This is an Accepted Manuscript for Epidemiology & Infection. Subject to change during the editing and production process.

DOI: 10.1017/S0950268825000172

Characteristics and risk factors associated with COVID-19 reinfection in Hong Kong: a retrospective cohort study

Wenhua LIN, Kin Hang KUNG, Chung Lam CHAN, Shuk Kwan CHUANG, Ka Wing AU

Communicable Disease Branch, Centre for Health Protection,

Department of Health, Hong Kong

Corresponding author: Dr Wenhua LIN

Email: wenhua_lin@dh.gov.hk

Phone: +852 2125 2393

Postal address: Communicable Disease Branch, 3/F, Centre for Health Protection, 147C Argyle Street, Kowloon, Hong Kong

Declaration of interest: none.

No funding for this study.

Abstract

We aimed to identify risk factors related to COVID-19 reinfection in Hong Kong. We performed a population-based retrospective cohort study and reviewed case-based data on COVID-19 infection reported to the Centre for Health Protection from 8 January 2020 to 29 January 2023. We analyzed the epidemiology of COVID-19 infections and performed Cox regression analysis. In this period, 3.32% (103,065/3,106,579) of COVID-19 infections recorded were classified as reinfection. Compared with primarily infected cases, a higher proportion of re-infected cases had chronic diseases (33.54% vs 27.27%) and were residents of residential care homes (RCH) (10.99% vs 1.41%). The time interval between the two episodes ranged from 31 to 1,050 days (median 282 days). Cox regression analysis of Omicron cases with the adjustment of covariates showed that being female (Hazard Ratio [HR] 1.12, 95% CI 1.11-1.13), chronic diseases (HR 1.18, 95% CI 1.16-1.20) and RCH residents (HR 6.78, 95% CI 6.61-6.95) were associated with reinfection, while additional vaccination after primary infection was protective (HR 0.80, 95% CI 0.79-0.81). Further analytical studies on the risk factors and protectors of COVID-19 reinfection are needed to guide targeted interventions.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Key results

- This was the first report on the situation of COVID-19 reinfection in Hong Kong based on the largest and most reliable population-based dataset recorded in Hong Kong.
- Cox regression showed that being female, having chronic diseases and RCH residents were independent risk factors of COVID-19 reinfection.
- Additional vaccination after primary infection was a protective factor against reinfection which could reduce 20% risk of COVID-19 reinfection.

Keywords: COVID-19, reinfection, risk factor, severity, death, chronic disease

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been declared by the World Health Organization (WHO) for more than three years since 2020. Although WHO announced that COVID-19 no longer constituted a public health emergency of international concern on 5 May 2023, COVID-19 still affects the daily lives of people in the world. As of 20 August 2023, over 769 million confirmed COVID-19 cases and over 6.9 million deaths were reported globally [1]. New mutant variants with the potential of immune evasion and increased transmissibility arising from the ongoing evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lead to recurring surges of COVID-19 infection in different communities worldwide.

With new SARS-CoV-2 mutant strains constantly emerging, there is an increasing concern about the risk and severity of COVID-19 reinfection. Hong Kong has recorded at least five waves of infections driven by different SARS-CoV-2 variants since 2020 with different sublineages of

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Omicron variants predominating the 5th wave starting from 31 December 2021.[2] Hong Kong had adopted a containment strategy with requirement of reporting of individual cases and the Department of Health (DH) of Hong Kong recorded the case-based data till 29 January 2023. Hong Kong has implemented a territory-wide COVID-19 Vaccination Programme free of charge for eligible persons since February 2021, providing the CoronaVac vaccine produced by Sinovac and the Comirnaty vaccine jointly developed by Pfizer and BioNTech. The Joint Scientific Committee on Vaccine Preventable Diseases and Scientific Committee on Emerging and Zoonotic Diseases under DH's Centre for Health Protection (CHP) in Hong Kong have revised the recommended regimen of initial doses of COVID-19 vaccines to three doses (i.e. Comirnaty or CoronaVac vaccine) for the general population since 6 April 2022 [3], as local studies have shown that three doses of vaccines were highly effective against severe diseases and death in the context of emerging SARS-CoV-2 variants. [4] As of the peak of the local Omicron wave in March 2022, 13.2 million vaccine doses were administered among Hong Kong's 7.4 million population. The Comirnaty Original/Omicron BA.4-5 bivalent vaccine became available for eligible persons from 1 December 2022 in Hong Kong. Up to 78.12% of the local population had completed at least three initial doses of COVID-19 vaccination by 29 January 2023 [5]. Since the Omicron wave started in December 2021, more and more re-infected cases of COVID-19 have been reported in Hong Kong. This study aimed to identify risk factors of COVID-19 reinfection in Hong Kong.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Methods

In this cohort study, we reviewed the case-based data on COVID-19 infections in Hong Kong maintained by DH. The study cohort recruited all confirmed cases tested positive for SARS-CoV-2 by polymerase-chain-reaction (PCR) of nucleic acid testing or rapid antigen test (RAT) and reported to CHP from 8 January 2020 to 29 January 2023. The database included line-listing data of COVID-19 cases and the epidemiological and clinical information provided by the cases, including travel history, date of symptom onset, past medical history and symptoms at the time of reporting such as fever, cough, sore throat, myalgia, fatigue, and headache. Chronic diseases in the medical history (hypertension, hyperlipidemia, diabetes, chronic respiratory diseases, cardio- or cerebrovascular diseases, etc.) were also recorded in the database. The first COVID-19 infection episode confirmed by the case and recorded in our database was considered as the primary infection. Reinfection was defined as an individual who had sequential positive tests with high viral load [Cycle threshold (Ct) value<30] at least 90 days after previous infection or who got infected by a different SARS-CoV-2 variant from the last episode confirmed by genomic characterization irrespective of the interval between two episodes. The cohort was followed up for a COVID-19 reinfection event till 29 January 2023. If an individual had a reinfection during the follow up period, the relevant reinfection data was linked and added to his or her original line-listing data. The individual was censored if he or she died of/with COVID-19 during the study period or reached the end of the study period.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

We compared the epidemiological characteristics of cases with various episodes of COVID-19 infections (including: sex, age, importation status, symptoms, chronic diseases, vaccination history, residential care home (RCH) status and severe clinical outcomes), where the characteristics at the last infection of each case were used for comparison. A valid dose of COVID-19 vaccination was counted if the vaccination was given at least 14 days before the concerned infection episode. Residential status in RCH was checked from the registered list of RCHs for the elderly and RCHs for persons with disabilities under the Social Welfare Department of Hong Kong. Severe clinical outcomes of COVID-19 infection were recorded, defined as patients presenting with severe pneumonia, sepsis, encephalopathy/encephalitis, myocarditis, multiple organ failure, shock or other severe complications of COVID-19 and requiring oxygen supplement of at least 3L/min, intubation or extracorporeal membrane oxygenation. Deaths attributed to COVID-19 (COVID-19 was listed on the death certificate as the immediate, intervening or underlying cause of death) were also included as severe clinical outcomes. Data from different sources were linked using the unique individual identifier to allow the curation of duplicates and identification of all infections.

Over 99% of COVID-19 cases recorded in Hong Kong were infected by Omicron strains and re-infected cases emerged after the start of the Omicron wave (31 December 2021). The Kaplan-Meier (KM) curves showing the probability of remaining reinfection-free in different groups of cases were plotted. To reduce the confounding effect of distinct SARS-CoV-2 virus

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

variants, we performed Cox proportional hazards regression on the sub-cohort of Omicron cases which only included those individuals who were recruited (got the primary infection) after the start of Omicron wave in Hong Kong. Cox regression analysis was conducted to identify the risk factors of COVID-19 reinfection. Cox regression model used reinfection as the outcome (only the first reinfection was included) and included those statistically significant factors identified from univariate analysis as the covariates. Age was entered as a categorical variable by age groups of 10-year intervals in the Cox regression to allow for a more flexible model. Cases with missing information of sex or age were excluded from regression analysis as sex and age were covariates in the model. Hazard Ratio (HR) and 95% confidence interval (CI) for each variate were identified.

We used the R software package (version 4.3.1) and R Studio (version 1.4.1106) for data analysis. Chi-square test was used to measure the frequency difference. The two-tailed student t-test was used for group mean comparison. The differences or associations were considered significant if the P value was less than 0.05.

Results

Among 3,106,579 confirmed COVID-19 infections (1,226,467 confirmed by PCR, 1,880,112 confirmed by RAT) reported to the CHP up to 29 January 2023, there were 103,065 (3.32%) infections classified as reinfections. There were 3,093,948 COVID-19 infections recorded from the start of Omicron waves, and it was estimated that almost all cases (99.59%)

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

in Hong Kong were infected by Omicron strains. COVID-19 reinfections emerged in the Omicron waves and their number followed the trend of overall COVID-19 infections. The proportion of reinfection recorded per month steadily increased and reached the highest proportion of 11.72% in January 2023 (Figure 1). During the first peak of the Omicron wave from 31 December 2021 to May 2022, BA.2 and its sublineages were predominating strains locally. With the spread of new Omicron variants of BA.2.12.1, BA.4 and BA.5 in the local community since June 2022, reinfections remarkably rose. In our database, 482 cases had available genetic information at both the primary infection and reinfection, and 89.42% of them got infected by Omicron variants at both infections.

Among the total 3,003,672 cases with at least one episode of COVID-19 infection (by head-count), 96.59% of them (2,901,238) had been infected once while 3.39% (101,806) had infected twice including 158 cases that reported their first episode outside Hong Kong without relevant primary infection records in CHP. There were 625 cases with three episodes recorded and even three cases who reported four episodes. Reinfection affected all age groups with age ranging from zero to 108 years (median 43 years). The most affected group was 30-39 years (18.54%), followed by the age groups of 40-49 and 20-29 years. Compared with cases with one infection (Table 1), cases with two infections were slightly younger with more females. A higher proportion of re-infected cases had chronic diseases (33.54% vs 27.27%) and were RCH residents (10.99% vs 1.41%). Most reinfections occurred within one year from the last episode

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

and the median interval between two consecutive episodes was 282 days (Figure 2). The time interval between two episodes ranged from 31 to 1,050 days. Most cases (96.49%) were locally acquired infections and more cases (46.96%) self-reported as asymptomatic at the detection of reinfection. Although more cases had vaccinated at least two doses at the reinfection (81.57% vs 80.15%), the proportion of cases who received at least three doses was significantly lower at reinfection compared with cases of primary infection (46.56% vs 49.73%). Overall the proportion of severe clinical outcomes was similar in reinfections and primary infections (0.55% vs 0.6%), but a lower proportion of re-infected cases died of COVID-19 than primarily infected cases (0.15% vs 0.35%).

The sub-cohort of Omicron cases included 2,990,810 cases (99.57% of all COVID-19 cases), with 96.68% of them (2,891,019) who were infected once, 3.32% (99,236) infected twice, and 0.019% (555) infected more than twice. The comparison of primarily infected cases with re-infected cases in this sub-cohort showed similar results as those in the whole cohort (Table 2).

Median follow-up time for cohort cases was 193 days (Interquartile range, 69-330 days), with a maximum of 1,104 days. KM curve for the whole cohort cases by the date of recruitment (Figure 3) showed Omicron cases had much higher risk of reinfection than cases who was primarily infected with non-Omicron strains, although Omicron cases had a shorter follow up time (median follow up for Omicron cases: 192 days vs median follow up for non-Omicron cases: 776 days). Figure 4 of KM curves for Omicron cases demonstrated cases with chronic

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

diseases or being RCH residents had a higher risk of reinfection while cases who received vaccination with at least three doses at the time of censoring or received additional vaccination after primary infections had a lower risk of reinfection.

There were 2,975,948 cases included in Cox regression analysis after excluding 14,862 cases with missing information of sex or age. The flowchart of the population selection process was illustrated in Figure 5. Cox regression (Table 3) of Omicron cases adjusted with covariates showed that being female (adjusted HR 1.12, 95% CI 1.11-1.13), having chronic diseases (adjusted HR 1.18, 95% CI 1.16-1.20) and RCH residents (adjusted HR 6.78, 95% CI 6.61-6.95) were independent risk factors of COVID-19 reinfection. Compared with vaccination of less than three doses, vaccination with at least three doses of vaccines at the time of censoring demonstrated the protective effect (crude HR 0.94, 95% CI 0.93-0.96) in the univariate model but failed to be protective in the multivariate model. Additional vaccination after primary infection was protective against reinfection (adjusted HR 0.80, 95% CI 0.79-0.81). Regarding vaccine types, most cases in our study received CoronaVac or Comirnaty vaccine (either one was not targeting an Omicron variant) except 76,425 cases (2.57% of 2,975,948) had taken the Comirnaty Original/Omicron BA.4-5 bivalent vaccine as a booster dose in the survival study.

Discussion

This is the first report on the situation of COVID-19 reinfection in Hong Kong. We found the proportion of reinfection in Hong Kong was 3.32% up to 29 January 2023, which was

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

comparable to the pooled estimated prevalence of reinfection in Asia (3.8%) from studies conducted in 2019 and 2022. [6] The 5th wave of COVID-19 infection in Hong Kong was caused by Omicron variants BA.1, BA.2, BA.4, BA.5 and their sublineages, and reinfections started to appear since then. These Omicron variants of SARS-CoV-2 showed the capacity to escape from neutralizing antibodies. [7] High transmissibility and extensive immune escape from hybrid immunity of new variants increased the risk of reinfection in the general population, even when the majority of the population had protection from natural infection and high vaccination coverage. Our results found that most COVID-19 cases in Hong Kong were infected by Omicron strains and a small percentage of cases had more than one time infections. Infection-induced immunity confers less protection against Omicron than against non-Omicron variants six or more months after a prior infection. [8,9] Diverse Omicron variants showed their capacity to infect individuals again within a short period. [10] Only a very small group of reinfection (0.55%) had severe clinical outcomes and there was no overall difference from that in primary infections. Many studies demonstrated prior COVID-19 infection had protection from severe diseases. [11,12] A lower proportion of re-infected cases died of COVID-19 were observed in our results.

Being female has been repeatedly reported as a risk factor of reinfection [12-15], our study also found that being female was associated with COVID-19 reinfection. Although age was identified as a risk factor for reinfection in overseas studies [15-17], age groups of 10-39

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

years in our study had a higher risk of reinfection compared with the reference age group of 0-9 years. Chronic diseases or underlying comorbidities were reported linked with the occurrence [14,15,18,19] and severity of COVID-19 reinfection [12]. Our results also revealed that chronic diseases were associated with reinfection. However, people with chronic diseases might be more concerned about the severe outcomes following reinfection and were prone to report their reinfections with the entitlement to receive free treatment under the self-reporting COVID-19 policy in Hong Kong.

Data provided RCH staff and RCH residents were less affected by surveillance bias. In Hong Kong, the Government of the Hong Kong Special Administrative Region (HKSARG) attached great importance to safeguarding vulnerable groups as the focus of protection against COVID-19. RCHs were designated as the key institutions requiring enhanced protection against the epidemic. All RCH staff and residents were required to undergo daily RATs or regular nucleic acid tests mandatorily, and RCHs were required to report positive cases to the CHP during the 5th wave on a daily basis, ensuring more complete case ascertainment. Therefore, reporting bias may be reduced in the RCH staff and residents, and a much higher proportion of RCH residents reporting the reinfection was observed. The long-term care facility residents were reported to have a higher risk of reinfection than the general population [17], and our study showed consistent results that RCH residents had 6.78 times the risk of reinfection compared with non-RCH residents.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Evidence showed that COVID-19 vaccination provided substantial added protection against SARS-CoV-2 reinfection among persons recovering from prior infection. [20-22] In Hong Kong, more than 80% of COVID-19 cases have completed two doses of vaccination at their primary infection. Although the Joint Scientific Committees recommended individuals with previous infection for COVID-19 vaccination as well as doses and timing for vaccination (i.e. at least six months since the last dose or infection, whichever is later) [23], the vaccine coverage of at least three valid doses was less in the re-infected cases than primarily infected cases. Vaccine-induced immunity against Omicron-related mild symptomatic disease, asymptomatic infection, and viral shedding is also modest and short-lived even following a booster dose [24]. Our results showed additional vaccination after primary infection could reduce 20% risk of reinfection, which reiterated the protection and importance of vaccination after recovery from last infection. Compared with vaccination of less than three doses, receiving more than three doses of vaccination showed protective effects in the univariate analysis but was not an independent risk factor in the multivariate model. Further studies are required to investigate the effectiveness of COVID-19 vaccination in terms of doses and timing.

Our study had some limitations. Firstly, the recorded COVID infections and reinfections might not represent the full picture of the COVID-19 situation in Hong Kong since the reporting of COVID-19 infection detected by self-performed RAT was voluntarily initiated by the citizens (particularly for the cases confirmed solely by RAT without PCR) and there were likely

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

unreported reinfections in the community. It is possible that those with more severe clinical presentations would seek medical attention and are more likely to be recorded by our surveillance system. Cases with chronic diseases tend to seek care more frequently, which might overestimate the effects of chronic disease on COVID-19 reinfection. Second, some confounders on COVID-19 reinfection were not included in the analysis due to lack of information, such as socioeconomic status, occupation and causative Omicron variants. We were unable to control the frequency of testing and adjust its effects since mandatory and voluntary PCR or RAT tests were widely available and sponsored by the HKSARG during the study period. The HKSARG distributed RAT testing kits to citizens freely to encourage early detection and an individual might have undergone multiple COVID-19 tests even on the same day. We were also unable to adjust for the potential confounder of vaccination timing, which could lead to the effect of vaccination being overestimated or underestimated. In addition, censoring associated with COVID-19 mortality was used as the information of all-cause mortality data was not available for individual cases in our registry. This study was based on the context of Hong Kong, which is a developed society with a well-established healthcare system, easy access to medical care and high COVID-19 vaccination coverage. The HKSARG adjusted the anti-epidemic strategies and measures (such as vaccine pass, social distancing, mandatory wearing of masks, compulsory isolation of infected patients, etc.) as the local situation of COVID-19 changed. Temporal variations on the COVID-19 epidemic situation and

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

evolving strategies in Hong Kong had impacts on our results. The aforesaid factors could affect the generalizability of our results, which might not be applicable for other parts of the world. Lastly, our retrospective observational study design limits causal inferences and the risk factors identified do not provide definitive evidence of causality.

Conclusion

COVID-19 reinfection varied following the overall COVID-19 trend in Hong Kong. Being female, having chronic diseases and RCH residents were independent risk factors of reinfection. Additional vaccination after primary infection remarkably reduced the risk of reinfection in previously infected COVID-19 cases. Further studies on risk factors and protectors of COVID-19 reinfection are needed to guide targeted interventions.

Information governance and ethical approval

Surveillance of COVID-19 was performed by the Department of Health under Cap. 599 Prevention and Control of Disease Ordinance in Hong Kong. All personal data collected during the surveillance were handled in accordance with the relevant provisions of the Personal Data (Privacy) Ordinance in Hong Kong. Informed consent was obtained from all cases via the Personal Information Collection Statement. All datasets were encrypted and kept securely. Only anonymized and integrated data was used in this study. The use of data for this study has

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

been approved by the Department of Health, Hong Kong.

Data availability statement

Data related to COVID-19 in Hong Kong are available at the thematic website of "COVID-19" (https://www.coronavirus.gov.hk/eng/index.html), which is subject to copyright owned by the Government of the Hong Kong Special Administrative Region, China, under conditions set out at https://www.coronavirus.gov.hk/eng/important.html.

Authorship contribution statement

All authors contributed to the study's conception and design. The first draft of the manuscript was written by Dr LIN. Data analysis was performed by Mr CHAN. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all the teams of the Department of Health, HKSARG, for their tireless work during the COVID-19 pandemic, particularly thank all colleagues in the Surveillance Division under the Communicable Disease Branch, Centre for Health Protection, for their dedicated efforts on the surveillance of COVID-19 infection.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

References

[1] (2023) Weekly epidemiological update on COVID-19 - 25 August 2023, 25 August. World Health Organization. Available at https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---30-august-2023 (accessed.

[2] **Yang B, Lin Y, Xiong W, Liu C, Gao H, Ho F, Zhou J, Zhang R, Wong JY, Cheung JK, Lau EHY, Tsang TK, Xiao J, Wong IOL, Martin-Sanchez M, Leung GM, Cowling BJ and Wu P** (2024) Comparison of control and transmission of COVID-19 across epidemic waves in Hong Kong: an observational study. *Lancet Regional Health - Western Pacific* **43,** 100969. https://doi.org/10.1016/j.lanwpc.2023.100969.

[3] (2022) Consensus Interim Recommendations on the Use of COVID-19 Vaccines in Hong Kong (As of 6 April 2022). In: Health Do (ed). Scientific Committee on Emerging and Zoonotic Diseases and Scientific Committee on Vaccine Preventable Diseases.

[4] **McMenamin ME, Nealon J, Lin Y, Wong JY, Cheung JK, Lau EHY, Wu P, Leung GM and Cowling BJ** (2022) Vaccine effectiveness of one, two, and three doses of BNT162b2 and CoronaVac against COVID-19 in Hong Kong: a population-based observational study. *Lancet Infectious Diseases* **22**(10)**,** 1435-1443. https://doi.org/10.1016/S1473-3099(22)00345-0.

[5] (2023) Statistics on 5th wave of COVID-19 in Hong Kong, 27 July 2023. Available at https://www.coronavirus.gov.hk/pdf/5th_wave_statistics/5th_wave_statistics_20230727.pdf (accessed.

[6] **Ukwishaka J, Ndayishimiye Y, Destine E, Danwang C and Kirakoya-Samadoulougou F** (2023) Global prevalence of coronavirus disease 2019 reinfection: a systematic review and meta-analysis. *BMC Public Health* **23**(1)**,** 778. https://doi.org/10.1186/s12889-023-15626-7.

[7] **Hachmann NP, Miller J, Collier AY and Barouch DH** (2022) Neutralization Escape by SARS-CoV-2 Omicron Subvariant BA.4.6. *New England Journal of Medicine* **387**(20)**,** 1904-1906. https://doi.org/10.1056/NEJMc2212117.

[8] **Altarawneh HN, Chemaitelly H, Ayoub HH, Tang P, Hasan MR, Yassine HM, Al-Khatib HA, Smatti MK, Coyle P, Al-Kanaani Z, Al-Kuwari E, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM, Abdul-Rahim HF, Nasrallah GK, Al-Kuwari MG, Butt AA, Al-Romaihi HE, Al-Thani MH, Al-Khal A, Bertollini R and Abu-Raddad LJ** (2022) Effects of Previous Infection and Vaccination on Symptomatic Omicron Infections. *New England Journal of Medicine* **387**(1)**,** 21-34. https://doi.org/10.1056/NEJMoa2203965.

[9] **Cerqueira-Silva T, de Araujo Oliveira V, Paixao ES, Florentino PTV, Penna GO, Pearce N, Werneck GL, Barreto ML, Boaventura VS and Barral-Netto M** (2022) Vaccination plus previous infection: protection during the omicron wave in Brazil. *Lancet Infectious Diseases* **22**(7)**,** 945-946. https://doi.org/10.1016/S1473-3099(22)00288-2.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

[10] **Cai C, Li Y, Hu T, Liang R, Wang K, Guo C, Li Y, Zhang M and Kang M** (2023) The Associated Factors of SARS-CoV-2 Reinfection by Omicron Variant - Guangdong Province, China, December 2022 to January 2023. *China CDC Weekly* **5**(18), 391-396. https://doi.org/10.46234/ccdcw2023.075.

[11] **Team C-F** (2023) Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. *Lancet* **401**(10379), 833-842. https://doi.org/10.1016/S0140-6736(22)02465-5.

[12] **Mensah AA, Lacy J, Stowe J, Seghezzo G, Sachdeva R, Simmons R, Bukasa A, O'Boyle S, Andrews N, Ramsay M, Campbell H and Brown K** (2022) Disease severity during SARS-COV-2 reinfection: a nationwide study. *Journal of Infection* **84**(4), 542-550. https://doi.org/10.1016/j.jinf.2022.01.012.

[13] **Flacco ME, Soldato G, Acuti Martellucci C, Di Martino G, Carota R, Caponetti A and Manzoli L** (2022) Risk of SARS-CoV-2 Reinfection 18 Months After Primary Infection: Population-Level Observational Study. *Frontiers in Public Health* **10**, 884121. https://doi.org/10.3389/fpubh.2022.884121.

[14] **Nguyen NN, Nguyen YN, Hoang VT, Million M and Gautret P** (2023) SARS-CoV-2 Reinfection and Severity of the Disease: A Systematic Review and Meta-Analysis. *Viruses* **15**(4). https://doi.org/10.3390/v15040967.

[15] **Gomez-Gonzales W, Chihuantito-Abal LA, Gamarra-Bustillos C, Moron-Valenzuela J, Zavaleta-Oliver J, Gomez-Livias M, Vargas-Pancorbo L, Auqui-Canchari ME and Mejia-Zambrano H** (2023) Risk Factors Contributing to Reinfection by SARS-CoV-2: A Systematic Review. *Advances in Respiratory Medicine* **91**(6), 560-570. https://doi.org/10.3390/arm91060041.

[16] **Tavakoli A, Lotfi F, Lotfi M, Bayati M, Seif M, Salesi M, Emadi M, Keshavarz K and Delavari S** (2023) COVID-19 Reinfection Rate and Related Risk Factors in Fars Province, Iran: A Retrospective Cohort Study. *Iranian Journal of Medical Sciences* **48**(3), 302-312. https://doi.org/10.30476/IJMS.2022.94615.2598.

[17] **Lee JH, Hwang JH, Jang EJ, Kim RK, Lee KH, Park SK, Gwack J and Park YJ** (2023) Risk Factors Related to COVID-19 Reinfection and Fatality During the Omicron (BA.1/BA.2) Period in Korea. *Journal of Korean Medical Science* **38**(34), e269. https://doi.org/10.3346/jkms.2023.38.e269.

[18] **Fakhroo A, AlKhatib HA, Al Thani AA and Yassine HM** (2021) Reinfections in COVID-19 Patients: Impact of Virus Genetic Variability and Host Immunity. *Vaccines (Basel)* **9**(10). https://doi.org/10.3390/vaccines9101168.

[19] **Bisharat N and Campisi-Pinto S** (2023) Determinants of reinfection with SARS-CoV-2 Omicron variant. *Journal of Infection* **87**(2), 163-165. https://doi.org/10.1016/j.jinf.2023.06.002.

[20] **Hammerman A, Sergienko R, Friger M, Beckenstein T, Peretz A, Netzer D, Yaron S and**

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Arbel R (2022) Effectiveness of the BNT162b2 Vaccine after Recovery from Covid-19. *New England Journal of Medicine* **386**(13), 1221-1229. https://doi.org/10.1056/NEJMoa2119497.

[21] **Hall V, Foulkes S, Insalata F, Kirwan P, Saei A, Atti A, Wellington E, Khawam J, Munro K, Cole M, Tranquillini C, Taylor-Kerr A, Hettiarachchi N, Calbraith D, Sajedi N, Milligan I, Themistocleous Y, Corrigan D, Cromey L, Price L, Stewart S, de Lacy E, Norman C, Linley E, Otter AD, Semper A, Hewson J, D'Arcangelo S, Chand M, Brown CS, Brooks T, Islam J, Charlett A, Hopkins S and Group SS** (2022) Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection. *New England Journal of Medicine* **386**(13), 1207-1220. https://doi.org/10.1056/NEJMoa2118691.

[22] **Lewis N, Chambers LC, Chu HT, Fortnam T, De Vito R, Gargano LM, Chan PA, McDonald J and Hogan JW** (2022) Effectiveness Associated With Vaccination After COVID-19 Recovery in Preventing Reinfection. *JAMA Network Open* **5**(7), e2223917. https://doi.org/10.1001/jamanetworkopen.2022.23917.

[23] (2022) Consensus Interim Recommendations on the Use of COVID-19 Vaccines in Hong Kong (As of 13 October 2022) In: Health Do (ed). Scientific Committee on Emerging and Zoonotic Diseases and Scientific Committee on Vaccine Preventable Diseases.

[24] **Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, Gower C, Kall M, Groves N, O'Connell AM, Simons D, Blomquist PB, Zaidi A, Nash S, Iwani Binti Abdul Aziz N, Thelwall S, Dabrera G, Myers R, Amirthalingam G, Gharbia S, Barrett JC, Elson R, Ladhani SN, Ferguson N, Zambon M, Campbell CNJ, Brown K, Hopkins S, Chand M, Ramsay M and Lopez Bernal J** (2022) Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *New England Journal of Medicine* **386**(16), 1532-1546. https://doi.org/10.1056/NEJMoa2119451.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Table 1. Comparison of COVID-19 cases with one and two infections in Hong Kong from 8 January 2020 to 29 January 2023

	Cases with one infection	**Cases with two infections**	P value
N (%, 95%CI)	2,901,238	101,806	
Female : Male	1.18 : 1	1.29 : 1	<0.001
• Female	1,566,282 (53.99%, 53.93%-54.04%)	57,425 (56.41%, 56.10%-56.71%)	
• Male	1,322,804 (45.59%, 45.54%-45.65%)	44,361 (43.57%, 43.27%-43.88%)	
Sex information unavailable	12,152 (0.42%, 0.41%-0.43%)	20 (0.02%, 0.01%-0.03%)	
Median age (Range, IQR), years	44 (0 – 112, 29-60)	43 (0 – 108, 29-62)	<0.001
Age group, years			<0.001
■ 0-9	187,584 (6.47%, 6.44%-6.49%)	5,352 (5.26%, 5.12%-5.40%)	
■ 10-19	211,765 (7.30%, 7.27%-7.33%)	6,839 (6.72%, 6.57%-6.87%)	
■ 20-29	330,272 (11.38%, 11.35%-11.42%)	13,908 (13.66%, 13.45%-13.87%)	
■ 30-39	478,204 (16.48%, 16.44%-16.53%)	18,874 (18.54%, 18.30%-18.78%)	
■ 40-49	475,949 (16.41%, 16.36%-16.45%)	15,585 (15.31%, 15.09%-15.53%)	
■ 50-59	460,916 (15.89%, 15.84%-15.93%)	12,893 (12.66%, 12.46%-12.87%)	
■ 60-69	410,563 (14.15%, 14.11%-14.19%)	11,606 (11.40%, 11.21%-11.60%)	
■ 70-79	199,475 (6.88%, 6.85%-6.90%)	6,918 (6.80%, 6.64%-6.95%)	
■ >= 80	132,386 (4.56%, 4.54%-4.59%)	9,810 (9.64%, 9.46%-9.82%)	
■ Age information	14,124 (0.49%, 0.48%-0.49%)	21 (0.02%, 0.01%-0.03%)	

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

unavailable			
Importation status at the last infection • Local • Imported	 2,821,008 (97.23%, 97.22%-97.25%) 80,230 (2.77%, 2.75%-2.78%)	 98,235 (96.49%, 96.38%-96.60%) 3,571 (3.51%, 3.40%-3.62%)	<0.001
With available symptoms information at the last infection: • Symptomatic • Asymptomatic	2,447,602 1,388,246 (56.72%, 56.66%-56.78%) 1,059,356 (43.28%, 43.22%-43.34%)	96,977 51,441 (53.04%, 52.73%-53.36%) 45,536 (46.96%, 46.64%-47.27%)	<0.001
Cases with chronic diseases	791,305 (27.27%, 27.22%-27.33%)	34,147 (33.54%, 33.25%-33.83%)	<0.001
Residential care home (RCH) residents	40,777 (1.41%, 1.39%-1.42%)	11,193 (10.99%, 10.80%-11.19%)	<0.001
Severe clinical outcomes at the last infection ● Deaths	17,436 (0.60%, 0.59%-0.61%) 10,111 (0.35%, 0.34%-0.36%)	565 (0.55%, 0.51%-0.60%) 150 (0.15%, 0.13%-0.17%)	0.062 <0.001
Time interval between primary and the 2nd infection (median days)	NA	31 - 1,050 days (282 days)	
Vaccination ≥ 2 valid	2,325,295(80.15%, 80.10%-80.19%)	83,041 (81.57%, 81.33%-81.81%)	<0.001

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

doses at the last infection			
Vaccination ≥ 3 valid doses at the last infection	1,442,745 (49.73%, 49.67%-49.79%)	47,403 (46.56%, 46.26%-46.87%)	<0.001

NA: Not applicable; IQR: Interquartile range

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Table 2. Comparison of Omicron cases with one and two infections in Hong Kong from 31 December 2021 to 29 January 2023

	Cases with one infection	**Cases with two infections**	P value
N (%, 95%CI)	2,891,019	99,236	
Female : Male	1.18 : 1	1.30 : 1	<0.001
• Female	1,561,010 (54.00%, 53.94%-54.05%)	56,080 (56.51%, 56.20%-56.82%)	
• Male	1,317,858 (45.58%, 45.53%-45.64%)	43,136 (43.47%, 43.16%-43.78%)	
Sex information unavailable	12,151 (0.42%, 0.41%-0.43%)	20 (0.02%, 0.02%-0.03%)	
Median age (Range, IQR), years	44 (0 – 112, 29-60)	43 (0 – 108, 29-62)	<0.001
Age group, years			<0.001
■ 0-9	187,105 (6.47%, 6.44%-6.50%)	5,289 (5.33%, 5.19%-5.47%)	
■ 10-19	211,119 (7.30%, 7.27%-7.33%)	6,720 (6.77%, 6.62%-6.93%)	
■ 20-29	328,744 (11.37%, 11.33%-11.41%)	13,526 (13.63%, 13.42%-13.85%)	
■ 30-39	476,310 (16.48%, 16.43%-16.52%)	18,389 (18.53%, 18.29%-18.77%)	
■ 40-49	474,261 (16.40%, 16.36%-16.45%)	15,134 (15.25%, 15.03%-15.48%)	
■ 50-59	459,355 (15.89%, 15.85%-15.93%)	12,477 (12.57%, 12.37%-12.78%)	
■ 60-69	409,140 (14.15%, 14.11%-14.19%)	11,214 (11.30%, 11.10%-11.50%)	
■ 70-79	198,826 (6.88%, 6.85%-6.91%)	6,743 (6.79%, 6.64%-6.95%)	
■ >= 80	132,035 (4.57%, 4.54%-4.59%)	9,723 (9.80%, 9.61%-9.98%)	
■ Age information unavailable	14,124 (0.49%, 0.48%-0.50%)	21 (0.02%, 0.01%-0.03%)	
Importation status at			<0.001

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

the last infection • Local • Imported	 2,813,766 (97.33%, 97.31%-97.35%) 77,253 (2.67%, 2.65%-2.69%)	 95,844 (96.58%, 96.47%-96.69%) 3,392 (3.42%, 3.31%-3.53%)	
With available symptoms information at the last infection: • Symptomatic • Asymptomatic	2,437,433 1,381,749 (56.69%, 56.63%-56.75%) 1,055,684 (43.31%, 43.25%-43.37%)	94,834 50,414 (53.16%, 52.84%-53.48%) 44,420 (46.84%, 46.52%-47.16%)	<0.001
Cases with chronic diseases	788,457 (27.27%, 27.22%-27.32%)	33,297 (33.55%, 33.26%-33.85%)	<0.001
Residential care home (RCH) residents	40,669 (1.41%, 1.39%-1.42%)	11,138 (11.22%, 11.03%-11.42%)	<0.001
Severe clinical outcomes at the last infection ● Deaths	16,817 (0.58%, 0.57%-0.59%) 9,914 (0.34%, 0.34%-0.35%)	559 (0.56%, 0.52%-0.61%) 146 (0.15%, 0.12%-0.17%)	0.500 <0.001
Time interval between primary and the 2nd infection (median days)	NA	31 - 371 days (281 days)	
Vaccination ≥ 2 valid doses at the last infection	2,324,762 (80.41%, 80.37%-80.46%)	81,332 (81.96%, 81.72%-82.20%)	<0.001
Vaccination ≥ 3 valid	1,442,721 (49.90%, 49.85%-49.96%)	46,783 (47.14%, 46.83%-47.45%)	<0.001

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

doses at the last infection			

Note: The sub-cohort of Omicron cases referred to those individuals who were recruited (got the primary infection) after the start of Omicron wave (31 December 2021) in Hong Kong. NA: Not applicable; IQR: Interquartile range.

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Table 3. Risk factors associated with COVID-19 reinfection in Hong Kong identified by Cox regression

	COVID-19 reinfection						
Risk factor	Crude HR	95% CI of Crude HR	P value	Coefficient of multivariate Cox regression	Adjusted HR	95% CI of adjusted HR	P value
Sex							
• **Male**	1	—		Reference	1	—	
• **Female**	1.12	1.11, 1.14	<0.001	0.11	1.12	1.11, 1.13	<0.001
Age (in years)							
0 – 9	1	—		Reference	1	—	
10 – 19	1.22	1.18, 1.27	<0.001	0.18	1.19	1.15, 1.24	<0.001
20 – 29	1.27	1.23, 1.31	<0.001	0.16	1.17	1.13, 1.21	<0.001
30 – 39	1.24	1.20, 1.28	<0.001	0.11	1.12	1.09, 1.16	<0.001
40 – 49	1.04	1.01, 1.08	0.009	-0.08	0.92	0.89, 0.95	<0.001
50 – 59	0.85	0.82, 0.87	<0.001	-0.31	0.73	0.71, 0.76	<0.001
60 - 69	0.83	0.80, 0.86	<0.001	-0.39	0.68	0.66, 0.70	<0.001

https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

	COVID-19 reinfection						
Risk factor	Crude HR	95% CI of Crude HR	P value	Coefficient of multivariate Cox regression	Adjusted HR	95% CI of adjusted HR	P value
70 – 79	1.03	0.99, 1.06	0.160	-0.31	0.73	0.70, 0.76	<0.001
>= 80	2.11	2.04, 2.18	<0.001	-0.18	0.83	0.80, 0.87	<0.001
Chronic diseases							
• **No**	1	—		Reference	1	—	
• **Yes**	1.18	1.16, 1.19	<0.001	0.17	1.18	1.16, 1.20	<0.001
RCH residents							
• **No**	1	—		Reference	1	—	
• **Yes**	6.08	5.96, 6.20	<0.001	1.91	6.78	6.61, 6.95	<0.001
Vaccinated doses at censoring							
• **0-2**	1	—		Reference	1	—	
• **3+**	0.94	0.93, 0.96	<0.001	-0.003	0.997	0.982, 1.012	0.689
Additional vaccination after primary infection							

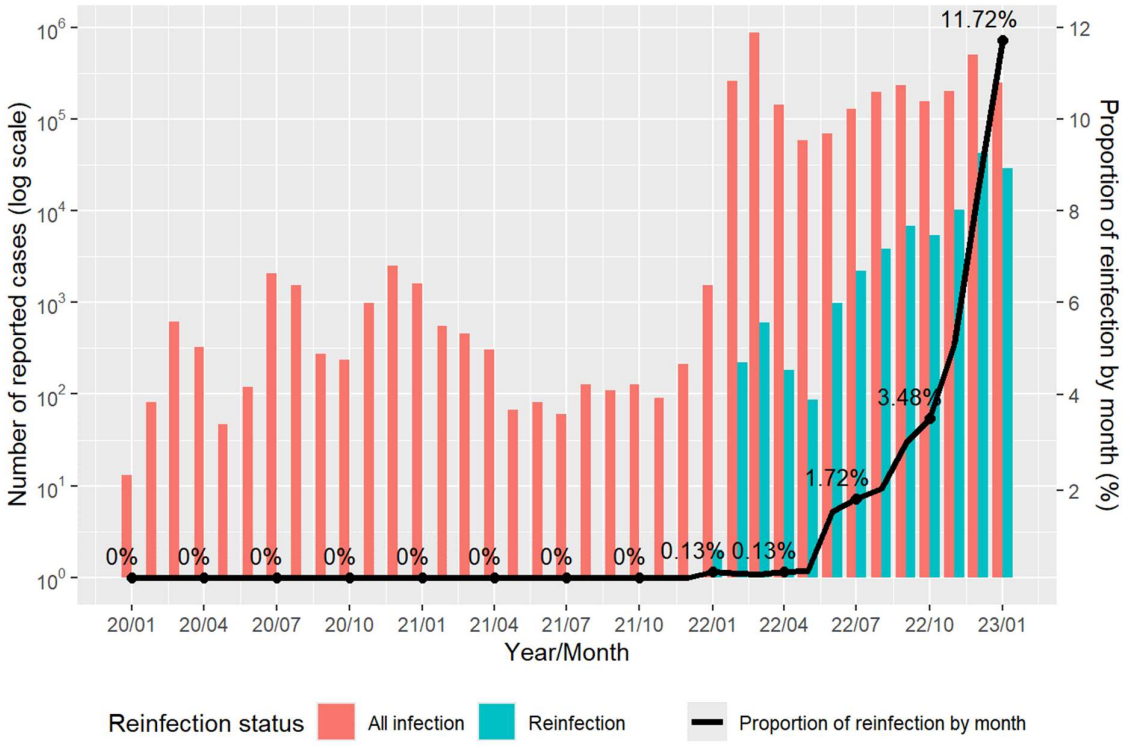
https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

	COVID-19 reinfection						
Risk factor	Crude HR	95% CI of Crude HR	P value	Coefficient of multivariate Cox regression	Adjusted HR	95% CI of adjusted HR	P value
• **No**	1	—		Reference	1	—	<0.001
• **Yes**	0.89	0.88, 0.90	<0.001	-0.22	0.80	0.79, 0.81	<0.001

HR = Hazard Ratio, CI = Confidence Interval.

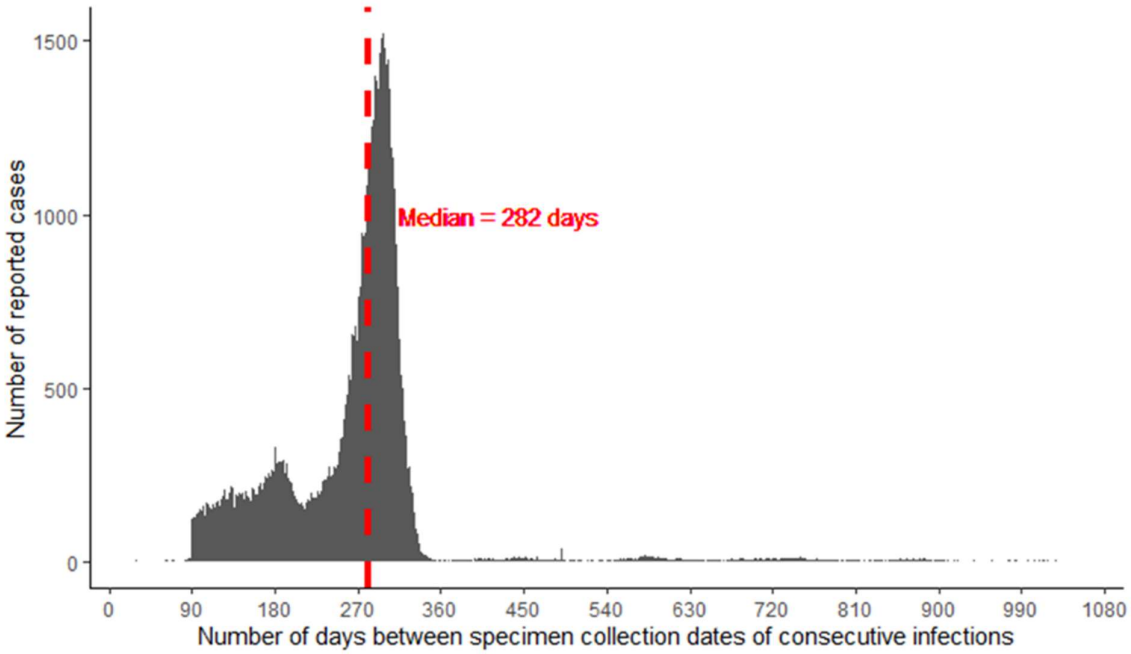
https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Figure 1



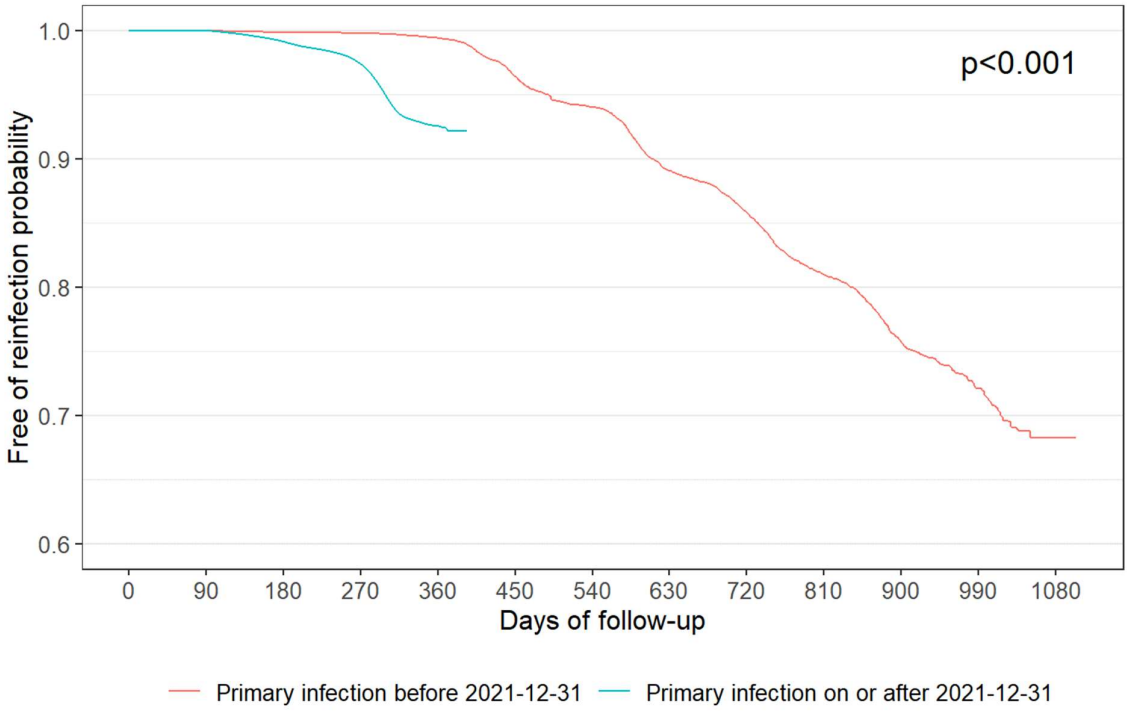
https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Figure 2



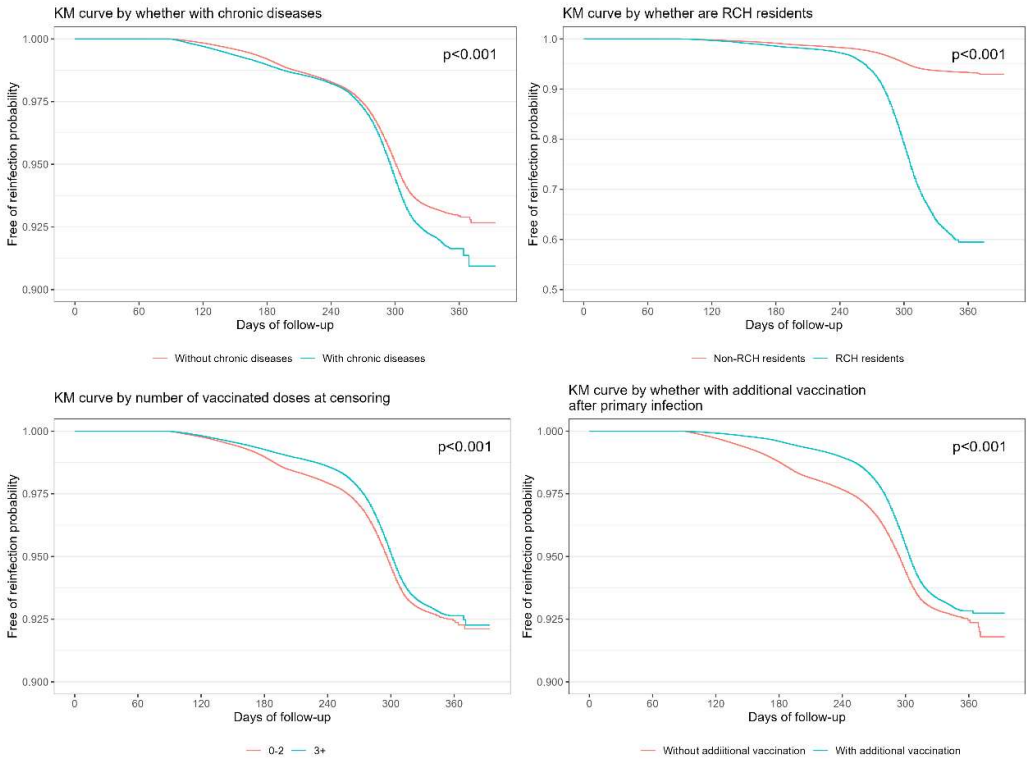
https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Figure 3



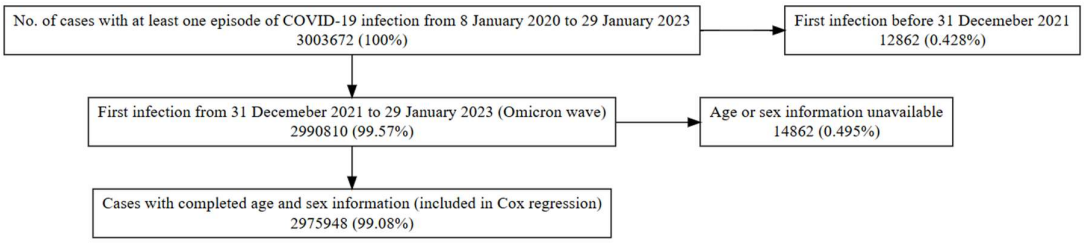
https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Figure 4



https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press

Figure 5



https://doi.org/10.1017/S0950268825000172 Published online by Cambridge University Press