Protective effect of previous infection and vaccination against reinfection with BA.5 Omicron subvariant: a nationwide population-based study in Japan

*Noriko Kitamura, Kanako Otani, Ryo Kinoshita, Fangyu Yan, Yu Takizawa, Kohei Fukushima, Daisuke Yoneoka, Motoi Suzuki, and Taro Kamigaki**

Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, Tokyo, Japan

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Summary

Background The Omicron variant of SARS-CoV-2 was reported to evade immunity derived from vaccination and previous infection. A better understanding of hybrid immunity informs effective infection control strategies. Since the reinfection risk was not well-assessed in East Asia, this study aims to evaluate the risk of infection with Omicron subvariant BA.5 among previously infected individuals in Japan.

Methods All notified cases were extracted from the Japanese national COVID-19 surveillance database including 20,297,335 records up to 25 September 2022. Reinfection with BA.5 was defined as the infection notified during the BA.5 dominated period with any prior SARS-CoV-2 infection. The protective effect of prior infections against reinfections with BA.5 was estimated by applying a case-population design and the protective effect of vaccination was estimated by a multivariable Cox regression adjusting for age, sex, variants of prior infection, and the time since the last vaccination.

Findings Among 19,830,548 SARS-CoV-2 first infections, 233,424 (1.2%) were reinfected with BA.5. The protective effect against BA.5 reinfection of prior infection with Wuhan strain was 46%, Alpha variant was 35%, Delta variant was 41%, and BA.1/BA.2 subvariant was 74%. The reduced risk of BA.5 reinfection by 7%, 33%, and 66% was associated with two, three, and four doses of vaccination, respectively, compared with one-dose vaccination.

Interpretation The prior infections with Omicron subvariant BA.1/BA.2 protected BA.5 reinfection more than pre-Omicron variants. Increased frequency of vaccination led to more protection from reinfection with BA.5. Up-to-date vaccination may be encouraged to prevent future reinfection among the previously infected population.

Funding None.

Keywords: SARS-CoV-2; COVID-19; Surveillance; Vaccine; Hybrid immunity; Reinfection; Omicron

Introduction

The risk for infection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals is partially determined by immunity derived from previous infection or vaccination, while both vaccine-derived and naturally acquired immunity are known to wane over time. The Omicron variant of SARS-CoV-2, first identified in South Africa, became responsible for the epidemic surges in many parts of the world in 2022. Hybrid immunity refers to the immunity protection in individuals who received at least one dose of vaccine and had one infection before or after the vaccination.[1] Hybrid immunity was particularly highlighted after Omicron infection emerged worldwide since previous studies revealed that Omicron subvariant escapes from the immunity obtained by previous infections or vaccination.[2,3]

Booster vaccination remains one of the key control strategies for SARS-CoV-2 infection, while breakthrough infection among vaccinated individuals is a major concern.[4,5] The previous study suggested that the breakthrough infection with BA.5, the latest Omicron subvariant, was less likely among the highly vaccinated population due to the hybrid immunity. A better understanding of hybrid immunity will be valuable to assess the infection risk in the community where many infection control measures are lifted.

*Corresponding author. Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, 1-23-1, Toyama, Shinjyuku-ku, Tokyo, 162-8640, Japan.
E-mail address: kamigakit@niid.go.jp (T. Kamigaki).

Research in context

Evidence before this study

We searched PubMed using search terms ("COVID-19" OR "SARS-CoV-2") AND ("reinfection*" OR "hybrid") AND ("Omicron" OR "BA.5") for the articles published between 1 January 2022 and 31 March 2023. We identified the previous epidemiological studies assessing the reinfection risk of SARS-CoV-2 Omicron subvariant BA.5 in Denmark, Portugal, Qatar, the US, and Singapore. The protective effect against reinfection with BA.5 was between 12% and 96%, which varied by different variants of prior infection and vaccination history.

Added value of this study

In the East Asian region, the incidence of SARS-CoV-2 was relatively low compared to Europe and North American regions, especially in the pre-Omicron period. Therefore, the study assessing the reinfection risk against the Omicron variant was not vigorously conducted in this region to the best of our knowledge. Our study was conducted to demonstrate the protective effect of hybrid immunity against Omicron subvariant BA.5 using national surveillance data in Japan.

Implications of all the available evidence

This epidemiological study reconfirmed that the risk of reinfection with SARS-CoV-2 BA.5 Omicron lineage was reduced by previous infection and up-to-date vaccination. This finding is especially important for the current society where most of the infection control measures against COVID-19 have been lifted.

The protective effect of prior infections with different variants against BA.5 infections was studied in Portugal, Qatar, Denmark, and the US.[4,6–8] Furthermore, the protective effect of hybrid immunity with different variants of SARS-CoV-2 against BA.5 has been evaluated in Denmark and Singapore.[9,10] All studies suggested the higher protective effect of previous Omicron subvariant infection compared with Alpha and Delta variants. However, no similar study has been conducted in the East Asian population to present.

In Japan, seven prominent epidemic peaks of Coronavirus Disease 2019 (COVID-19) were observed between January 2020 and September 2022. Wuhan strain caused the first three epidemics. The transmission of emerging variants of concern of SARS-CoV-2, B.1.1.7 (Alpha) was responsible for the fourth epidemic, B.1.617.2 (Delta) was responsible for the fifth, B.1.1.529 (Omicron) subvariants, BA.1 or BA.2 was responsible for the sixth, and BA.5 have been responsible for the seventh epidemic waves.[11–13]

This study aims to evaluate the protective effect of the prior infections with Alpha, Delta, and Omicron (BA.1 or BA.2) variants against any BA.5 infection. This study also aimed to identify the reinfection risk for different vaccination histories considering other factors, such as age, sex, variant of the prior infection, and the time since the last vaccination.

Methods

Data source and study design

The study population was all 126,149,099 residents in Japan, according to the population census as of 1 October 2020.[14] All SARS-CoV-2 cases notified to the national COVID-19 registry in Japan, Health Center Real-time Information-sharing System (HER-SYS), between 16 January 2020 and 25 September 2022 were extracted for this study as infected cases.[15] HER-SYS contained demographic information, e.g., age and sex, date of onset or reporting date, and vaccination history of cases. The infection of SARS-CoV-2 was confirmed by mainly RT-PCR, but LAMP (Loop-mediated Isothermal Amplification) test or antigen detection test (29%) was also used for the confirmatory testing. Confirmatory laboratory tests were conducted at medical facilities, local health authorities, and designated academic or private laboratories. A clinically diagnosed case was defined as an individual whose family member or a person living in the same household tested positive had a compatible symptom of COVID-19 and considered positive without conducting any laboratory test. Clinically diagnosed cases, which accounted for 1.2% of the record in the dataset, were excluded from the analyses.

More than one SARS-CoV-2 infection in the same individual was identified by an exact match of two or more records in HER-SYS using first name, last name, sex, and date of birth. Reinfection was defined as an individual diagnosed with two or more infections at least 90 days apart from the prior infection.[6] Two or more infections in the same individual notified within 90 days were excluded as duplication. The first and second infections in the same individuals were used for our analyses.

The COVID-19 vaccination program targeting healthcare workers started in February 2021 when the Alpha variant started circulating in Japan. The vaccination program was initiated for the general population prioritizing those who were aged 65 years and older in April 2021 and expanded to younger age groups consecutively; to children aged between 12 and 17 years in August 2021, to children aged between 5 and 12 years in February 2022, and children between six months and four years in October 2022. Booster dose vaccination started in January 2022, Omicron variant BA.1 or BA.2 dominant period. Four types of vaccine were approved for use in Japan: mRNA-1273 (Moderna, https://www.

modernatx.com), BNT162b2 vaccine (Pfizer-BioNTech, https://www.pfizer.com), ChAdOx1 nCoV-19 vaccine (AstraZeneca, https://www.astrazeneca.com), and NVX-CoV2373 vaccine (Novavax, https://www.novavax.com/). Among these four, mRNA vaccines (Moderna and Pfizer) were predominantly used in Japan. As of 7 November 2022, 89% of the population ≥12 years of age had completed the two-dose regimen and 73% had completed three doses, while only 19% among children 5–11 years of age had completed two doses and 2% of them had completed three doses.[16]

As a part of the national SARS-CoV-2 genomic surveillance, about 5–10% of PCR-positive isolates were sequenced to monitor the circulating variants of the SARS-CoV-2 in Japan. Sequencing was conducted at the Prefecture Institutes of Public Health, the National Institute of Infectious Diseases, and the affiliated laboratories. The proportion of the variant among the total number of tested cases was estimated per epidemiological week, assuming that the proportion of each variant follows a multinomial distribution (Fig. 1). We analyzed cases identified during the dominant period and defined dominance when each variant accounted for more than 90% of the total sequenced isolates infected with that dominant variant (i.e., transition periods between epidemic waves were excluded from the analysis).[6] All the test-positive cases identified during the defined period were counted as infections of the dominant variant.

Five periods were defined according to the above criteria: Wuhan (16 January 2020–7 February 2021), Alpha (5 April 2021–20 June 2021), Delta (5 August 2021–5 December 2021), Omicron subvariant BA.1 or BA.2 (10 January 2022–12 June 2022), and Omicron subvariant BA.5 (25 July 2022–25 September 2022). The period of Wuhan was further split into three, corresponding to the first three epidemic periods: wave 1 (16 January 2020–10 May 2020), wave 2 (11 May 2020–13 September 2020), and wave 3 (14 September 2020–31 January 2021) for the time-dependent analyses. Infections that occurred between 25 July and 25 September 2022 were considered as infections with BA.5. Individuals who were infected with BA.5 and had a prior infection history during one of the defined periods were included in the analysis as reinfection cases.

We first implemented a case-population approach,[17] which used the uninfected population as a control group assuming the unnotified population was uninfected, to estimate the protective effect of previous infection against reinfection with BA.5. Secondly, we used a cohort design to estimate the risk of reinfection against BA.5 by a different number of vaccine doses adjusting for other confounders.

Statistical analysis

The epidemic curve for the first SARS-CoV-2 infections up to 25 September 2022 and the epidemic curve for the second infections (reinfections) were plotted to describe the temporal distribution of notified cases.

For the first analysis, we estimated the protective effect of the prior infection with different variants

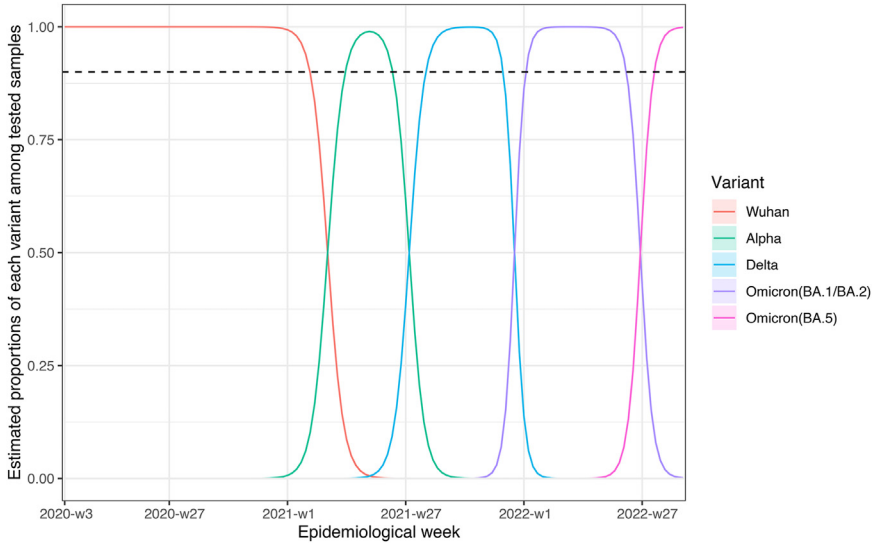

***Fig. 1:* The defined periods of the SARS-CoV-2 epidemic due to different variants in Japan.** The dashed line represents the threshold that each predominant variant accounted for 90% of the total sequenced SARS-Cov-2 positive samples. Colored lines show the change of proportion of each dominant variant among total sequenced samples fitted with multinomial logistic regression and its 95% CIs. The period between two crossing points of the dotted line and each colored line defines the period of each epidemic wave with Wuhan, Alpha, Delta, Omicron subvariant BA.1/BA.2 and Omicron subvariant BA.5. The corresponding epidemiological week is available at: https://www.niid.go.jp/niid/ja/calendar.html.

against reinfections with BA.5. We applied a case-population design for this analysis, which is derived from the case-control design and consists of comparing past exposure to a given risk factor in cases with the exposure rate to this factor in the source population of cases. The risk of BA.5 reinfection among those who had prior infections with any other variants was estimated referencing the risk of BA.5 infections among uninfected individuals. The absolute risk of primary infection of BA.5 was calculated as the proportion of BA.5 infections among uninfected individuals. Then, the relative risk (RR) was calculated by the BA.5 infection risk among individuals with prior infection with each variant over the BA.5 infection risk among the uninfected population. The number of uninfected individuals was calculated by subtracting the number of all primary infections from the population in Japan. The protective effect of each variant was calculated by $1-RR$ along with its 95% confidence intervals (CI), which is estimated based on the (asymptotic) normal approximation. $1-RR$ was interpreted as a protective effect analogous to commonly applied methods to estimate vaccine effectiveness. This analysis was considered as a crude analysis without adjusting any confounders.

For the second analysis, we estimated the risk of reinfection with BA.5 among those who received a different number of vaccine doses by Cox proportional hazard regression analysis. In this analysis, all registered individuals who were infected with BA.5 and also infected with any type of variant previously. Sex, age, different variants of prior infection, and the time since the last vaccination were considered potential confounders. First, a multivariable Cox regression was used to compare the risk of reinfection adjusting for sex and age only (model 1). Vaccination-related variables were not included in the model 1 since vaccination records were missing among a large proportion of cases with Omicron infection as case reporting activities were marginalized due to the high caseload. Second, we attempted to incorporate vaccine-related variables in a multivariable Cox regression model as well as age and sex (model 2). Individuals with missing vaccination records were not included in model 2. The interval between the first and second infection should be a time variable for our purpose; however, it was largely determined by the calendar time when the dominant variants circulated. Thus, the time from 25 July 2022, when the BA.5 epidemics started, to the time of reinfection was considered as a time variable for all the survival analyses. All analyses were conducted by using R software, version 4.2.1 (R Core team).

No ethical approval was required because this study was conducted at the national public health agency for public health purposes using national surveillance data collected under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases.

Role of funding source

There is no funding source involved in this study.

Results

According to the HER-SYS database, 20,297,335 cases were reported by 25 September 2022. After excluding the duplicated records, 20,201,842 cases were identified as SARS-CoV-2 cases. Among them, 19,830,548 cases were first infections, and 371,294 cases (1.9%) were reinfections. A total of 233,424 reinfection cases (69%) were caused by BA.5, which accounted for 1.2% of first infections (Fig. 2). Characteristics of the first infections and reinfections with BA.5 included in the analyses, e.g., sex, age, variant of the first infection, and vaccination history, are summarized in Table 1. The proportion of reinfection cases among first infection cases was highest among children aged 12 years or younger (1.9%), while it was lowest among adults aged 65 years and older (0.4%).

Epidemic curves were plotted for the first infections and reinfection separately with the Japanese vaccination program (Fig. 3). Fig. 3 clearly shows that the number of COVID-19 cases with pre-Omicron variants (before wave 6) was limited in Japan, and the number of cases drastically increased after the introduction of the Omicron variant in December 2021.

Applying the case-population approach, the protective effects of prior infection with Alpha and Delta variants were estimated as 35.2% and 40.6%, respectively, which were lower than 73.9% of Omicron subvariant (BA.1 or BA.2). Wuhan strain had a slightly higher protective effect than Alpha and Delta (46.2%) (Table 2).

The Kaplan–Meier curve was plotted to visualize the crude reinfection probability by different variants of prior infection over time without adjusting any confounders. The maximum follow-up period was 61 days (between 25 July 2022 and 25 September 2022). Fig. 4 shows the Omicron subvariant BA.1 or BA.2 had the lowest probability of reinfection with BA.5 (3.1%), followed by Wuhan (4.5%–6.7%), Delta (5.1%), and Alpha (5.6%) at the time of 60 days follow-up (Supplemental Figure S1).

The Cox regression analysis also assessed the reinfection risk with BA.5 by different variants of prior infection. The crude hazard ratio (crude HR) in Cox regression analysis shows that the prior infection with Wuhan (wave 1 and wave 2) strain had the highest risk of reinfection, followed by Alpha, Wuhan (wave 3), Delta, and Omicron (BA.1 or BA.2) variants in descending order. The higher crude HR was found in the variant dominated in the more recent epidemic in both crude and adjusted analyses. The reinfection risk of the prior infection with the Wuhan strain was not estimated adjusting for vaccination histories (model 2), as the vaccination program started after the Alpha variant-dominated period in Japan (Table 3).

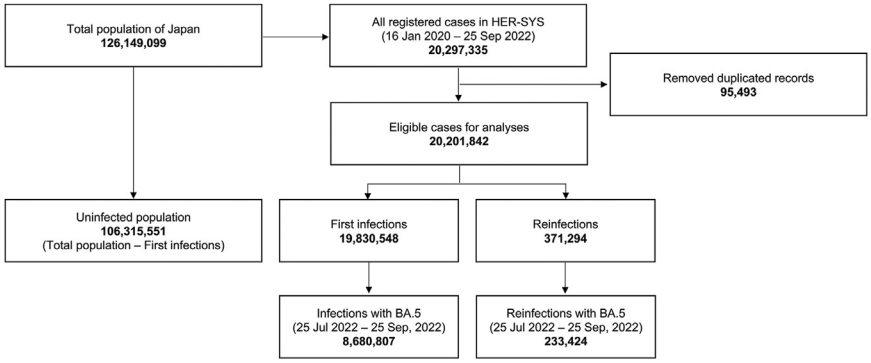

Fig. 2: **Surveillance data included for analyses.** HER-SYS: Health Center Real-time Information-sharing System.

The multivariable Cox regression assessed the risk of reinfection with BA.5 among those who received different vaccination histories adjusting for all the potential confounders (model 2). Those who completed two, three, and four doses was associated with a 7%, 33%, and 66% reduced risk of reinfection compared with those who received only one dose. It was not possible to evaluate the reinfection risk by different vaccination histories compared with the unvaccinated group since all reinfection cases had received at least one dose of vaccine. The lower risk of reinfection was associated with the longer time since the last vaccination unexpectedly, although the effect size was nearly 1 (Table 3).

The reinfection risk increased with age in multivariable Cox regression analyses. Notably, there were large differences between the adjusted hazard ratio (aHR) in model 1 and model 2 when age was categorized into seven groups (0–11, 12–19, 20–29, 30–39, 40–49, 50–64, ≥65 years). aHR in model 1 for those aged 12–19 years was 1.1, and for those above 65 years old was 1.2 referencing the children younger than 12 years old, while aHR in model 2 was 2.0 and 2.8, respectively (Supplemental Table S1).

Discussion

This study aimed to estimate the protective effect of different variants of prior infection with SARS-CoV-2 and different vaccination histories against reinfection with Omicron subvariant BA.5, which was the dominant variant for the surge of COVID-19 cases since July 2022 in Japan.

Our analysis found that the protective effect against BA.5 reinfection of prior infection with Wuhan was 46.2%, Alpha was 35.2%, Delta was 40.6%, and BA.1 or BA.2 was 73.9%, respectively, compared with individuals who have never been infected. Our result in the protective effect of the prior infections with BA.1 or BA.2 was similar to the result of a cohort study conducted in Portugal (75.3%), a test-negative study in Qatar (76%), and a cohort study in Singapore

	First infections		Reinfection cases with BA.5		Proportion (reinfection/ first infection) (%)
	n	(%)	n	(%)	
Sex					
Male	9,821,158	49.5	119,240	51.1	1.2
Female	9,920,061	50.0	114,170	48.9	1.2
Unknown	89,329	0.5	14	0.0	0.0
Age group (years)					
0–11	3,360,470	16.9	62,247	26.7	1.9
12–19	2,114,085	10.7	24,562	10.5	1.2
20–29	3,135,805	15.8	50,790	21.8	1.6
30–39	3,077,622	15.5	40,586	17.4	1.3
40–49	3,089,371	15.6	28,790	12.3	0.9
50–64	2,810,390	14.2	17,392	7.5	0.6
≥65	2,219,355	11.2	8890	3.8	0.4
Unknown	23,450	0.1	167	0.1	0.7
Variant of first infection					
Wuhan (wave 1)	17,406	0.1	574	0.2	3.3
Wuhan (wave 2)	62,199	0.3	2817	1.2	4.5
Wuhan (wave 3)	331,178	1.7	14,645	6.3	4.4
Alpha	297,250	1.5	15,728	6.7	5.3
Delta	670,702	3.4	32,515	13.9	4.8
Omicron (BA.1/BA.2)	6,949,419	35.0	148,235	63.5	2.1
Omicron (BA.5)	8,680,807	43.8	0	0.0	0.0
Vaccine history					
0 dose	1,972,980	9.9	0	0.0	0.0
1 dose	192,827	1.0	286	0.1	0.1
2 doses	2,890,725	14.6	4985	2.1	0.2
3 doses	3,850,421	19.4	6969	3.0	0.2
4 doses	469,497	2.4	740	0.3	0.2
Unknown	10,454,098	52.7	220,444	94.4	2.1
Time since the last vaccination					
n	3,676,265	18.5	27,132	1.2	0.7
Median (IQR) days	145 (111)		161 (182)		
Min–max days	0–585		0–571		
Total	19,830,548	100	233,424	100	1.2

Individuals who were infected with BA.5 and had prior infection history during one of the defined periods were included in the analysis as reinfection cases.

Table 1: **The characteristics of all infected cases and reinfection cases with BA.5 included in analyses.**

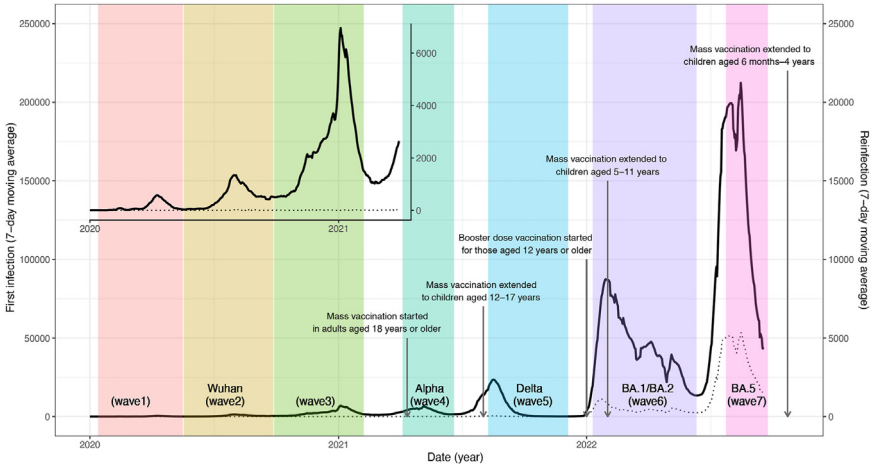

***Fig. 3:* Epidemic curve of SARS-CoV-2 infection and reinfection with the vaccination activities.** The bold line shows the number of all infections of SARS-CoV-2 applying 7-day moving average corresponding to the left y-axis. The dashed line shows the number of reinfections of SARS-CoV-2 applying 7-day moving average corresponding to the right y-axis. The color shows the dominant period of the variant defined in Fig. 1.

(55–80%).[4,6,10] The protective effect of pre-Omicron (Alpha and Delta) variants was, however, not as high as reported in the study in Portugal, which was reported as 55% and 61% for Alpha and Delta variants, respectively.[6] We note that the protective effect of the Delta and BA.1/BA.2 against reinfection with BA.5 was higher than what has been reported in a retrospective cohort study in the US (11.9% and 45.9%, respectively).[8]

Notably, we estimated the protective effect of prior infections against diagnosed infections using routine COVID-19 surveillance data. Since test-negative cases were not reported in HER-SYS, a typical test-negative case-control design was not applicable. Instead, the case-population approach was applied to analyze the protective effect of prior infection. There are several limitations in this approach. We assumed that unnotified cases were not infected with SARS-CoV-2; however, asymptomatic or mild infection cases or self-tested cases might be underreported, and the results of the protective effect of previous infection might be overestimated. A national seroprevalence survey conducted in December 2021 in Japan indicated that the true number of cases might be 1.8 times higher than the number of notified cases.[18] If we assumed that the true number of cases was twice as high as the number of notified cases, estimated protective effects became slightly higher (44%, 49%, and 77% for the prior infection with Alpha, Delta, and BA.1 or BA.2, respectively). A few more serosurvey conducted in 2020 and 2021, suggested that three to four times more individuals were infected with COVID-19 during the Alpha and Delta dominant period.[19,20] In that case, the estimated protective effect of these two variants increases more.

The case-population study was a crude analysis without adjusting any confounders. Therefore, the survival analysis was conducted to estimate the protective effect adjusting for potential confounders. The higher risk of BA.5 reinfection after the prior infections with pre-Omicron variants compared with the Omicron subvariant (e.g., BA.1 or BA.2) was also endorsed by the survival analysis. The potential reason for the higher protective effect of BA.1 or BA.2 against BA.5 reinfection may be due to the shorter duration between prior infection and reinfection, which enables hosts to maintain stronger acquired immunity than pre-Omicron variants. Another reason may be the similar

Variant of the first infection	Uninfected with BA.5	First infection	Infection with BA.5	Absolute risk	Relative Risk	Protection effectiveness (1–RR) (%)
	106,315,551	–	8,680,807			
Wuhan		410,783	18,036	0.044	0.54	46.2
Alpha		297,250	15,728	0.053	0.65	35.2
Delta		670,702	32,515	0.048	0.59	40.6
BA.1/BA.2		6,949,419	148,235	0.021	0.26	73.9
Any variants		8,328,154	214,514	0.026	0.32	68.5

***Table 2:* Protective effect of the prior infection against the reinfection with BA.5.**

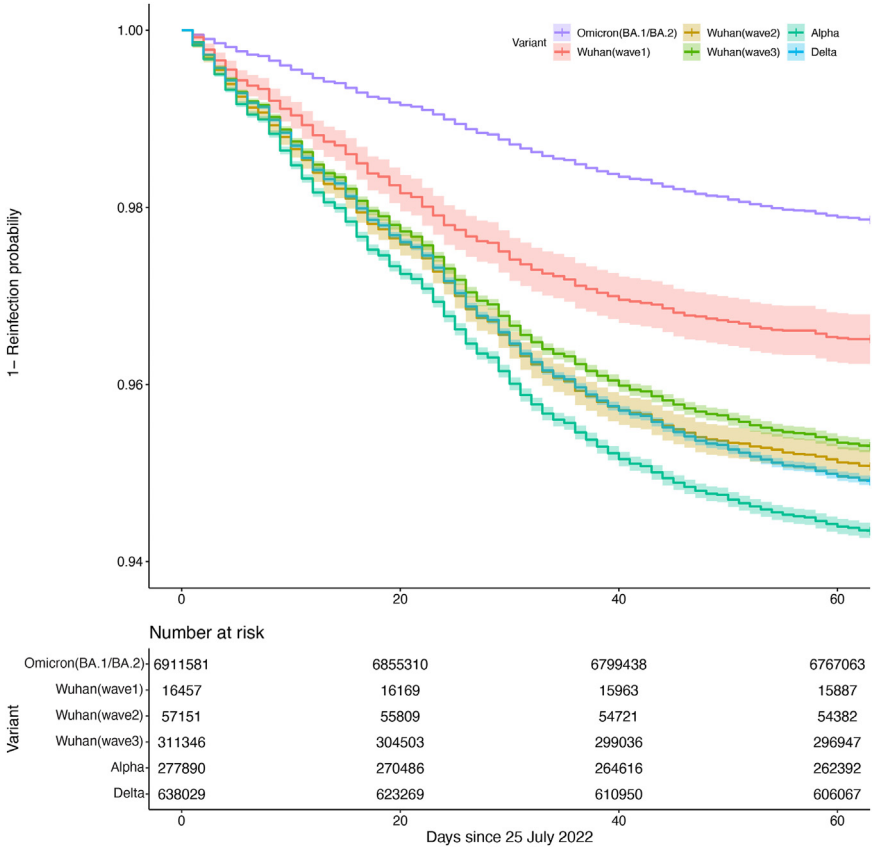

Fig. 4: **Probability of reinfection with BA.5 since the beginning of BA.5 dominant epidemic period by different variants of prior infection.** We defined the BA.5 epidemic period starting on 25 July 2022 for analysis purpose. The x-axis (time) was days from 25 July 2022 till the reinfection with BA.5.

antigenicity elicited by BA.1 or BA.2 belonging to the same lineage as BA.5.[21] The protective effect of previous infection with Wuhan was higher than that of Alpha and Delta variants, which was also consistent with the results of the cohort study in Qatar.[22] This may be because the more severe infection was identified during the Wuhan dominant period (early phase of the pandemic) and those who survived after the infection with Wuhan might have more protective immunity. Wuhan infection always occurred before the vaccination, but the order of the vaccination and infection varied after the Alpha variant. The order of naturally acquired immunity and vaccine-induced immunity might result in different protection levels.[23] In general, the estimated protective effect of the prior infections with pre-Omicron against infection with Omicron subvariant in our study was consistent with other studies.[5,24–28]

In addition, we assessed the protective effect of vaccination by survival analysis. We identified that a higher frequency of immunization was associated with a lower risk of reinfection compared with a single dose of vaccination. At most, four doses of vaccination with prior infection prevent 66% of any BA.5 reinfection compared with one dose of vaccine and prior infection. Similar findings were reported from Denmark using a test-negative case-control study, which demonstrated that pre-Omicron variant infection with two or more doses of vaccination reduced any BA.5 infection risk by 96%.[27] As the outcome of our analysis was reinfection, a lower hazard ratio among more frequently vaccinated individuals suggested that hybrid immunity appears to reduce the reinfection risk of SARS-CoV-2. This finding is similar to two other studies that assessed hybrid immunity against reinfection with the Omicron variant in Qatar and Israel.[6,29] Since the Omicron variant has multiple spike protein mutations, it can evade the antibody neutralization conferred by currently available vaccines or past infections.[2,30] However, previous studies reported that both vaccine and natural infection-derived T-cell immunity may be effective in preventing severe outcomes caused by the Omicron variant since T-cell immunity is not affected by the changes in spike proteins of SARS-CoV-2.[1,31,32] Hybrid immunity, which are immune responses derived from various combinations

	Univariate analysis	Model 1	Model 2
	Crude HR	aHR	aHR
Sex			
Male	ref	ref	ref
Female	1.00	1.00	1.04
Age	1.00	1.00	1.00
Variant of the first infection			
Wuhan (wave 1)	1.39	1.36	NA
Wuhan (wave 2)	1.32	1.29	NA
Wuhan (wave 3)	1.27	1.24	NA
Alpha	1.28	1.25	1.53
Delta	1.22	1.21	1.24
Omicron BA.1/BA.2	ref	ref	ref
Vaccine history			
1 dose	ref		ref
2 doses	0.88		0.93
3 doses	0.92		0.67
4 doses	0.6		0.34
Time since the last vaccination (days)	1.00		1.00

Crude HR: crude hazard ratio; aHR: adjusted hazard ratio. BA.1/BA.2 was used as a reference for the comparison of the protective effect of each variant as the Omicron subvariant was reported to have a higher protective effect against BA.5 infection. No individuals were classified as unvaccinated among reinfection cases. Individuals with missing vaccination records were not included in model 2. Japanese mass vaccination for COVID-19 started after the Alpha variant dominant period; therefore, three Wuhan dominant periods were not included in model 2.

***Table 3*: Risk of reinfection of BA.5 by age, sex, variants of the first infection, and vaccination history.**

of previously infected strains and vaccination histories, provide further insight to understand the protective effects of different variants.[23]

We also considered the time since the last vaccination in our analysis. It was expected that the protective effect would decline over time since vaccination due to the waning of vaccine-derived immunity; however, our results revealed that reinfection risk slightly increased over time. As a sensitivity analysis, we categorized the time since the last vaccination by six months and considered the interaction between time and the number of vaccine doses. The result of the sensitivity analysis clearly shows the association between the longer time elapsed since the last vaccination and the higher reinfection risk.

In addition, the reinfection risk with BA.5 was assessed by sex and age. There was no association between reinfection risk and sex adjusting for other confounders. The reinfection was more common among children (1.9% of the first infection) than any other age group. This result implies that the risk of repeated infection was not apparently low among children, although some previous studies reported that the reinfection risk of SARS-CoV-2 among children was lower than among adults.[33,34] It may be noteworthy that children younger than 12 years old had a similar reinfection risk compared to older age groups adjusting for sex and prior infection; however, their risk decreased significantly after adjusting for vaccination history. This result indicated that some of the reinfections with Omicron subvariant BA.5 among children might have been prevented by vaccination, as a previous study reported that two-dose vaccination and previous infection conferred higher protection among children aged 5–11 years than those aged 12–17 years.[35] Since the mass vaccination started by targeting adults aged 65 years and older and gradually extended to younger age groups, a confounding effect exists between the vaccination history and age. It might be difficult to remove this confounder completely from the analyses as the number of children who received three doses or more was limited.

There were several limitations in this study. First, since a unique identifier was not assigned to each individual due to the Japanese COVID-19 registration system, our data might contain mislinkage. However, given the enormous pattern of the combination of Japanese names, date of birth, and sex, we believe the proportion of mislinkage was negligible. Second, missing vaccination status was automatically counted as unvaccinated in the HER-SYS until November 2021, although this number was ignorable after vaccination coverage increased over time. Third, 53% of the positive cases registered in the HER-SYS database had missing vaccination records. Therefore, potential bias due to missing vaccination records should be recognized when interpreting the results of the protective effect of vaccination in model 2. Fourth, the time from the first infection to the second infection was not used as a time variable as it was highly correlated with the interval between epidemic waves, which attributed to dominant variants. Instead, the days since BA.5 epidemic started till reinfections were used as a proxy measure. This time setting might have caused a bias in the estimates of the HR, specifically to lower reinfection risk for individuals with longer time elapsed since the last vaccination. Fifth, we did not quantify the protective effect by vaccine type. Sixth, heterogeneities in ascertainment rate (e.g., age, past infection history) could potentially affect our estimate. Finally, based on the variant-dominant periods defined by multinomial regression, all infections at each defined period were assumed to be infections from the corresponding variant. As such, we may not have been able to exclude the misclassification of variants completely.

Despite the limitations of using routine surveillance data, this study thoroughly analyzed reinfection risk with population-based national surveillance data collected over two years in Japan. Our study confirmed that the protective effect against reinfection was high among those infected with Omicron subvariants. Relative vaccine effectiveness increased by the number of vaccine doses among those who had prior infection with SARS-CoV-2. Mirroring previous studies, our study

confirmed the protective effect of natural infection and vaccination in East Asia.

This study reconfirmed that prior infection protects individuals against reinfection of SARS-CoV-2, while the extent of that protection differs between pre-Omicron and Omicron. Since vaccination provides an additional protective effect against natural infection, repeated up-to-date vaccination may be encouraged to prevent future reinfections among previously infected population.

Contributors

NK: Conceptualization (lead), Formal Analysis, Visualization, Writing–Original Draft Preparation.
KO: Methodology, Data Curation, Writing–Review & Editing.
RK: Methodology, Visualization, Writing–Review & Editing.
FY: Data Curation.
YT: Data Curation.
KF: Data Curation.
DY: Formal Analysis, Writing–Review & Editing.
MS: Writing–Review & Editing.
TK: Conceptualization, Writing–Review & Editing.

Data sharing statement

Data can be obtained upon formal request in writing to the Ministry of Health, Labour, and Welfare in Japan.

Declaration of interests

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100911.

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