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Original article

Protection of Omicron XBB.1.5 vaccine, previous infection, and their induced neutralizing antibodies against symptomatic SARS-CoV-2 infection during Omicron KP.3 wave

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ABSTRACT

Background: Data are limited on the protection of Omicron XBB.1.5 vaccine, previous infection, and their induced neutralizing antibodies against Omicron KP.3 infection.
Methods: Among 1826 tertiary hospital staff in Tokyo who had received three or more doses of COVID-19 mRNA vaccines and provided blood samples in June 2024, we prospectively examined the associations of XBB.1.5 vaccination and previous infection (classified by the timing of the last infection as pre-Omicron XBB, Omicron XBB, or Omicron JN.1 waves) with the risk of symptomatic SARS-CoV-2 infection during the Omicron KP.3 wave (June to September 2024). In a nested case-control analysis, we compared pre-infection live-virus KP.3.3-neutralizing antibody titers between cases and 1: 1 propensity-score matched controls.
Results: XBB.1.5 vaccination was not associated with measurable protection against symptomatic infection (4%, 95% CI, −88 to 51). Previous infection conferred protection that increased with its recency: 26% (95% CI, −26 to 56) for pre-Omicron XBB, 44% (95% CI, 2 to 68) for Omicron XBB, and 89% (95% CI, 52 to 97) for Omicron JN.1 waves. Pre-infection KP.3.3-neutralizing titers tended to be lower in cases than in matched controls (GMT ratio 0.68, 95% CI, 0.35 to 1.33); KP.3.3-neutralizing activity was only modestly elevated by XBB.1.5 vaccination but markedly higher after recent JN.1 infection.
Conclusions: During the Omicron KP.3 wave, when an updated vaccine was unavailable, XBB.1.5 vaccination administered approximately 7 months earlier conferred no measurable neutralizing activity or protection against symptomatic KP.3 infection. Previous SARS-CoV-2 infection, particularly recent JN.1-wave infection, affords substantial neutralizing titers and protection.

1. Introduction

Throughout the COVID-19 pandemic, SARS-CoV-2 has continued to evolve antigenically, driven by the sequential emergence of new variants. Updated vaccines have been developed to keep pace with this evolution, and immunity has built up in the population through vaccination and prior infection [1]. During the 2023–2024 season, XBB.1.5-based vaccines were introduced in October 2023. During the XBB-predominant period, effectiveness of the XBB.1.5 vaccine against infection was 64% at its peak 4 weeks after vaccination and declined to

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37% by 12 weeks [2]. During the JN.1-predominant period, effectiveness was lower at its peak, 44%, and declined further to 14% by 12 weeks [2]. Prior SARS-CoV-2 infection also provided protection against subsequent infection during the XBB and JN.1 predominant waves, with greater protection from more recent infection [3,4].

KP.3, a JN.1 sublineage with two additional substitutions in the receptor-binding domain, F456L and Q493E [5,6], became dominant in Japan in the summer of 2024, before another updated vaccine was available. Thus, protection against KP.3 depended on existing immunity acquired from earlier vaccines, including the XBB.1.5 vaccine, or from prior infection with earlier variants, including JN.1. Given that KP.3 is a descendant of JN.1, the protection provided by the XBB.1.5 vaccine against JN.1 might also have been expected against KP.3. Two factors, however, suggested that protection against KP.3 would be limited. Immunological studies have shown that XBB.1.5 vaccination induces only modest neutralizing activity against KP.3, with lower activity against KP.3 than against JN.1 [5–7]. In addition, the KP.3 wave occurred more than 6 months after the autumn 2023 XBB.1.5 vaccination campaign. By that time, the modest KP.3-neutralizing activity induced by XBB.1.5 vaccination has been reported to decline further [8]. Consistent with these immunological data, a Spanish study found no protection by the XBB.1.5 vaccine against symptomatic SARS-CoV-2 infection during the KP.3 wave [9]. Prior infection, by contrast, might provide protection against KP.3, particularly if it occurred more recently. JN.1 circulated after the XBB.1.5 vaccination campaign and immediately before the KP.3 wave, and infection during the JN.1 wave has been shown to elicit strong neutralizing activity against KP.3 [5,10]. To our knowledge, however, no study has estimated how well prior infection protects against KP.3 infection. It is also unknown whether KP.3-neutralizing titers measured more than 6 months after an XBB.1.5 dose or after prior infection are associated with subsequent KP.3 infection risk.

To address these knowledge gaps, we conducted a seroepidemiologic survey among healthcare workers in Tokyo at the start of the KP.3 wave in Japan (June to September 2024). We prospectively examined associations of XBB.1.5 vaccination and prior infection (during the JN.1, XBB, or earlier periods) with breakthrough infection risk, and performed a nested case-control analysis comparing pre-infection KP.3-neutralizing antibody titers between cases and matched controls. We hypothesized that XBB.1.5 vaccination would provide limited protection against KP.3 infection, that infection during the JN.1 wave would confer stronger protection than infection during the XBB or earlier waves, and that pre-infection KP.3-neutralizing antibody titers would be lower in cases than in controls.

2. Methods

2.1. Study setting

A repeat serological study was launched in July 2020 among staff of the National Center for Global Health and Medicine (NCGM; reorganized and renamed as the Japan Institute for Health Security [JIHS] in April 2025) in Tokyo, Japan, to monitor the spread of SARS-CoV-2 infection during the COVID-19 epidemic. As of June 2024, we have completed ten serosurveys, where we measured anti-SARS-CoV-2 nucleocapsid- (all serosurveys) and spike-protein antibodies (from the second serosurvey onward) for all the participants using both Abbott and Roche assays, stored serum samples at −80 °C, and collected information on COVID-19–related factors (vaccination, occupational infection risk, infection prevention practices, behavioural factors, etc.) via a questionnaire. The self-reported vaccination status was validated using objective information from the JIHS Labor Office. We ascertained incident COVID-19 using records from the JIHS Hospital Infection Prevention and Control Unit; staff with COVID-19–compatible symptoms were required to undergo PCR or antigen testing and report any positive result, and staff identified as close contacts were tested irrespective of symptoms. Informed consent was obtained from all participants in written or electronic form. This study was approved by the JIHS Ethics Committee (approval number: JIHS-S-003598).

2.2. Case definition

Cases were participants with symptomatic COVID-19 during follow-up, defined as a positive PCR or antigen test result accompanied by COVID-19–compatible symptoms and recorded in the in-house COVID-19 registry. Asymptomatic infection was identified only when contact tracing prompted testing, so ascertainment of asymptomatic infection was incomplete. Asymptomatic infection was therefore not counted as a case.

2.3. Analytic samples for a prospective study

This study was based on participants in the 10th serosurvey conducted in June 2024 (Fig. S1). A total of 1942 staff members participated in the 10th serosurvey; of these, 1827 had received three or more doses of a COVID-19 mRNA vaccine and were at least 14 days after their most recent vaccination at the time of the survey. We followed these 1827 participants from June to September 2024. After excluding one participant with an asymptomatic infection during follow-up, 1826 participants were included in the prospective cohort analysis of symptomatic breakthrough infection.

2.4. Analytic samples for a case-control study

We then nested a case-control set within the prospective cohort (n = 1826) to compare baseline antibody titers between cases and controls. During the follow-up, we identified 104 symptomatic COVID-19 patients. We selected a control for each COVID-19 case using propensity score matching to compare pre-infection anti-spike and -nucleocapsid antibody titers between the groups. The details of the case-control matching algorithm are described in **Supplemental Text 1**. From these matched pairs, we randomly selected 50 pairs and measured live-virus neutralizing antibody titers.

2.5. Statuses of XBB.1.5 vaccination and previous infection at baseline

Vaccination history was ascertained from self-reported questionnaires at each serosurvey and institutional records maintained by the Labor Office, including the date and manufacturer of each dose. All participants had received at least three COVID-19 mRNA vaccine doses. Participants were classified as XBB.1.5-vaccinated if they had received at least one dose of the XBB.1.5-updated vaccine between October 2023 (when it became available in Japan) and baseline, or as XBB.1.5-unvaccinated if they had received only earlier formulations (original monovalent, BA.1 bivalent, or BA.2 bivalent).

Previous infection was defined as a self-reported history of COVID-19 (confirmed against the in-house COVID-19 registry) at baseline or anti-N seropositivity with either of the two assays (Roche ≥1.0 cutoff index [COI] or Abbott ≥1.40 signal to cutoff [S/C]) at any of the first (July 2020) through tenth (June 2024: baseline) serosurveys. Participants without a history of COVID-19 but with N-antibody seropositivity were classified as having an undiagnosed infection [11]. We defined phases of previous infection according to the timing of the last diagnosis: Pre-Omicron XBB (February 2020 to December 2022), Omicron XBB (January 2023 to December 2023), and Omicron JN.1 (January 2024 to June 2024) [12].

2.6. Antibody testing

We measured live-virus neutralizing activity against Wild-type, Omicron XBB.1.16, and Omicron KP.3.3 in the sera of patients and controls by quantifying the serum-mediated suppression of the

cytopathic effect of each SARS-CoV-2 strain in $HeLa_{hACE2\text{-}TMPRSS2}$ cells [13,14]. The details of the measurement methods are described in **Supplemental Text 2**.

We assessed anti-SARS-CoV-2 antibodies in all participants at baseline and retrieved data for the case-control pairs. Using assays with different targets and formats, we measured antibodies against the spike receptor-binding domain (RBD) using the AdviseDx SARS-CoV-2 IgG II assay (Abbott; anti-RBD immunoglobulin G [IgG]) and Elecsys® Anti-SARS-CoV-2 S (Roche; anti-RBD total antibodies, including IgG), and against the nucleocapsid (N) using the SARS-CoV-2 IgG assay (Abbott; anti-N IgG) and Elecsys® Anti-SARS-CoV-2 (Roche; anti-N total antibodies, including IgG).

2.7. Statistical analysis

Person-time was calculated from baseline blood sampling (18–28 June 2024) until subsequent SARS-CoV-2 infection, additional COVID-19 vaccination, or censoring (6 September 2024), whichever occurred first. If participants received an additional COVID-19 vaccine, follow-up was censored at 13 days postvaccination, assuming that they were not sufficiently immunized with the additional booster until then. We fitted a Cox proportional hazards regression analysis to examine the associations of XBB.1.5 vaccination status and prior SARS-CoV-2 infection history with the risk of breakthrough infection during the Omicron KP.3 wave. The multivariable model was adjusted for age, sex, occupation, occupational SARS-CoV-2 exposure risk, body mass index, chronic health impairment, immunosuppressive condition, tobacco use, frequency of alcohol consumption, cohabitation status, child-related living arrangements, time since last COVID-19 vaccination, and each of the two exposures (XBB.1.5 vaccination status and previous infection status) when the other was being examined. We assessed the proportional hazards assumption using Schoenfeld residuals and log–log plots. The global test indicated no evidence of violation ($p = 0.86$). Although one category of occupation was statistically significant, no time-varying effects were observed; thus, all variables were included as standard covariates. Multicollinearity was assessed using variance inflation factors (VIFs), with all values below 5 (mean VIF = 1.71).

We used a generalized estimating equation (GEE) with group assignment (case or control) and a robust variance estimator to compare preinfection antibody levels between cases and controls. For comparisons of anti-N antibody indexes, we restricted the analysis to participants with evidence of prior SARS-CoV-2 infection up to baseline (self-reported COVID-19 and/or anti-N seropositivity at any prior serosurvey or at baseline). Because antibody titers approximately follow a log-normal distribution, we treated each titer as a log-transformed variable in the model and then back-transformed the estimates, presenting them as geometric mean titers (GMTs) with 95% confidence intervals (CIs).

To examine differences in neutralizing antibody titers according to XBB vaccination status and infection history, we used linear regression models with log-transformed NT_{50} as the dependent variable. *P* values for category-level comparisons were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) procedure. We further examined whether the association between infection phase and neutralizing antibody titers differed according to XBB vaccination status by adding an interaction term between infection phase and vaccination status to the linear regression models and testing the interaction with a Wald test. The models in Fig. 2 were not adjusted for covariates, because they were intended to describe the observed distributions of titers. In a sensitivity analysis, we additionally adjusted for age, sex, chronic health impairment, and immunosuppressive condition, which could confound these associations.

For the analyses of neutralizing antibody titers, values below the limit of detection (LOD) ($NT_{50} < 40$) were given the LOD value. Statistical analyses were performed using Stata version 18.0 (StataCorp LLC), and graphics were generated using GraphPad Prism 9 (GraphPad, Inc.). All *P* values were two-sided, with statistical significance set at $P < 0.05$; exact *P* values are reported throughout the Results, except where $P < 0.001$ (in which case this convention is used).

3. Results

3.1. Distribution of circulating SARS-CoV-2 variants during follow-up

Fig. 1 shows the distribution of SARS-CoV-2 lineages in Japan during the study period (June to September 2024), analysed using all domestic genome sequences registered in the GISAID EpiCov database (https://gisaid.org). During the study period, 9241 sequences were analysed, and Omicron KP.3 sublineages accounted for 84.2%. Among these, KP.3.3 was the most frequent (54.2%), followed by KP.3.3.3 (15.7%) and KP.3.1.1 (5.6%).

3.2. Baseline characteristics

Among the 1826 participants, the median age was 36.5 years (interquartile range: 27–49) and 71.2% were female. The most common occupation was nurse (35.5%), followed by doctor (15.7%), administrative staff (14.8%), allied healthcare workers (14.7%), and researchers (13.9%). Overall, 16.8% of participants had high occupational SARS-CoV-2 exposure risk. A history of COVID-19 diagnosis was reported by 58.0% of participants (once: 48.9%; twice or more: 9.1%). When undiagnosed infections identified by anti-N seropositivity were included, 81.7% had evidence of prior SARS-CoV-2 infection.

We ascertained 104 symptomatic breakthrough infection cases during follow-up, with an incidence rate of 7.8 per 10,000 person-days. Cases were younger, more likely to be female, and less likely to be current tobacco users. They also included a lower proportion of doctors and researchers and a higher proportion of nurses (Table 1). After 1:1 propensity matching, the 104 pairs were well balanced across baseline characteristics.

3.3. Vaccination and prior infection statuses and risk of SARS-CoV-2 infection

Table 2 presents the associations of XBB.1.5 vaccination and prior SARS-CoV-2 infection with protection against symptomatic infection during the KP.3-predominant wave. The median time since XBB.1.5 vaccination to baseline was 200 days (IQR 195–215), compared with 582 days (IQR 543–689) since the last dose among those who had not received the XBB.1.5 vaccine. XBB.1.5 vaccination was not associated with a measurably higher protection against symptomatic infection (4%, 95% CI −88 to 51).

Regarding prior infection, the median time since last infection to baseline was 680 days (IQR 645–713) for those infected during pre-Omicron XBB waves, 317 days (IQR 290–376) for Omicron XBB waves, and 118 days (IQR 51–151) for Omicron JN.1 waves. Protection increased with more recent infection: 26% (95% CI −26 to 56) for pre-Omicron XBB waves, 44% (95% CI 2 to 68) for Omicron XBB waves, and 89% (95% CI 52 to 97) for Omicron JN.1 waves. Participants with undiagnosed prior infection had a protection estimate of 38% (95% CI −9 to 64).

3.4. Preinfection antibody titers between the cases and matched controls

Among total samples of cases and controls, the GMTs of preinfection neutralizing antibodies against Wild-type, Omicron XBB.1.16, and KP.3.3 were 470, 151, and 112, respectively; detection rates (>40 NT_{50}) were 84%, 55%, and 38% (**Fig. S2**).

Preinfection antibody titers were generally lower in cases than in controls across all anti-RBD and anti-N antibody measures (Table 3). The GMTs of anti-RBD IgG (Abbott) were 11,710 AU/mL in cases and 15,836 AU/mL in controls (ratio 0.74, 95% CI 0.57–0.95), and those of

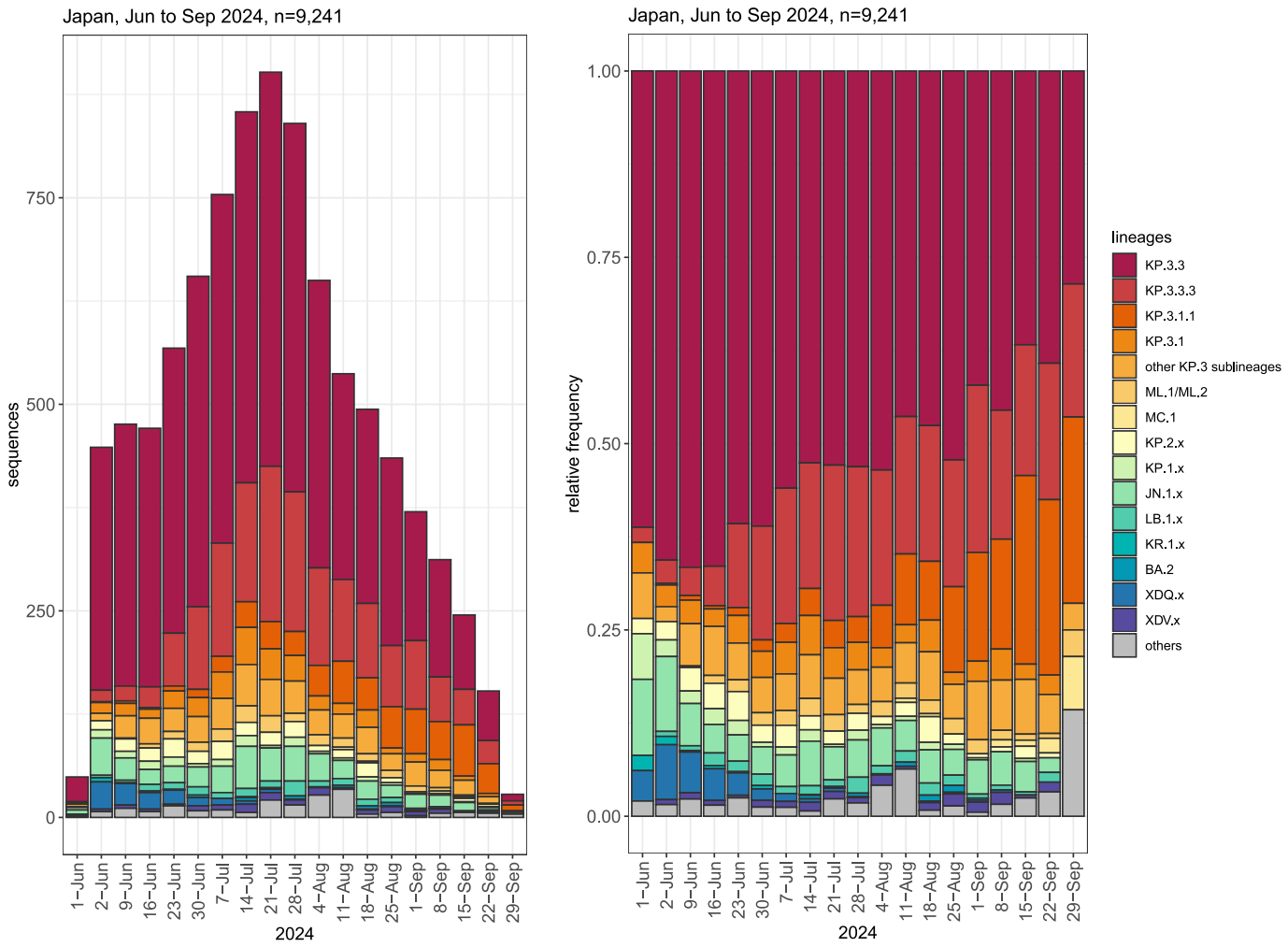

Fig. 1. Temporal distribution of SARS-CoV-2 lineages in Japan, June–September 2024. Weekly counts (left) and relative frequencies (right) of SARS-CoV-2 lineages in Japan from June to September 2024 ($n = 9241$ sequences). The distribution was analysed using all domestic lineage data registered in the GISAID EpiCov database (https://gisaid.org) as of October 21, 2024. Bars represent the number or proportion of sequences assigned to each lineage, with minor lineages grouped as "others."

anti-RBD total antibody (Roche) were 13,506 U/mL and 17,733 U/mL, respectively (ratio 0.76, 95% CI 0.60–0.97). Among participants with evidence of prior SARS-CoV-2 infection, the GMTs of anti-N IgG (Abbott) were 0.35 S/C in cases and 0.73 S/C in controls (ratio 0.48, 95% CI 0.32–0.72), and those of anti-N total antibody (Roche) were 6.2 COI and 18.5 COI, respectively (ratio 0.33, 95% CI 0.18–0.62).

In the subset of 50 matched pairs, neutralizing antibody GMTs against all three strains tended to be lower in cases than in controls, although the ratio for wild-type was small with a wide confidence interval. The GMTs against wild-type were 451 NT_{50} in cases and 490 NT_{50} in controls (ratio 0.92, 95% CI 0.49–1.74). The corresponding GMTs against Omicron XBB.1.16 were 112 NT_{50} and 203 NT_{50} (ratio 0.55, 95% CI 0.30–1.03), and those against Omicron KP.3.3 were 92 NT_{50} and 136 NT_{50} (ratio 0.68, 95% CI 0.35–1.33).

3.5. Neutralizing antibody titers across statuses of XBB.1.5 vaccination and prior infection

Fig. 2 presents neutralizing antibody titers against wild-type, XBB.1.16, and KP.3.3 stratified by XBB vaccination status and prior infection history. Vaccinated participants had higher neutralizing titers against XBB.1.16 than unvaccinated participants (GMT 288 vs 120; GMT ratio 2.40; 95% CI, 1.19 to 4.85), whereas the difference against KP.3.3 was smaller and the confidence interval included the null (GMT 162 vs 98; GMT ratio 1.64; 95% CI, 0.81 to 3.35) (Fig. 2A). In Fig. 2B, where participants were grouped by their most recent infection phase, titers against all three strains were consistently higher in those with more recent infection. For KP.3.3, geometric mean titers were 69, 122, 114, and 380 NT_{50} among infection-naive participants and those infected during the pre-XBB, XBB, and JN.1 predominant waves, respectively. The association between the phase of previous infection and neutralizing antibody titers did not differ by XBB vaccination status for any strain ($P = 0.60$ for wild-type, $P = 0.89$ for XBB.1.16, and $P = 0.41$ for KP.3.3). KP.3.3 titers were highest in participants with both XBB.1.5 vaccination and JN.1-wave infection (Fig. 2C). These results were materially unchanged after adjustment for age, sex, chronic health impairment, and immunosuppressive condition (Fig. S3).

4. Discussion

We conducted a prospective study of healthcare workers in Tokyo who had received three or more doses of COVID-19 mRNA vaccines and were followed for the incidence of breakthrough infection during the Omicron KP.3-predominant wave. XBB.1.5 vaccination was not associated with measurable protection against symptomatic SARS-CoV-2 infection. Prior infection conferred protection that varied by the timing of the last infection: 26% for pre-Omicron XBB waves, 44% for the Omicron XBB wave, and 89% for the Omicron JN.1 wave. In a nested case-control analysis within this cohort, pre-infection live-virus neutralizing titers against KP.3.3 (GMT ratio 0.68) tended to be lower in

Table 1
Baseline characteristics before and after propensity score matching.

Characteristics	Before Matching ($N = 1826$)			After Matching ($N = 208$)		
	Cases	Controls	Standardized difference	Cases	Controls	Standardized difference
	$N = 104$	$N = 1722$		N = 104	N = 104	
Age, y	36.1 ± 13.4	39.0 ± 13.1	0.22	36.1 ± 13.4	36.9 ± 12.0	0.06
Female	81.7	70.6	0.26	81.7	80.8	0.02
Job						
Doctor	8.7	16.1	0.23	8.7	9.6	0.03
Nurse	47.1	34.8	0.25	47.1	48.1	0.02
Allied healthcare worker	19.2	14.4	0.13	19.2	21.2	0.05
Researcher	8.7	14.2	0.17	8.7	7.7	0.04
Administrative staff	12.5	14.9	0.07	12.5	11.5	0.03
Others	3.8	5.6	0.08	3.8	1.9	0.12
Occupational SARS-CoV-2 exposure risk[a]						
Low	57.7	62	0.09	57.7	55.8	0.04
Moderate	22.1	21.5	0.02	22.1	26.9	0.11
High	20.2	16.6	0.09	20.2	17.3	0.07
Body mass index, kg/m^2	21.9 ± 3.8	21.8 ± 3.4	0.01	21.9 ± 3.8	21.8 ± 3.6	0.01
Chronic health impairment[b]	12.5	9.5	0.10	12.5	12.5	0.00
Immunosuppression[c]	3.8	1.7	0.13	3.8	3.8	0.00
Tobacco product users[d]	1.0	7.3	0.32	1.0	1.0	0.00
Frequency of alcohol drinking						
None	32.7	27.6	0.11	32.7	29.8	0.06
Occasional	29.8	30.1	0.01	29.8	33.7	0.08
Weekly/Daily	37.5	42.3	0.10	37.5	36.5	0.02
No. of household members	2 ± 1	2 ± 1	0.07	2 ± 1	2 ± 1	0.04
Child-related living arrangements[e]						
Without school-age children	74	71.1	0.07	74	75	0.02
With younger school-age children	15.4	15.2	0.00	15.4	19.2	0.10
With older school-age children	10.6	13.6	0.09	10.6	5.8	0.17
Infection prevention practice score[f]	5 ± 2	5 ± 2	0.06	5 ± 2	5 ± 2	0.07

Data are presented as mean ± standard deviation for continuous variables and as percentages for categorical variables.
Abbreviations: 3Cs, crowded places, close-contact settings, and confined and enclosed spaces; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Occupational SARS-CoV-2 exposure risk was categorized as low (those not engaged in COVID-19–related work), moderate (those engaged in COVID-19–related work without heavy exposure to SARS-CoV-2), or high (those heavily exposed to SARS-CoV-2).
[b] Chronic health impairment is defined as a self-reported condition characterized by limitations in daily life due to chronic illnesses or health problems.
[c] Immunosuppression was defined as having an immunosuppressive disease or using steroids [except topical or inhaled], immunosuppressants or anticancer drugs
[d] Tobacco products include conventional cigarettes, heated tobacco products, chewing tobacco, pipes, cigars, and water pipes (shisha).
[e] School-age children were categorized as younger (children in nurseries, in kindergartens, in the first to third grades of elementary school, and with disabilities) or older.
[f] Infection prevention practice score was calculated based on the total score of adherences to avoiding the 3Cs, hand washing, wearing a mask in the 3Cs, and wearing the mask in the non-3Cs, assigning 2 points to "always," 1 point to "often," and 0 points to others ("seldom" and "not at all").

Table 2
Protection of the XBB vaccine and a previous infection against symptomatic SARS-CoV-2 infection during KP.3 predominant waves among a prospective cohort ($N = 1826$).

Variables	Participants, n	Days since last exposure, median (IQR)	Cases/person-days	Adjusted HR (95% CI)	Protection (95% CI)
Omicron XBB vaccination					
Unvaccinated (historical or BA vaccine only)	1335	582 (543–689)	72/96,948	Reference	Reference
Vaccinated	491	200 (195–215)	32/35,653	0.96 (0.49–1.88)	4% (−88 to 51)
Prior SARS-Cov-2 infection phase					
Infection naive	334	NA	28/23,913	Reference	Reference
Undiagnosed infection	433	NA	22/31,515	0.62 (0.36–1.09)	38% (−9 to 64)
Pre-Omicron XBB waves (Wild-type, Delta, BA)	457	680 (645–713)	30/33,040	0.74 (0.44–1.26)	26% (−26 to 56)
Omicron XBB waves	419	317 (290–376)	22/30,458	0.56 (0.32–0.98)	44% (2 to 68)
Omicron JN.1 waves	183	118 (51–151)	2/13,675	0.11 (0.03–0.48)	89% (52 to 97)

HRs (95% CI) were estimated with a Cox proportional hazards regression while adjusting for age, sex, occupation, occupational SARS-CoV-2 exposure risk, BMI, chronic health impairment, immunosuppressive condition, use of tobacco products, frequency of alcohol drinking, no. of household members, child-related living arrangements, and time since last COVID-19 vaccination, as well as XBB vaccination and previous infection statuses, which were mutually adjusted.
Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NA, not applicable.

cases than in matched controls.

In our cohort, XBB.1.5 vaccination, received approximately 7 months before baseline, was not associated with measurable protection against symptomatic infection during the KP.3-predominant wave (4%; 95% CI, −88 to 51). A test-negative case-control study of adults aged ≥60 years in Spain similarly found no evidence of protection from

Table 3
Comparison of preinfection antibody titers between COVID-19 cases during the KP.3 predominant wave and their matched controls.

Preinfection antibody titer	No. of cases/ controls	Geometric mean titer (95% CI)		Ratio for cases to controls (95% CI)
		Cases (n = 104)	Controls (n = 104)	
Anti-RBD IgG antibody (Abbott, AU/mL)	104/ 104	11,710 (9812–13,974)	15,836 (13,068–19,189)	0.74 (0.57–0.95)
Anti-RBD total antibody (Roche, U/ mL)	104/ 104	13,506 (11,414–15,982)	17,733 (14,923–21,072)	0.76 (0.60–0.97)
Anti-N IgG antibody (Abbott, S/ C)[a]	76/86	0.35 (0.26–0.48)	0.73 (0.55–0.99)	0.48 (0.32–0.72)
Anti-N total antibody (Roche, COI)[a]	76/86	6.2 (4.0–9.5)	18.5 (12.6–27.2)	0.33 (0.18–0.62)
Neutralizing antibody (Wild-type, NT_{50})[b]	50/50	451 (284–715)	490 (305–787)	0.92 (0.49–1.74)
Neutralizing antibody (Omicron XBB.1.16, NT_{50})[b]	50/50	112 (75–167)	203 (127–323)	0.55 (0.30–1.03)
Neutralizing antibody (Omicron KP.3.3, NT_{50})[b]	50/50	92 (60–142)	136 (87–212)	0.68 (0.35–1.33)

The geometric mean titers and their ratios were estimated using a generalized estimating equation model with group assignment (case or control).
Abbreviations: AU, arbitrary units; CI, confidence interval; COI, cutoff index; IgG, immunoglobulin G; N, nucleocapsid; NT50, 50% neutralization titer; RBD, receptor-binding domain; S/C, signal to cutoff.
[a] Analysed the case-control samples restricted to those with a history of COVID-19 or seropositive for anti-nucleocapsid antibodies (Abbott or Roche) at baseline.
[b] Analysed on the basis of 50 matched pairs randomly selected from 104 matched pairs.

XBB.1.5 vaccination at a comparable post-vaccination interval of 7 months, with a point estimate in the negative range (−39%) [9]. Two explanations are likely to operate together: the antigenic distance between the XBB.1.5 vaccine strain and the circulating variant, and the decline in vaccine-induced immunity over the interval since vaccination. XBB.1.5 vaccination has been reported to raise neutralizing titers against KP.3 only modestly even when serum is sampled within weeks of the dose [5–7]. That limited activity declines further by 6 months after XBB.1.5 vaccination [8,15]. Both conditions applied here, where the XBB.1.5 dose was given approximately 7 months before a wave caused by a variant of a different lineage. We observed a similar combination during the 2023 summer wave, when the BA-bivalent vaccine, given the previous autumn, also failed to protect against the then-circulating XBB.1.16 and EG.5.1 variants [4]. Autumn COVID-19 vaccination may therefore offer limited protection against the antigenically distinct variants that circulate the following summer, and this may be one reason why summer waves of SARS-CoV-2 have recurred each year.

Previous SARS-CoV-2 infection was associated with protection against symptomatic infection during the KP.3-predominant wave, and the estimate increased with the recency of the last infection: 26% for the pre-Omicron XBB waves, 44% for the Omicron XBB wave, and 89% for the Omicron JN.1 wave. Antigenic relatedness between the infecting variant and KP.3 offers the most direct reading of this gradient. KP.3 descends from JN.1 and differs from it by only two substitutions in the receptor-binding domain, F456L and Q493E [5,6]; it differs from XBB.1.5 by more than 30 substitutions across the spike [16,17]. Infection during the JN.1 wave therefore presented a spike closely resembling that of the KP.3 sublineages circulating during follow-up, whereas infection during the XBB or earlier waves did not.

Infection during the XBB wave was associated with 44% protection, whereas XBB.1.5 vaccination was associated with 4%. Both exposures present a spike of the same XBB lineage, so antigenic distance alone does not explain this difference. Infection may engage parts of the immune response that intramuscular vaccination does not. Antibodies at the respiratory mucosa act where the virus first enters the body [18,19]. Infection has also been reported to remodel the memory B-cell repertoire and improve its neutralizing breadth [20], and it elicits T cells against viral proteins other than spike, which the XBB.1.5 vaccine does not encode [21]. We measured none of these, so this explanation remains a possibility.

In our nested case-control analysis, cases had 32% lower pre-infection KP.3.3 neutralizing titers than matched controls. While variant-specific neutralizing antibodies have been identified as correlates of protection against earlier SARS-CoV-2 variants [4,22,23], the present analysis extends this evidence by showing that lower pre-infection KP.3-specific neutralizing titers were associated with a higher risk of symptomatic KP.3 infection. When compared by vaccination and infection history, KP.3.3 neutralizing titers were not substantially higher with XBB.1.5 vaccination, but were markedly higher after prior infection, particularly with more recent infection from variants such as JN.1. These findings align with the protection estimates observed in the present prospective analysis for XBB.1.5 vaccination and JN.1-wave infection. Participants with both XBB.1.5 vaccination and JN.1-wave infection had the highest KP.3.3 titers of any group (Fig. 2C), consistent with reports that hybrid immunity elicits stronger neutralizing responses than vaccination or infection alone [1,24].

This study has several strengths. First, we adjusted for a comprehensive set of potential risk factors, including occupational exposure, infection-prevention practices, comorbidities, and household composition in the prospective cohort analysis, and further balanced these factors between cases and controls through rigorous propensity score matching in the case-control analysis. Second, pre-infection antibody titers were measured immediately before the onset of the KP.3-predominant wave, providing a precise serological snapshot of immune status at the point of exposure. Third, neutralizing antibody titers were measured with authentic SARS-CoV-2 isolates. While titers from live-virus and pseudovirus assays agree closely [25], authentic virus, unlike a pseudovirus, retains the complete viral particle and undergoes the full replication cycle, so neutralization is measured under conditions closer to natural infection [26]. Fourth, previous SARS-CoV-2 infection was determined according to the history of COVID-19 diagnosis and results of anti-SARS-CoV-2 N assays, allowing us to identify undiagnosed infections.

This study has limitations. First, cases were restricted to diagnosed symptomatic COVID-19, and because we did not conduct active surveillance, our findings do not apply to asymptomatic infection. Second, viral sequences were not obtained from individual cases; however, KP.3 accounted for 84% of sequenced samples in Japan during the follow-up period (Fig. 1), making it the most likely cause of the observed cases. Third, no severe cases occurred during the follow-up period; therefore, our estimates do not apply to protection against severe disease. Fourth, we did not assess mucosal or cellular immunity, which may also contribute to protection against SARS-CoV-2 infection [18,19,21].

5. Conclusions

During the Omicron KP.3 predominant wave, among healthcare workers who had received three or more doses of COVID-19 mRNA

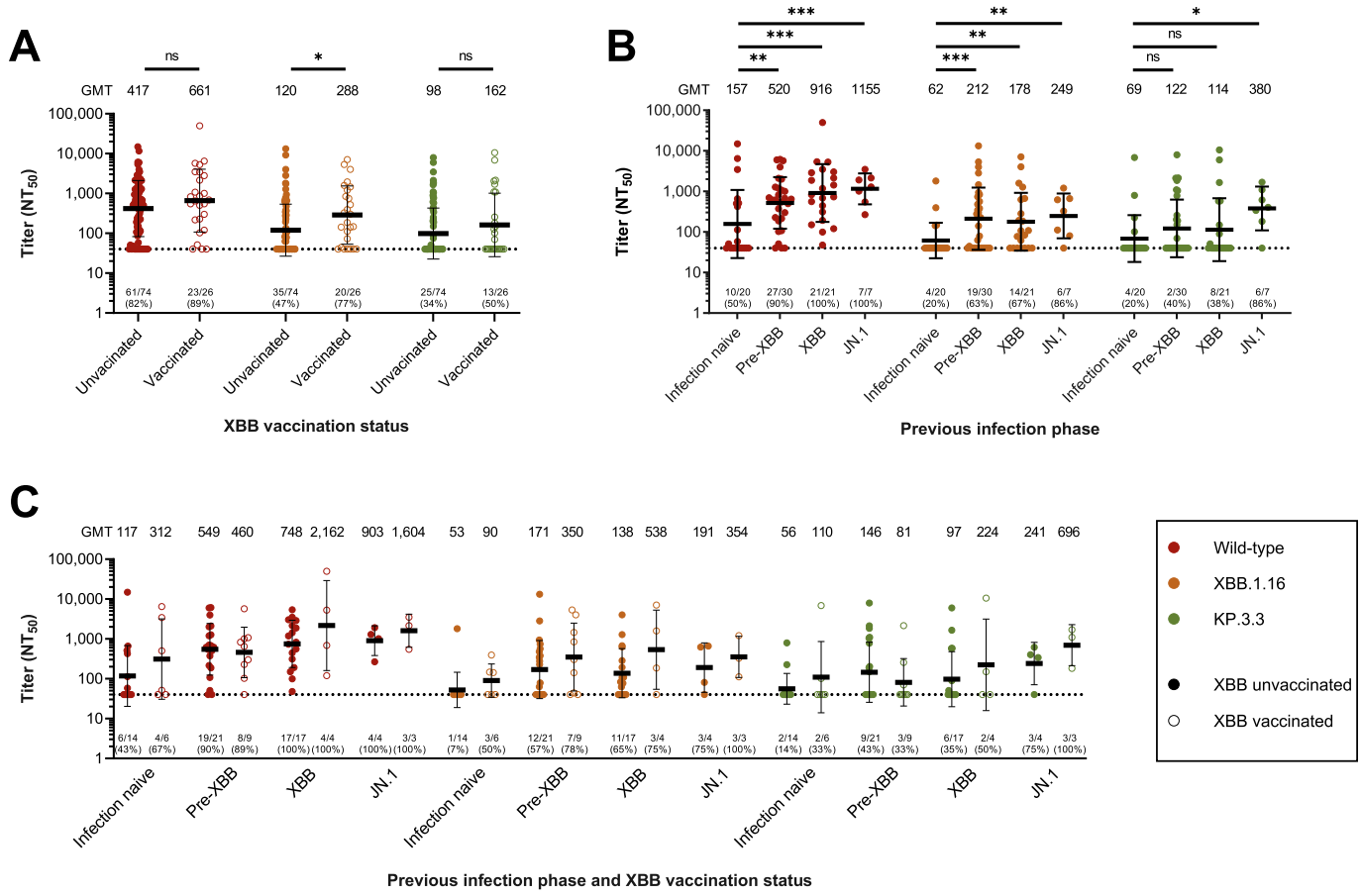

Fig. 2. Neutralizing antibody titers against wild-type, XBB.1.16, and KP.3.3 by XBB vaccination status and infection history. Neutralizing antibody titers (NT_{50}) are shown on a logarithmic scale. Each dot represents an individual; horizontal bars indicate geometric mean titers with geometric standard deviations. Numbers above each group denote geometric mean titers. Numbers below indicate the number and proportion with detectable neutralizing activity. The dotted line indicates the lower limit of detection. Panel A: stratified by XBB vaccination status. Panel B: stratified by previous infection phase (infection-naive, pre-XBB, XBB, JN.1). Panel C: stratified by XBB vaccination status and previous infection phase. Panels B and C exclude 22 participants whose infection phase could not be assigned ($n = 78$). Differences in log-transformed NT_{50} between groups were evaluated using unadjusted linear regression models. *P* values for pairwise comparisons are adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate procedure (ns, not significant; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$). In Panel C, whether the association between infection phase and titers differed by XBB vaccination status was tested using a Wald test for the interaction term ($P = 0.60$, 0.89, and 0.41 for wild-type, XBB.1.16, and KP.3.3). Results adjusted for age, sex, chronic health impairment, and immunosuppressive condition are shown in Fig. S3.

vaccines, XBB.1.5 vaccination administered approximately 7 months earlier did not confer measurable protection against SARS-CoV-2 infection. Previous SARS-CoV-2 infection, particularly with JN.1 infection, was associated with strong protection. The preinfection KP.3.3 neutralizing antibody titers were lower in infected cases than in their matched controls and were only modestly elevated by XBB.1.5 vaccination, whereas they were markedly higher in those recently infected during the JN.1 wave. Our results highlight the importance of infection prevention practices during summer waves driven by antigenically distinct variants, when protection from the preceding autumn vaccination campaign has waned and updated vaccines are not yet available.

Ethics declarations

This study was approved by the Ethics Committee of the Japan Institute for Health Security (approval number: JIHS-S-003598). Written or electronic informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used Claude (Anthropic) and ChatGPT (OpenAI) for organizing and refining the structure and wording of the manuscript, and additionally used Claude to support literature searching. The authors reviewed and edited the output as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Shohei Yamamoto: Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kouki Matsuda:** Writing – review & editing, Resources, Investigation. **Kenji Maeda:** Writing – review & editing, Resources, Investigation. **Tetsuya Mizoue:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Kumi Horii:** Writing – review & editing, Resources, Investigation, Data curation. **Yusuke Oshiro:** Writing – review & editing, Resources, Investigation. **Natsumi Inamura:** Writing – review & editing, Resources, Investigation. **Takashi Nemoto:** Writing – review & editing, Resources, Investigation. **Yuichi Akahori:** Writing – review & editing, Resources, Investigation. **Junko S. Takeuchi:** Writing – review & editing, Visualization, Resources. **Maki Konishi:** Writing – review & editing, Software, Investigation, Data curation. **Wataru Sugiura:**

Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Norio Ohmagari:** Writing – review & editing, Supervision, Resources, Conceptualization.

Ethics declaration

Informed consent and patient details

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

Human and biological material

This study included organ or tissue donors. This study includes human biological material and consent was obtained by donors, or their next of kin or legal representatives, for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

Studies in human

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the Japan Institute for Health Security (Approval No. JIHS-S-003598).

Code availability

The statistical code used in this study is available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.129242.

Data availability

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants. De-identified data may be made available from the corresponding author upon reasonable request and with permission of the Ethics Committee of the Japan Institute for Health Security.

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