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Effectiveness of the severe acute respiratory syndrome coronavirus 2 Omicron BA.5 bivalent vaccine on symptoms in healthcare workers with BA.5 infection

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ABSTRACT

Background: The infection status of healthcare workers (HCWs) with coronavirus disease 2019 has become a major concern worldwide. In this study, we investigated the efficacy of the number of vaccine doses on symptoms after BA.5-adapted bivalent vaccination in HCWs.

Methods: We analyzed the occupation, route of infection, symptoms, and vaccination history of all HCWs who tested positive for severe acute respiratory syndrome coronavirus 2 and worked in our hospital from November 2020 to March 2023. A logistic regression analysis was performed to examine the association between the presence of BA.5-adapted bivalent vaccination and symptoms.

Results: During the observation period, 531 HCWs became infected. Of these, 72 % were women, with a median age of 30 years. Nurses accounted for 57 % of the infected cases, and many of the infection routes were from family members. We examined the relationship between symptoms in 352 HCWs infected with the Omicron BA.5* variant and the number of vaccine doses. As the number of vaccine doses increased, the rate of fever decreased, while symptoms such as a runny nose and sore throat tended to increase. The logistic regression analysis showed that the rate of fever tended to decrease (odds ratio = 0.52, 95 % confidence interval: 0.26–1.01, p = 0.056) and that of a runny nose increased (odds ratio = 3.68, 95 % confidence interval: 1.17–10.6, p = 0.018) after BA.5-adapted bivalent vaccination.

Conclusion: This study shows that fever is reduced and mild symptoms are increased after BA.5-adapted bivalent vaccination in BA.5-infected HCWs. This result highlights the potential effectiveness of tailored vaccination strategies in the management of emerging COVID-19 variants.

Introduction

Healthcare workers (HCWs) are at the frontline of the healthcare setting during the coronavirus disease 2019 (COVID-19) pandemic and are at a high risk of infection [1]. HCWs are more susceptible to COVID-19 than non-HCWs because of their frontline work with infected patients [2–4]. This situation not only puts HCWs at risk, but also their patients and those who interact with them. HCWs who have infected COVID-19 show various symptoms, such as fever, cough, shortness of breath, fatigue, muscle aches, headache, loss of taste or smell, a sore throat, nasal congestion, rhinorrhea, vomiting, diarrhea, and skin rashes [5,6]. The most common early symptoms reported by HCWs who were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and developed COVID-19 are cough, fever, and muscle aches [5].

COVID-19 mRNA vaccines induce a strong immune response against SARS-CoV-2 and are effective in reducing the risk of SARS-CoV-2 infection [7,8]. Studies on the effectiveness of COVID-19 mRNA vaccines in HCWs conducted by the Centers for Disease Control and Prevention showed that mRNA vaccines were effective in reducing the risk of SARS-CoV-2 infection under real-world conditions [9,10].

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Furthermore, studies conducted specifically on HCWs showed that the BNT162b2 mRNA vaccine was effective in preventing COVID-19-related isolation and quarantine [11]. A bivalent vaccine against the Omicron BA.5 variant has been developed, and its effectiveness against the Omicron variant has been demonstrated [12,13]. However, information on the effect of symptoms before and after vaccination with the BA.5 bivalent vaccine is limited.

In this study, we included all HCWs who were infected with SARS-CoV-2 from November 2020 to March 2023. We collected information on the occupation, estimated route of infection, vaccination history, symptoms, and viral load of HCWs. This study aimed to investigate HCWs infected with the BA.5 variant before or after a dose of the BA.5-adapted bivalent vaccine.

Methods

Subjects

We conducted a survey to determine positive or negative SARS-CoV-2 infection among HCWs, including hospital administrative staff. From 10 November 2020 to 28 March 2023, 531 HCWs were positive for SARS-CoV-2 infection (among 1405 hospital staffs in March 2023) (Supplementary Table 1 and 2). The 531 HCWs included the following: (1) COVID-19-positive HCWs whose test results had already been collected by the infection control office within the hospital; (2) COVID-19-positive HCWs who had an infected family member; (3) COVID-19-positive HCWs who were suspected of having close contact with infected people; (4) COVID-19-positive HCWs who were suspected of having close contact with an infected HCW in the past 2 days; and (5) COVID-19-positive HCWs who had domestic or international traveled, went out locally, returned to their hometown, or had concerns about infection.

When an HCW was found to be infected while working at the hospital, we performed a screening test on other HCWs and inpatients who were suspected of having close contact with that infected HCW in the past 2 days. In addition, testing was made available upon request to HCWs who traveled, returned to their hometown, or had concerns about infection.

In HCWs who were found to be infected, certified infection control nurses (M.T.) conducted direct telephone interviews to collect information on their symptoms, estimated routes of infection, vaccination history, date of onset of symptoms, and occupation. To prevent nosocomial infection, HCWs who tested positive were required to self-isolate at home, as per the COVID-19 national policy. In symptomatic individuals, symptom onset was considered as day 0, and these individuals were required to self-isolate for 10 days. In asymptomatic individuals, the first positive test result was considered as day 0, and these individuals were required to self-isolate for 7 days. In both instances, individuals were allowed to return to work only after a low antigen concentration (<200 mg/mL) had been confirmed, which is the original criterion of our hospital. The HCWs received the monovalent mRNA vaccine (Moderna or Pfizer-BioNTech) for their first to fourth doses (V1–V4) and the BA.5-adapted bivalent mRNA vaccine (Pfizer-BioNTech) for their fifth dose ($V5_{bivalent}$).

SARS-CoV-2 test

Several molecular diagnostic platforms for nucleic acid amplification and antigen testing were used to diagnose SARS-CoV-2 infection. The diagnostic tests used were TaqMan real-time reverse transcription-polymerase chain reaction (PCR) targeting the nucleocapsid gene in the StepOne plus real-time PCR system (Thermo Fisher Scientific, Waltham, MA, USA) according to the protocol developed by the National Institute of Infectious Diseases in Japan [14,15], the FilmArray Respiratory Panel 2.1 test in the FilmArray Torch system (bioMérieux, Marcy-l'Etoile, France) [16], the Xpert Xpress SARS-CoV-2 test in the Cepheid GeneXpert system (Cepheid, Sunnyvale, CA) [17], cobas SARS-CoV-2 & influenza A/B in the cobas Liat system (Roche Diagnostics, Basel, Switzerland), and the Lumipulse antigen test in the LUMIPULSE G600II system (Fujirebio, Inc., Tokyo, Japan) [18,19]. Screening tests for close contacts and suspected cases were performed by pooling PCR [20]. All tests were performed with material obtained from nasopharyngeal swabs immersed in viral transport medium, including UTM Viral Transport (Copan, Murrieta, CA) or ALLTM set medium (SG Medical, Seoul, Republic of Korea).

SARS-CoV-2 genotyping by the TaqMan assay

We used the predesigned TaqMan SARS-CoV-2 Mutation Panel (Thermo Fisher Scientific) to design a custom TaqMan assay to detect spike protein mutations with Δ69–70, G339D, Q493R, K417N, K417T, K444T, L452R, T478K, E484K, Q493R, N501Y, P681H, P681R, and G769V, and membrane protein mutation with D3N [21]. The TaqMan probe detected wild-type and variant sequences of SARS-CoV-2. The TaqMan minor groove binder probe for the wild-type allele was labeled with VIC dye, and the variant allele was labeled with FAM dye fluorescence.

TaqPath 1-Step RT-qPCR Master Mix CG was used as the master mix, and quantitative PCR was performed using the Step-One Plus Real-Time PCR System (Thermo Fisher Scientific). Allelic discrimination software (Thermo Fisher Scientific) was used to analyze the data and identify variant and wild-type alleles. Amplification curves of each data set were confirmed visually. In the case of a low viral load in the sample or poor amplification due to mutations around the primers or probes [22], the result was reported as "unknown." Detailed lineages are indicated by an asterisk without distinction (i.e., BA.1*, BA.2*, BA.2.75*, BA.5*, BQ.1*, and XBB*) owing to the large number of sublineages of Omicron variants.

Ethics statement

The Institutional Review Board of the Clinical Research and Genome Research Committee of Yamanashi Central Hospital approved this retrospective study (Approval No. C2019-30). Participation in the study was optional following informed consent. All study procedures were performed in accordance with the relevant guidelines and regulations, and as set out in the Helsinki Declaration.

Statistical analysis

Interquartile range calculations, statistical analyses, and logistic regression analyses were performed using R version 4.1.1 (https://www.r-project.org/). The following R packages were used for data cleaning, analysis, and visualization: ggplot2 (v3.3.5), dplyr (v1.0.7), tidyr (v1.1.3), patchwork (v1.1.1), lubridate (v1.9.0), rstatix (v0.7.1), gtsummary (v1.5.2) flextable (v.0.7.0), incidence2 (v1.2.3), viridis (v0.6.2), and RColorBrewer (v1.1–3). The Kruskal–Wallis rank sum test and Fisher's exact test were used for statistical analysis. Statistical significance was defined as a p value < 0.05.

Results

Characteristics of infected HCWs

This study included 531 HCWs infected with SARS-CoV-2, who represented approximately 40 % of all hospital staff. The median age of the HCWs was 30 years (interquartile range: 26–40), with 379 (71 %) women and 152 (29 %) men. There were 74 (14 %) asymptomatic and 457 (86 %) symptomatic individuals. The most common symptoms were a sore throat (58 %, 307/531), fever (50 %, 266/531), and cough (25 %, 132/531).

With regard to occupation, the study population consisted of 305 (57 %) nurses, 88 (17 %) doctors, 50 (9.4 %) hospital administrators, 29 (5.5 %) nursing assistants, 12 (2.3 %) medical laboratory technicians, 10 (1.9 %) clinical engineers, 10 (1.9 %) pharmacists, 9 (1.7 %) physiotherapists, 9 (1.7 %) radiologic technologists, and 9 (1.7 %) individuals from other occupations (Supplementary Table 1). These results indicated that nurses accounted for more than half of the total cases.

The estimated routes of infection were family (n = 257, 48 %), the hospital (n = 93, 18 %), meals together outside of the hospital (n = 30,

5.6 %), friends (n = 16, 3.0 %), public places (n = 12, 2.3 %), travel (n = 12, 2.3 %), weddings (n = 3, 0.6 %), and unknown (n = 108, 20 %) (Supplementary Table 1). Familial transmission often occurred when infections were transmitted from a child to nurses or doctors. While familial transmission occurred at a constant rate throughout the observation period, hospital infections were more common around week 45 of 2022 during the period of increasing cases (Fig. 1a).

There were several types of variants, including D614G (n = 9, 1.7 %), Alpha (n = 1, 0.2 %), Delta (n = 6, 1.1 %), BA.1* (n = 10, 1.9 %), BA.2* (n = 38, 7.2 %), BA.5* (n = 352, 66.3 %), BA.2.75* (n = 12, 2.3 %), BQ.1* (n = 21, 4.0 %), XBB* (n = 2, 0.4 %), and unknown (n = 80, 15.1 %). The most common variant was BA.5* and it increased after week 26 of 2022 (Fig. 1b). The other variants accounted for < 8 % each.

Symptoms of HCWs infected with the Omicron BA.5 variant

We analyzed the association between the number of vaccine doses and symptoms in HCWs infected with the most common BA.5* variant. Of the 352 HCWs infected with the BA.5* variant, 5 were unvaccinated, 8 had received 2 doses (V1 + V2), 142 had received 3 doses (V1 + V2 + V3), 143 had received 4 doses (V1 + V2 + V3 + V4), 44 had received 5 doses (V1 + V2 + V3 + 4 + $V5_{bivalent}$), and 10 had an unknown vaccination history (Table 1).

After excluding HCWs with an unknown vaccination history, the proportion of HCWs with a fever decreased as the number of vaccine doses increased (Fisher's exact test, $p < 0.001$), while the proportion of HCWs with a runny nose increased (Fisher's exact test, $p = 0.047$) (Table 1). The proportion of HCWs with a sore throat increased after four doses (Fisher's exact test, $p = 0.044$) (Table 1). There was no significant difference in the rate of development of a cough, fatigue, an abnormal taste or smell, headache, nasal obstruction, or sputum discharge. These results suggested that the number of vaccine doses affected the development of some symptoms in HCWs infected with the BA.5* variant.

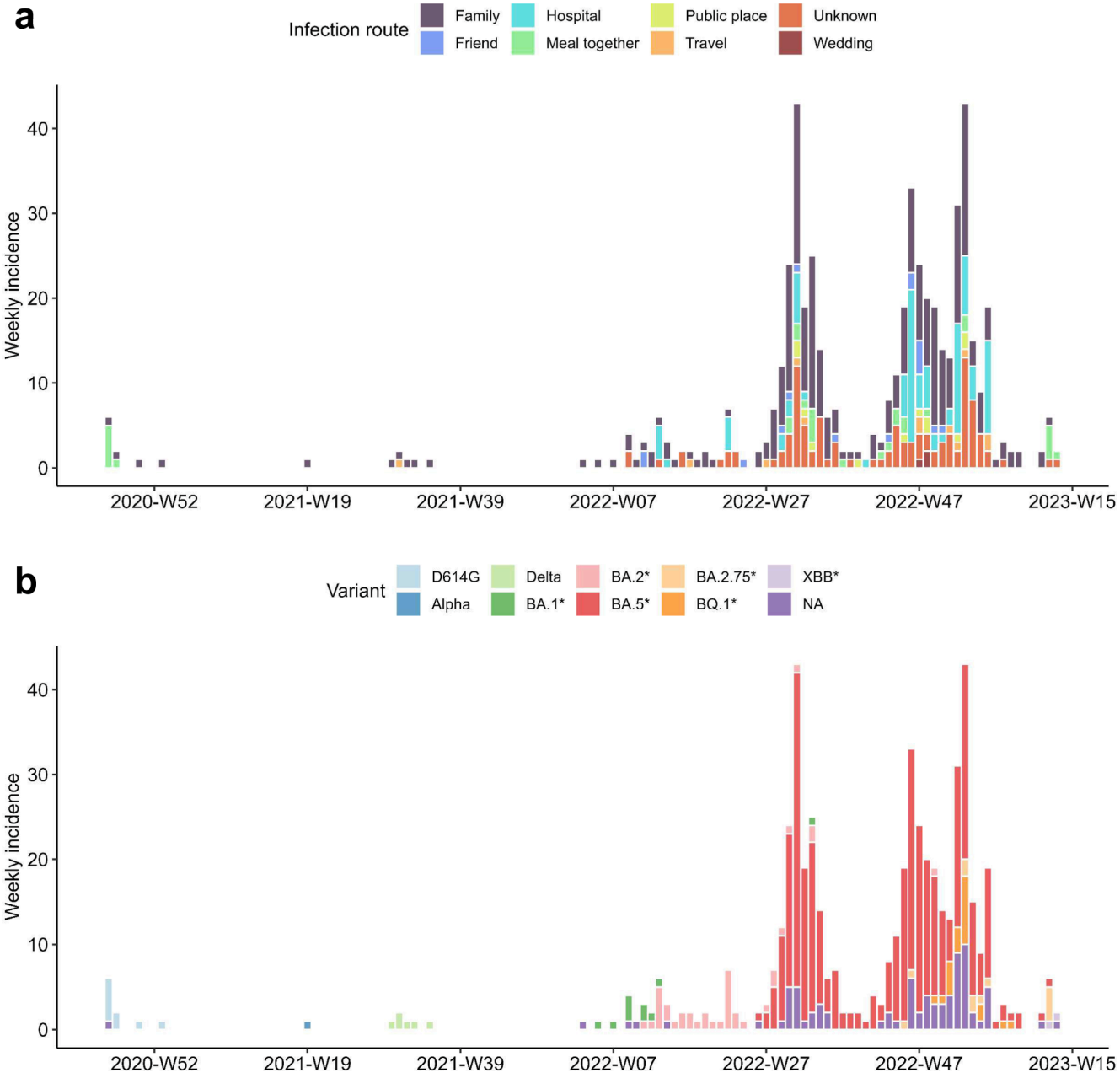

Fig. 1. Trend of infection in healthcare workers The bar graphs show the number of healthcare workers (n = 531) infected each week during the observation period. (**A**) Trend by infection route obtained through phone interviews. (**B**) Trend by variant classified using the TaqMan assay.

Table 1
The number of vaccine doses and symptoms of healthcare workers.

Characteristic	Unvaccinated, n = 5	V1 + V2, n = 8	V1 + V2 + V3, n = 142	V1 + V2 + V3 + 4, n = 143	V1 + V2 + V3 + 4 + V5 $_{bivalent}$, n = 44	p-value[2]
Age, median (IQR)	45 (45–49)	32 (24–38)	29 (26–38)	31 (26–40)	34 (28–40)	**0.04** †
Sex, n (%)						0.2 ‡
Woman	5 (100 %)	8 (100 %)	102 (72 %)	98 (69 %)	34 (77 %)	
Man	0 (0 %)	0 (0 %)	40 (28 %)	45 (31 %)	10 (23 %)	
Symptom, n (%)						0.7 ‡
Asymptomatic	0 (0 %)	0 (0 %)	16 (11 %)	14 (9.8 %)	7 (16 %)	
Symptomatic	5 (100 %)	8 (100 %)	126 (89 %)	129 (90 %)	37 (84 %)	
Fever, n (%)	3 (60 %)	6 (75 %)	90 (63 %)	61 (43 %)	16 (36 %)	**<0.001** ‡
Cough, n (%)	1 (20 %)	2 (25 %)	28 (20 %)	46 (32 %)	8 (18 %)	0.11 ‡
Sore throat, n (%)	3 (60 %)	4 (50 %)	81 (57 %)	104 (73 %)	31 (70 %)	**0.044** ‡
Fatigue, n (%)	1 (20 %)	2 (25 %)	21 (15 %)	19 (13 %)	4 (9.1 %)	0.6 ‡
Abnormal taste or smell, n (%)	0 (0 %)	1 (12 %)	1 (0.7 %)	2 (1.4 %)	1 (2.3 %)	0.2 ‡
Headache, n (%)	0 (0 %)	0 (0 %)	7 (4.9 %)	5 (3.5 %)	2 (4.5 %)	0.9 ‡
Runny nose, n (%)	0 (0 %)	0 (0 %)	3 (2.1 %)	10 (7.0 %)	6 (14 %)	**0.047** ‡
Nasal obstruction, n (%)	0 (0 %)	0 (0 %)	1 (0.7 %)	1 (0.7 %)	1 (2.3 %)	0.6 ‡
Sputum, n (%)	0 (0 %)	0 (0 %)	1 (0.7 %)	1 (0.7 %)	0 (0 %)	>0.9 ‡
Others, n (%)	1 (20 %)	1 (12 %)	18 (13 %)	22 (15 %)	10 (23 %)	0.5 ‡
Viral loads (log_{10} copies/mL),median (IQR)	5.50 (4.00–5.70)	4.65 (4.00–5.78)	5.15 (3.50–6.40)	4.70 (2.85–6.00)	4.50 (2.40–5.73)	0.5 †

IQR, interquartile range; V, vaccine. Statistical analysis was performed with the Kruskal-Wallis rank sum test †, Fisher's exact test ‡.
Note: Healthcare workers received monovalent vaccines from the first to the fourth dose, and a BA.5-adapted bivalent vaccine was administered for the fifth dose.

Effect of the bivalent vaccine on symptoms

The fifth vaccine dose received by HCWs was the BA.5-adapted bivalent vaccine (Pfizer-BioNTech). To investigate the effect of the BA.5-adapted bivalent vaccine on symptoms, we divided the subjects into pre-vaccination (n = 298) and post-vaccination (n = 44) groups (Table 2). There was no significant difference in the median age, sex, or viral load in nasopharyngeal swabs between the groups (Table 2).

As mentioned above, the proportion of HCWs with a fever was significantly reduced by the BA.5-adapted bivalent vaccination (Fisher's exact test, p = 0.032), while that in HCWs with a runny nose was significantly increased (Fisher's exact test, p = 0.024) (Table 2). However, there was no significant difference in the proportion of HCWs with a cough, a sore throat, fatigue, an abnormal taste or smell, a headache, nasal congestion, or sputum discharge between the groups.

We performed a logistic regression analysis to predict the incidence of symptoms according to the administration of the BA.5-adapted bivalent vaccine. The odds ratio for the symptom of nasal discharge significantly increased to 3.68 (95 % CI: 1.17–10.6) (p = 0.018) when the BA.5-adapted bivalent vaccine was administered (Table 3). However, although there was no significant difference, there was a tendency for fever to decrease with bivalent vaccination, with an odds ratio of 0.52 (95 % confidence interval: 0.26–1.01, p = 0.056) (Table 3). Our results suggested that BA.5-adapted bivalent vaccination can alleviate the symptoms following BA.5 infection. Specifically, vaccinated individuals showed a decrease in the rate of fever and only mild symptoms such as a runny nose.

Table 2
Symptoms of BA.5-infected HCWs before and after receiving the BA.5-adapted bivalent vaccine.

Characteristic	Before bivalent vaccine, N = 298[1]	After bivalent vaccine, N = 44[1]	p-value[2]
Age, median (IQR)	30 (26–39)	34 (28–40)	0.088 †
Sex, n (%)			0.4 ‡
Woman	213 (71 %)	34 (77 %)	
Man	85 (29 %)	10 (23 %)	
Symptom, n (%)			0.3 ‡
Asymptomatic	30 (10 %)	7 (16 %)	
Symptomatic	268 (90 %)	37 (84 %)	
Fever, n (%)	160 (54 %)	16 (36 %)	**0.032** ‡
Cough, n (%)	77 (26 %)	8 (18 %)	0.3 ‡
Sore throat, n (%)	192 (64 %)	31 (70 %)	0.4 ‡
Fatigue, n (%)	43 (14 %)	4 (9.1 %)	0.3 ‡
Abnormal taste or smell, n (%)	4 (1.3 %)	1 (2.3 %)	0.5 ‡
Headache, n (%)	12 (4.0 %)	2 (4.5 %)	0.7 ‡
Runny nose, n (%)	13 (4.4 %)	6 (14 %)	**0.024** ‡
Nasal obstruction, n (%)	2 (0.7 %)	1 (2.3 %)	0.3 ‡
Sputum, n (%)	2 (0.7 %)	0 (0 %)	>0.9 ‡
Others, n (%)	42 (14 %)	10 (23 %)	0.14 ‡
Viral loads (log_{10} copies/mL),median (IQR)	4.95 (3.23–6.18)	4.50 (2.40–5.73)	0.2 †

IQR, interquartile range. Statistical analysis was performed with the Kruskal-Wallis rank sum test †, Fisher's exact test ‡.

Discussion

In this study, we investigated the characteristics of 531 HCWs who tested positive for COVID-19 between 10 November 2020 and 28 March 2023. The majority of infected HCWs were female nurses. The most common route of infection was through family members, followed by hospitals, meals together outside of the hospital, and contact with friends. Among the infected HCWs, the Omicron BA.5* variant was the most common, accounting for 66 % of the cases.

This study suggests an association between the symptoms of HCWs infected with the BA.5 variant and their vaccination history. Specifically, we found that as the number of vaccine doses increased, the rate of fever decreased, and that of nasal discharge increased. The Omicron variant has reduced transmissibility to the lungs [23–25]. Therefore, this reduced transmissibility may be due to a decrease in pathogenicity compared with previous variants (D614G, Alpha and Delta). By focusing on BA.5*-infected HCWs, we provide insights into the potential benefits of the BA.5-adapted bivalent vaccine. While definitively stating that the BA.5-adapted bivalent vaccine is effective may be premature, our

Table 3
Logistic regression analysis for the effect of the bivalent vaccine on symptoms.

Characteristic	OR	95 % CI	p-value
Fever	0.52	0.26–1.01	0.056
Cough	0.57	0.23–1.27	0.2
Sore throat	1.42	0.71–2.96	0.33
Fatigue	0.77	0.22–2.12	0.65
Abnormal taste or smell	2.73	0.14–20.1	0.38
Headache	0.84	0.12–3.54	0.83
Runny nose	3.68	1.17–10.6	**0.018**

OR, odds ratio; CI, confidence interval.

findings indicate its potential in mitigating symptoms in healthy HCWs in a high-risk environment, thereby highlighting the ongoing importance of vaccination. Our findings also suggest a possible decrease in pathogenicity since the emergence of the Omicron variant. This possibility raises the prospect that, with acquired immunity, symptoms could resemble those of a common cold in the future.

Interestingly, the main route of infection for HCWs was through family members. In the medical setting, basic infection control measures, such as personal protective equipment, mask wearing, environmental management, and hand hygiene, have been reported to be effective [26–29]. In fact, the hospital staff in this study implemented basic infection control measures. However, implementing similar infection control measures at home is unrealistic. Moreover, vaccinated HCWs with mild or no symptoms might have infected patients, who then infected other HCWs during the study period. We found that 18 % (93/531) of HCWs were infected inside the hospital. Therefore, missed COVID-19-positive HCWs might be associated with nosocomial infection. In this study, many COVID-19-positive HCWs were identified when a parent was infected after their child tested positive. Our data indicate the requirement for daily temperature measurements and health management at home. Additionally, testing and self-isolation when a family member is confirmed positive is important to avoid infection spreading to the hospital and putting vulnerable hospital patients at risk [30].

This study has several limitations. First, the study population was limited to HCWs in a single hospital, and it did not include children, elementary, middle or high school students, university students, or older individuals aged > 70 years. Further research is required to generalize these findings to young or older populations. Second, there may have been selection bias and potential confounders. This study relied on self-reported symptoms, which may have been incomplete. Furthermore, because regular testing was not conducted for all HCWs in this study, many COVID-19-positive asymptomatic HCWs were likely excluded, which would have affected the logistic regression calculations. In our analysis, 17 % (74/531) of HCWs were asymptomatic, but the actual proportion of asymptomatic HCWs may have been higher. Asymptomatic cases were overlooked because symptomatic individuals were mainly tested. Third, while this study was able to examine the relationship between vaccination status and symptoms for one specific variant (BA.5*), performing comparisons for other variants was difficult owing to the small sample size. Fourth, the bivalent vaccine adapted to BA.5 is less effective against other variants, such as BA.2.75.2, BQ.1.1, and XBB.1 [31,32]. Therefore, we will need to determine whether similar results are obtained for emerging variants in the future.

Conclusion

In summary, this study showed the effectiveness of the BA.5 bivalent vaccine in alleviating symptoms in HCWs at high risk of infection who are involved in the diagnosis and treatment of infected patients. This finding emphasizes the importance of additional vaccinations to achieve an early return to work and prevent the loss of HCWs from illness. On the other hand, as the virus acquires mutations, it changes its antigenicity. Therefore, vaccine development is expected to progress against newly-emerging variants. Further analysis of the effect of vaccination on a wider range of regions and different variants is required in future research.

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.

Data availability

Data will be made available on request.

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Author contributions

Y.H. drafted the manuscript, visualized the data, and performed the statistical analyses. M.T. collected HCW's data including the vaccination status and infection history. H.S. organized and supervised the study. M.O. conceptualized the study design and revised the manuscript. All authors reviewed and approved the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100433.

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