428 (5.83%)	5,002.52	85.56	Baseline	–
Female	5498	466 (8.48%)	4,102.04	113.60	1.33	< 0.001
Age group (yrs.)						
0–18	2126	86 (4.05%)	1,325.73	64.87	Baseline	
18–35	3658	324 (8.86%)	2,545.51	127.28	1.96 (1.55–2.50)	< 0.001
35–50	3242	248 (7.65%)	2,379.11	104.24	1.61 (1.26–2.06)	< 0.001
50–60	2243	145 (6.46%)	1,552.34	93.41	1.44 (1.11–1.89)	0.007
60+	1568	91 (5.8%)	1,301.88	69.90	1.08 (0.80–1.45)	0.62
Initial virus strain						
Original (2020)	827	361 (43.65%)	2,407.75	149.93	Baseline	–
Delta (2021)	933	173 (18.54%)	1,423.66	121.52	0.81 (0.67–0.97)	0.023
Omicron (2022)	1,1077	360 (3.25%)	5,273.16	68.27	0.46 (0.39–0.53)	< 0.001
No. vaccine doses						
0	1,634	183 (11.2%)	1,549.02	118.14	Baseline	–
1	567	112 (19.75%)	723.54	154.79	1.31 (1.03–1.65)	0.024
2	3,920	241 (6.15%)	2,654.75	90.78	0.77 (0.63–0.93)	0.007
3	6,451	349 (5.41%)	3,942.83	88.51	0.75 (0.63–0.90)	0.002
4	115	3 (2.61%)	105.18	28.52	0.24 (0.06–0.63)	0.015
5	1	0 (0%)	0.21	0.00	0.00 (0.00–0.00)	0.976
Vaccine type						
None	1,634	183 (11.20%)	1,549.02	118.14	Baseline	–
mRNA	15	1 (6.67%)	13.36	74.83	0.63 (0.04–2.81)	0.648
Inactivated	9,814	630 (6.42%)	6,542.79	96.29	0.81 (0.69–0.96)	0.014
Adenovirus vector	150	8 (5.33%)	108.51	73.72	0.62 (0.28–1.18)	0.191
Recombinant protein	313	16 (5.11%)	162.23	98.63	0.83 (0.48–1.34)	0.486
Heterologous boosting	654	40 (6.12%)	537.31	74.45	0.63 (0.44–0.88)	0.008

The cumulative risk intervals for individuals who received three or fewer doses of any vaccine type overlapped, indicating no statistically significant differences in re-infection risk among those groups. In contrast, individuals who received four doses of the vaccine exhibited consistently lower cumulative re-infection risk. However, this finding should be interpreted with caution, as the relatively short observation period following the fourth dose may not have captured enough re-infection cases. Additionally, the cumulative re-infection risk curves for individuals vaccinated with different types of vaccines were interwoven and overlapped over time, further suggesting no statistically significant differences in re-infection rates based on vaccine type (Figure 4).

Univariate Poisson regression analysis

To enhance the response rate among participants, the first-stage telephone survey was designed to be concise, collecting only base information such as age, gender, time of initial infection, and vaccination status. Consequently, the analysis of COVID-19 re-infection risk factors in this study focused on these variables.

Among the 12,837 study participants, 7,339 (57.2%) were male and 5,498 (42.8%) were female, with incidence densities of 85.56 and 113.60 per 1000 person-years, respectively. Using males as the reference group, the relative risk (RR) for the females was 1.33, indicating that females had a 1.33 times higher risk of re-infection compared to males ($p < 0.001$) (Table 2).

The disease density in different age groups was as follows: 0–18 years old, 64.87 cases per 1,000 person-years; 18–35 years old, 127.28 cases per 1,000 person-years; 35–50 years old, 104.24 cases per 1,000 person-years; 50–60 years old, 93.41 cases per 1,000 person-years; and above 60 years old, 69.90 cases per 1,000 person-years. Using the 0–18 age group as the reference, the RR values for the 18–35, 35–50, and 50–60 age groups were 1.96, 1.61, and 1.44, respectively, all of which were statistically significant. This indicates that individuals aged 18–60 years are more susceptible to re-infection compared to those under 18 and above 60 years (Table 2).

When participants were grouped based on the type of viral strain during their initial infection: original strain (infections in 2020), Delta variant (infections in 2021), and Omicron variant (infections in 2022), the re-infection cases were 361/827 (43.65%), 173/933 (18.54%), and 360/11,077 (3.25%), respectively. The re-infection incidence rates were 149.93, 121.52, and 68.27 per 1,000 person-years, respectively. Using the original strain group as the reference, the RR values for

Table 3. Multivariate Poisson regression results.

Group	Incidence rate ratio	RR 95% CI	*p*
Gender			
Female *vs*. male	1.35	1.18–1.54	< 0.001
Age group (years)			
18–35	1.77	1.38–2.29	< 0.001
35–50	1.44	1.11–1.88	0.007
50–60	1.32	1.00–1.76	0.056
60+	0.91	0.66–1.23	0.497
Initial virus strain			
Delta (2021)	0.87	0.72–1.04	0.125
Omicron (2022)	0.49	0.42–0.58	< 0.001
No. vaccine doses			
1	1.04	0.91–1.48	0.216
2	0.85	0.80–1.18	0.753
3	0.8	0.74–1.09	0.259
4	0.25	0.06–0.67	0.019
5	0	0.00–0.00	0.976

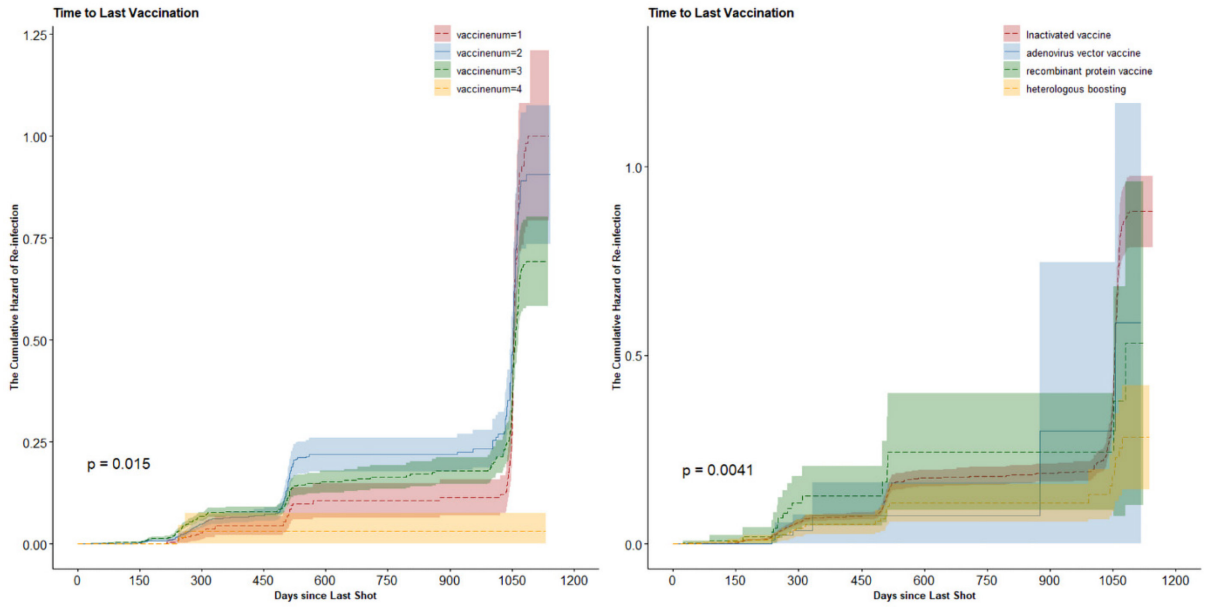
the Delta variant group and Omicron variant group were 0.81 (p = 0.023) and 0.46 (p < 0.001), respectively. These findings suggest that the risk of re-infection varies depending on the viral strain, with lower risks observed for the Delta and the Omicron variants compared to the original strain.

In terms of the number of vaccine doses received, the incidence rate of re-infection for individuals who did not receive any vaccines was 118.14 cases per 1,000 person-years. Overall, the incidence rate of re-infection decreased as the number of vaccine doses increased. The incidence rates for individuals who received 1–4 doses were all lower than those in the unvaccinated group, and these differences were statistically significant. Regarding the type of vaccine received, compared to the unvaccinated group, individuals who received only inactivated vaccines (incidence rate: 96.29 per 1,000 person-years) and those who received a combination of vaccines (heterologous boosting) (incidence rate: 74.45 per 1,000 person-years) exhibited lower incidence rates of re-infection. These differences were also statistically significant (Table 2).

Multivariate Poisson regression analysis

Multivariate Poisson regression analysis was performed by incorporating the significant variables identified in the univariate analysis into a multivariate model. The results indicated that the type of vaccine received was excluded during the stepwise regression process, while age, gender, viral strain type, and the number of vaccine doses were retained in the final model (Table 3). The findings showed that females and

Figure 4. Effect of vaccination status on the time-dependent risk of re-infection.



individuals aged 18–50 years exhibited a higher likelihood of re-infection compared to males and other age groups, respectively. Additionally, individuals who were initially infected with the Omicron variant demonstrated a lower risk of re-infection compared to those initially infected with the original strain. Furthermore, individuals who received four doses of the vaccine had a significantly lower risk of re-infection compared to those who were unvaccinated.

Discussion

This study identified a total of 908 re-infection cases, yielding a re-infection rate of approximately 7.0%. This rate aligns with those reported in a comprehensive review on the severity of SARS-CoV-2 re-infection and associated disease in 2023, where re-infection rates ranged from 0.1% to 6.8% [6]. In comparison to the nearly 80% infection rate observed in previously uninfected populations, these findings suggest that prior infection with SARS-CoV-2 acts as a protective factor against subsequent infections.

The findings from this investigation suggest that females and individuals aged 18–50 years are more prone to re-infection with COVID-19, possible explanations for the increased susceptibility in these groups may involve differences in immune response, level of exposure, and social behaviors. Individuals aged 18–50 years tend to have active roles in social and economic activities, which lead to more frequent social interactions and heightened exposure to the virus, thereby increasing the risk of re-infection [7]. Gender-based differences in immune responses may also play a role, as females are known to exhibit more complex and diverse immune responses compared to males [8]. Additionally, higher virus exposure among females may be linked to caregiving responsibilities, such as caring for ill family members.

The timing of the initial infection significantly influences re-infection rates, The re-infection rate decreased from 42.5% for individuals initially infected in February 2020 to 1.1% for those infected in September–October 2022. These findings suggested that the earlier the initial infection, the higher the likelihood of subsequent re-infection. Previous studies indicate that prior infection with COVID-19 can provide protection of 80% or higher for up to seven months, compared to unvaccinated and previously uninfected individuals [9]. In Jiangsu Province, the circulating strains have shifted from the original strain in 2020 to the Delta variant in 2021, and then to the Omicron variant in 2022. The cumulative risk of re-infection varied depending on the viral strain involved, with individuals initially infected with the Omicron variant exhibiting a lower risk of re-infection compared to those infected with the original strain. This finding aligns with a study from Denmark, which indicated that previous Omicron infection provides strong protection (92.7%) against subsequent BA.5 infections, while earlier Alpha or Delta infections confer moderate protection against BA.5 and BA.2 (61.2% and 73.4%, respectively) [10]. Another study from Singapore demonstrated that previous Omicron infection provides less and faster-declining protection against XBB re-infection compared to protection against BA.4 or BA.5 re-infections. Individuals previously infected with BA.1 or BA.2 exhibit low to moderate protective immunity against XBB re-infection (up to 51%), with protection declining over time, from 74% at 3–6 months to 49% at 7–8 months [11]. Further analysis of this study cohort suggests that the relatively lower re-infection rate among individuals initially infected with the Omicron variant in this study should be interpreted with caution. This result may be influenced by the relatively short observation period and the possibility that antibody titers among individuals initially infected with the Omicron variant remained high at the time of investigation, thereby limiting the number of observed re-infections.

With regard to vaccine administration, the univariate analysis demonstrated that the incidence density of re-infection decreased as the number of vaccine doses increased. Individuals vaccinated with inactivated vaccines and those who received combination vaccination (heterologous boosting) exhibited lower incidence densities compared to the unvaccinated group. However, multivariate analysis indicated that only individuals who received four doses of the vaccine had a significantly lower risk of re-infection compared to the unvaccinated group, with a RR of 0.25. This suggests that individuals who received four doses of the vaccine had a 75% reduced risk of re-infection compared to the unvaccinated group. The differences in re-infection risk among other vaccine dose groups and vaccine types, when compared to the unvaccinated group, were not statistically significant. A study from Singapore previously recommended the administration of an mRNA booster vaccine following three doses of inactivated vaccine immunization [12]. Additionally, a study from Israel found that a fourth dose of the BNT162b2 vaccine enhanced protection against severe COVID-19 in individuals aged 60 years and older [13]. These findings align with the conclusion of the current study, which observed the highest level of

protection in individuals who received four doses of the vaccine.

Conclusions

In conclusion, the findings indicate that females and young adults aged 18–50 years are more susceptible to COVID-19 re-infections, while receiving four or more doses of a vaccine significantly reduces the likelihood of re-infection. Additionally, the cumulative risk of re-infection increases over time for individuals infected with different strains. These results highlight the importance of promoting vaccine and protecting high-risk and vulnerable populations as part of ongoing COVID-19 prevention and control efforts.

Several limitations of this study should be acknowledged. Firstly, primary information regarding re-infections was obtained through telephone interviews, which may introduce the risk of subjective reporting by participants, this could lead to underreporting of mild and asymptomatic cases, potentially introducing biased in the analysis. Second, the reliance on self-reported data for survival analyses may limit the accuracy of the time intervals between infections. Additionally, the observation period of the study may have been insufficient to capture enough re-infection cases, particularly among individuals initially infected with the Omicron variant. Although the limitations have been noted, it's crucial to highlight that the relatively lower re-infection rate observed among the Omicron-infected population should be interpreted cautiously, considering the evolving nature of the pandemic and possible fluctuations in antibody titers over time. Ongoing monitoring of the re-infection status within the cohort will provide further insights into the dynamics of re-infections.

Acknowledgements

The authors express their sincere gratitude to the participants for their active participation and cooperation in the study. Appreciation is also extended to all staff members who contributed to the research, particularly those on the front lines of data collection. Finally, the first author would like to thank JJ for the companionship through the earphones during the writing process.

Authors' contributions

Z.F. conceptualized the study. B.C. and H.J. designed the survey and contributed to the critical review and revision of the report. D.Q., J.H., L.N., W.J., W.S. contributed to the data collection, data management, statistical analysis, coding and wrote the paper. All authors read and approved the final manuscript.

Funding

This study was supported by grants from the Natural Science Foundation of Jiangsu Province (No. BE2023601 to Fengcai Zhu), the Scientific Research Project of Jiangsu Provincial Health Commission (No. ZD2021037 to Changjun Bao; No. ZD202302 to Jianli Hu; No.M2020026 to Qigang Dai),National Key R&D Program of China(No.2023YFC260510102 to Qigang Dai; No.2023YFC2605104 to Lunbiao Cui), and Open Project of the Jiangsu Province TCM Epidemic Research Center(No.JSYB2024KF23 to Changjun Bao).

Availability of data and materials

The datasets used and analyzed during the current study and the program code are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The survey protocol and the informed-consent form were approved by the ethics committee of the Jiangsu provincial center for disease control and prevention before enrollment, written informed consent was obtained from each participant.

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Conflict of interests: No conflict of interests is declared.