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Vaccine Effect on Household Transmission of Omicron and Delta SARS-CoV-2 Variants

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ABSTRACT

Background: We evaluated the household secondary attack rate (SAR) of the omicron and delta severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, according to the vaccination status of the index case and household contacts; further, in vaccinated index cases, we evaluated the effect of the antibody levels on household transmission.
Methods: A prospective cross-sectional study of 92 index cases and 197 quarantined household contacts was performed. Tests for SARS-CoV-2 variant type and antibody level were conducted in index cases, and results of polymerase chain reaction tests (during the quarantine period) were collected from contacts. Association of antibody levels in vaccinated index cases and SAR was evaluated by multivariate regression analysis.
Results: The SAR was higher in households exposed to omicron variant (42%) than in those exposed to delta variant (27%) (P = 0.040). SAR was 35% and 23% for unvaccinated and vaccinated delta variant exposed contacts, respectively. SAR was 44% and 41% for unvaccinated and vaccinated omicron exposed contacts, respectively. Booster dose immunisation of contacts or vaccination of index cases reduced SAR of vaccinated omicron variant exposed contacts. In a model with adjustment, anti-receptor-binding domain antibody levels in vaccinated index cases were inversely correlated with household transmission of both delta and omicron variants. Neutralising antibody levels had a similar relationship.
Conclusion: Immunisation of household members may help to mitigate the current pandemic.

Keywords: COVID-19; Transmission; SARS-CoV-2; COVID-19 Vaccines; Antibody Level

INTRODUCTION

Several studies have shown that vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) effectively prevent infection, hospitalisation, and severe coronavirus disease 2019 (COVID-19) disease.[1-5] Vaccination also reduces onward

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Disclosure

The authors have no potential conflicts of interest to disclose.

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transmission by increasing immunity in vaccinated contacts or by lowering viral load in the upper respiratory tract of vaccinated indexes, thereby reducing infectiousness.[6-10]

Ever since the omicron variant was first reported in South Africa, it has been spreading rapidly worldwide.[11] With the recent explosive increase in the global number of SARS-CoV-2 cases caused by the omicron variant, there is a growing concern about the vaccine's effectiveness in reducing the transmission of the omicron variant. In South Korea, over 85% of the population has been vaccinated with a scheduled dose, and more than 50% have received the booster shot. Despite the vaccination of many people, the virus is spreading fast.[12,13] Multiple mutations of omicron enable the virus to evade the immunity elicited from vaccination, and waning immunity after completion of vaccination is estimated to contribute to the spread of the omicron variant.[14,15]

Previous studies demonstrated that the completion of vaccination could reduce the risk of transmission of alpha or delta variants.[8,9] However, limited data is available on the transmission of omicron according to the vaccination status in individuals who were infected with or exposed to the omicron variant. It is important to assess the extent of vaccine effectiveness in preventing omicron transmission to take measures to minimise the damage from the current pandemic.

Here, we performed a prospective cross-sectional study involving index cases admitted to a specific hospital and their household contacts. During the study period, quarantine for 7–14 days was mandatory for household contacts. They were required to undergo a reverse transcription-polymerase chain reaction (PCR) test at the entry to and exit from quarantine, according to national guidelines. This study aimed to determine the household transmission rates of omicron and delta variants according to the 1) vaccination status of contacts, 2) vaccination status of index cases, and 3) binding or neutralising antibody level of vaccinated index cases.

METHODS

Study design and population

This is a prospective cross-sectional study involving household contacts of SARS-CoV-2 confirmed patients admitted to Yongin Severance Hospital between December 11, 2021 and February 11, 2022. The study period was determined to assess the household transmission rates of delta and omicron variants; this period captured two different waves of COVID-19 (delta and omicron) in South Korea (**Supplementary Figs. 1** and **2**).

The patients were already included in another cohort study conducted by the authors.[16] Of the entire cohort, we recruited only those patients who had a history of contact with their household members during the specific period (between two days before and one day after the diagnosis) when SARS-CoV-2 could be transmitted.[17] We defined the patients as index cases if 1) they were the first household members with SARS-CoV-2 infections; and 2) each of them was the only one in the household who could have been a source of SARS-CoV-2 transmission to the other household members. Laboratory tests were performed to determine the factors that could affect transmission. First, PCR tests for SARS-CoV-2 variant typing were conducted using Novaplex SARS-CoV-2 Variants I, II, IV, VII assays (Seegene, Seoul, Korea). Second, we evaluated the humoral immunity of index cases by measuring

the antibody titres against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein using the Elecsys AntiSARS-CoV-2 S assay (Roche Diagnostics, Mannheim, Germany) and neutralising activities against SARS-CoV-2 using the cPass SARS-CoV-2 Neutralisation Antibody Detection Kit (GenScript, Piscataway, NJ, USA). Details about laboratory procedures are described in the **Supplementary Data 1**.

In South Korea, quarantine of all household members of SARS-CoV-2 confirmed cases was mandatory for a specific period, as described in the **Supplementary Data 1**. Therefore, we contacted the household members of our patients telephonically. Initial contacts were made 1–3 days after admission of the index cases to the hospital. Concise information about the purpose of study, duration of participation, and extent of data collected at initial contact was provided to them. Individuals who agreed to have a telephonic interview (for children, parents and caregivers could give consent) were included in the study. All household members underwent PCR tests for SARS-CoV-2 detection at the entry to and exit from quarantine according to national guidelines (they could also be re-tested when COVID-19-associated symptoms developed during the quarantine period). The results of the PCR test were shared by local public health centres through text messages. Household contacts who tested positive were considered to be infected with an identical SARS-CoV-2 variant as the index case.

Vaccination status was checked using the national COVID-19 vaccination reporting system, based on which we classified the subjects into the unvaccinated and vaccinated groups. The unvaccinated group included individuals who had never been vaccinated, those who had received one dose within the past three weeks, and those who were partially vaccinated (received one or two doses within the past two weeks). The vaccinated group included people who had received the second dose or a single dose of Janssen Ad26.COV2.S vaccine more than two weeks ago. The vaccinated group was further divided into booster-unvaccinated and booster-vaccinated; individuals were classified as the booster-vaccinated group if they received the booster shot before two weeks of enrolment.

Outcomes

The primary outcomes of this study were to evaluate the household transmission rate stratified by the 1) SARS-CoV-2 variant type (delta and omicron variants) and 2) vaccination status of household contacts. We also assessed the effect of the vaccination status of index cases and their vaccine-induced humoral immunity on household transmission.

Statistical analysis

Continuous variables were presented as the mean with standard deviation after the normality test, and the independent two-sample *t*-test were performed. Categorical variables were presented as the frequency with percentage, and χ^2 and Fisher's exact tests were appropriately used according to the expected frequency. The exact method was used for the confidence interval (CI) to calculate the secondary attack rate (SAR). We used the χ^2 or Fisher's exact test to compare the SAR between contacts exposed to the delta and omicron variants.

To evaluate the association between antibody levels in vaccinated index cases and household transmission, we transformed the antibody titres into a log scale. The probability of transmission was calculated using the logistic regression model. We refit the model for the probability of transmission using the variables that could affect the household transmission (meal with index, contact with index case ≥ 5/day, respiratory symptoms and immunocompromised status of index patients, and vaccination status of contacts).

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Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) for figures. Unless otherwise specified, the significance level was determined based on 0.05.

Ethics statement

This study was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Centre (9-2022-0013), and the study protocol adhered to the tenets of the Declaration of Helsinki. Written informed consent from all household contacts was waived by the board, considering its design.

RESULTS

Index cases and household contacts

A total of 187 SARS-CoV-2 patients were recruited for this study. Of those, 165 patients and 262 of their household members were eligible for inclusion. We excluded patients and members of households in which the primary case within the household was unknown and those who had a history of a previous infection. Finally, 77 household contacts of 41 index cases with delta variant infection and 120 household contacts of 51 index cases with omicron variant infection were included (**Fig. 1**).

Clinical characteristics of 92 index cases are described in **Supplementary Table 1**. Females were 51 (55.4%), and the mean age was 51.3 (± 19.2) years. Demographics, underlying comorbidity, symptoms at diagnosis, and time between diagnosis and admission were similar among index cases of delta and omicron variant infections. The time between symptom development and diagnosis was shorter in index patients with omicron variant infection than in those with delta variant infections ($P = 0.005$). There were more vaccinated persons infected with the omicron variant than with the delta variant ($P < 0.001$). Index cases with omicron variant infection had more household contacts than those with delta variant

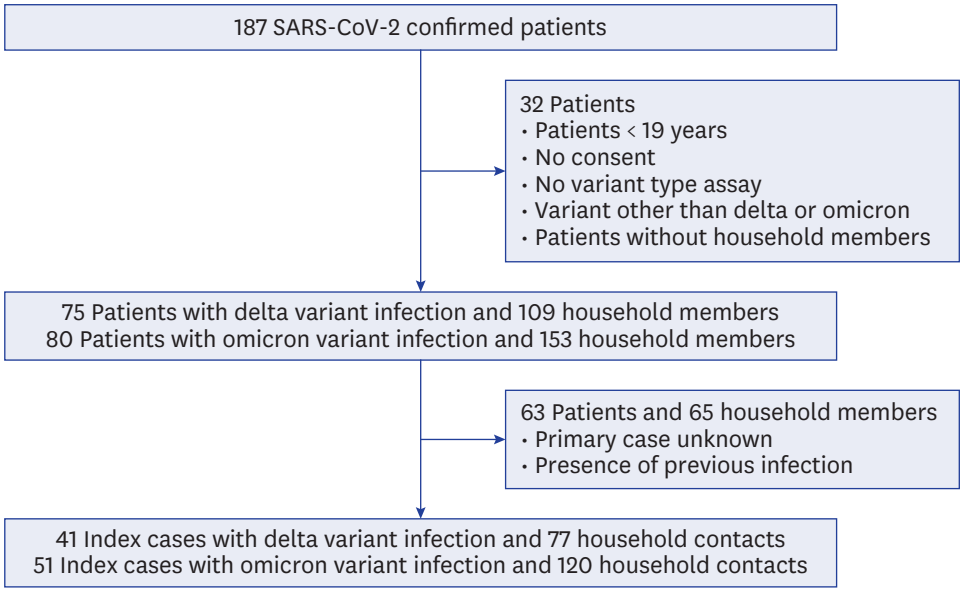

Fig. 1. Study flow chart.
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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infection (P = 0.036). The characteristics of unvaccinated index cases were similar to those of vaccinated index cases, except for fever at diagnosis; unvaccinated index cases complained of fever more frequently than vaccinated index cases (P = 0.046) (**Supplementary Table 2**).

Of 197 household contacts, 103 (52.3%) were female. The mean age was 41.4 (± 22.4) years, and most contacts had frequent and close contact with the index cases (**Supplementary Table 3**). Baseline characteristics were similar between the contacts of delta and omicron variant-infected index cases, except for booster vaccination status. There were more booster-vaccinated contacts of index cases with omicron variant infection than those with delta variant infection (P = 0.002). A total of 71 contacts had positive results at the PCR test performed during the quarantine period, for a SAR of 36% (95% CI, 29–43%). Respiratory symptoms at diagnosis were more common in contacts of index cases with omicron variant infection than in those with delta variant infection (P = 0.006). When contacts were classified according to the vaccination status, unvaccinated contacts were younger (P < 0.001) (**Supplementary Table 4**).

Like other countries, the National Immunization Program ensured that older adults and people with underlying comorbidities received booster doses prior to healthy populations in South Korea. As expected from the policy for booster doses, booster-unvaccinated individuals (including both index case and contact) were younger than booster-vaccinated individuals in the current study (P < 0.001) (**Supplementary Tables 5** and **6**).

Household transmission according to index cases and vaccination status of contacts

The link between index cases and household contacts according to their vaccination status is shown in **Fig. 2**. A total of 40, 27, and 10 contacts were linked with 20 unvaccinated index cases, 14 booster-unvaccinated index cases, and 7 booster-vaccinated index cases with delta variant infection, respectively. Among the contacts of index cases with omicron variant infection, 20, 65, and 35 contacts were exposed to 7 unvaccinated, 25 booster-unvaccinated, and 9 booster-vaccinated index cases, respectively.

The SAR was higher in contacts of index cases infected with the omicron variant (50 of 120; 42%, 95% CI. 33–51%) than in those infected with the delta variant (21 of 77; 27%, 95% CI, 18–39%) (P = 0.040) (**Table 1**). A total of 10 of 29 unvaccinated contacts of index cases with delta variant infection had positive results for the PCR test (35%, 95% CI, 18–54%), as did 11 of 48 vaccinated contacts (23%, 95% CI, 12–37%). Among the contacts of index cases with omicron variant infection, positive PCR results were observed in 15 of 34 unvaccinated contacts (44%, 95% CI, 27–62%) and 35 of 86 vaccinated contacts (41%. 95% CI, 30–52%). A significant difference in SAR was identified between the vaccinated contacts of index cases with delta and omicron variant infections (P = 0.038). In contrast to the decreased SAR in booster-vaccinated contacts exposed to the omicron variant (9 of 30; 30%, 95% CI, 15–49%), booster vaccination did not reduce the SAR in households exposed to the delta variant, although precise estimation was restricted due to the small sample size. The SAR was 30% (95% CI, 7–65%; 3 of 10).

Transmission rate was lowest in vaccinated contacts of vaccinated index cases (33 of 106; 31%, 95% CI, 28–66%) (**Table 2**). In households exposed to the omicron variant, the highest SAR was observed in unvaccinated contacts of vaccinated index cases (67%, 95% CI, 35–90%), and the lowest SAR in vaccinated contacts of vaccinated index cases (37%, 95% CI,

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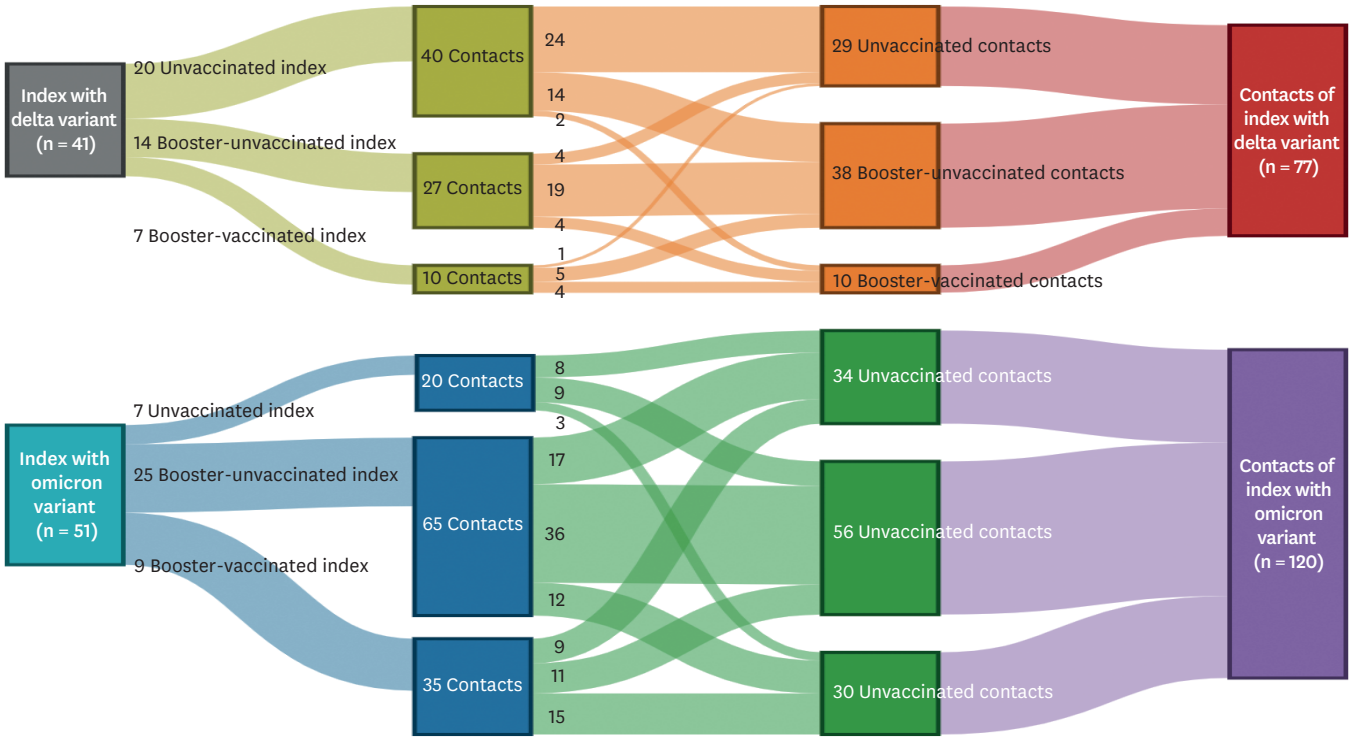

Fig. 2. The link between index cases and household contacts based on their vaccination status.

Table 1. The SAR among household contacts of index cases with delta and omicron variant infections according to vaccination status of contacts

Characteristics	Household exposed to delta variant			Household exposed to omicron variant			*P* value
	Total	PCR (+)	SAR (95% CI)	Total	PCR (+)	SAR (95% CI)	
All contacts	77	21	0.27 (0.18–0.39)	120	50	0.42 (0.33–0.51)	0.040*
Unvaccinated contacts	29	10	0.35 (0.18–0.54)	34	15	0.44 (0.27–0.62)	0.436
Vaccinated contacts	48	11	0.23 (0.12–0.37)	86	35	0.41 (0.3–0.52)	0.038*
Booster-vaccinated contacts	10	3	0.3 (0.07–0.65)	30	9	0.3 (0.15–0.49)	> 0.999[a]

SAR = secondary attack rate, PCR = polymerase chain reaction, CI = confidence interval.
[a]*P* value was calculated using the Fisher's exact test.
*$P < 0.05$.

Table 2. The SAR according to vaccination status of household contacts linked to that of index cases

Characteristics	Total			Household exposed to delta variant			Household exposed to omicron variant		
	Total	PCR (+)	SAR (95% CI)	Total	PCR (+)	SAR (95% CI)	Total	PCR (+)	SAR (95% CI)
Unvaccinated index cases-unvaccinated contacts	32	14	0.44 (0.26–0.62)	24	10	0.42 (0.22–0.63)	8	4	0.50 (0.16–0.84)
Unvaccinated index cases-vaccinated contacts	28	13	0.46 (0.28–0.66)	16	5	0.31 (0.11–0.59)	12	8	0.67 (0.35–0.9)
Vaccinated index cases-unvaccinated contacts	31	11	0.36 (0.19–0.55)	5	0	NA	26	11	0.42 (0.23–0.63)
Vaccinated index cases-vaccinated contacts	106	33	0.31 (0.28–0.66)	32	6	0.19 (0.07–0.36)	74	27	0.37 (0.26–0.49)

SAR = secondary attack rate, PCR = polymerase chain reaction, CI = confidence interval.

26–49%). In households exposed to the delta variant, unvaccinated contacts of unvaccinated index cases had the highest SAR (42%, 95% CI, 22–63%). Apart from vaccinated contacts of unvaccinated index cases with delta variant infection, which had a very small sample size for appropriate estimation of SAR, vaccinated contacts of vaccinated index cases with delta variant infection had the lowest SAR (19%, 95% CI, 7–36%).

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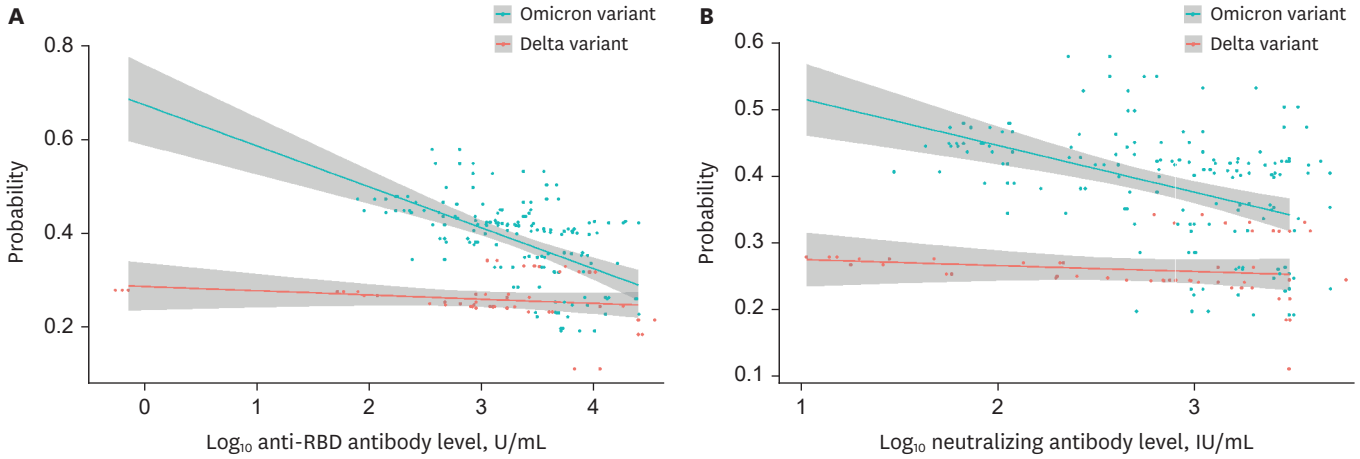

Fig. 3. The association of antibody levels in vaccinated index cases and household transmission. In a model with adjustment for factors that could affect the household transmission, the estimated probabilities of severe acute respiratory syndrome coronavirus 2 infection among 132 contacts according to the level of anti-RBD antibodies (**A**) and neutralising antibodies (**B**) of 62 index cases. Serum samples for antibody tests were collected within 7 days of symptom onset or diagnosis, whichever was earlier, in vaccinated index cases. Shaded areas indicate 95% confidence intervals.
RBD = receptor-binding domain.

The association of antibody levels in vaccinated index cases and household transmission

For this analysis, only vaccinated index cases who tested antibody levels within 7 days of symptom onset or diagnosis, whichever was earlier, were included. There were 62 vaccinated index cases and 132 contacts. In a model with adjustment, anti-RBD antibody levels in vaccinated index cases were inversely correlated with household transmission of both the delta (slope: −0.009, $P = 0.251$) and omicron variants (slope: −0.087, $P < 0.001$) (**Fig. 3**). A similar relationship was observed between the neutralising antibody levels in vaccinated index cases and household transmission (slope: −0.009, $P = 0.408$ for the delta variant; slope: −0.07, $P < 0.001$ for the omicron variant). When we performed sensitivity analyses using three-day and five-day thresholds for the period of antibody test, the results did not differ from the main analyses (**Supplementary Figs. 3** and **4**).

DISCUSSION

The spread of the omicron variant has caused a worldwide resurgence of COVID-19. With social distancing and masking outdoors, the household becomes one of the most important sites of SARS-CoV-2 transmission. The omicron variant had a higher SAR in households compared with the delta variant, regardless of the vaccination status of index cases and contacts. Although vaccination of household contacts decreased the SAR of the delta variant cases considerably, it was less effective in reducing onward transmission of the omicron variant. However, vaccination of index cases in addition to that of contacts could further decrease the household transmission of the omicron variant. The authors expect that the findings of the present study will enhance the understanding of SARS-CoV-2 transmission and help to minimise the damage from the current pandemic.

Studies in several other countries have found higher household SARs in households in which the index case was infected with the omicron variant than in those in which the index case was infected with the delta variant.[18-20] According to a meta-analysis of 135 studies with more than 1.3 million persons, conducted in 36 countries, the overall household SAR was

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42.7% and 29.7% in households in which the index case was infected with the omicron and delta variant, respectively, regardless of the vaccination status of the index case and the household contacts.[21] This finding is consistent with our study results. Index cases infected with the omicron variant had a shorter interval between symptom onset and diagnosis than those infected with the delta variant, which suggests that the virus exposure time was longer in households in which the index case was infected with the delta variant than in those in which the index case was infected with the omicron variant. However, we found that the omicron variant had a higher household SAR than the delta variant, especially among vaccinated contacts. The plausible explanation for the high SAR of the omicron variant is its stronger resistance to neutralisation by therapeutic antibodies than other variants.[22] As is well established, the omicron variant has a large number of mutations in spike protein, and this feature makes this variant resistant to neutralisation by COVID-19 or vaccine-induced antibodies.[15,22] Therefore, the vaccine effectiveness is significantly reduced in the omicron variant compared with that of other variants.[23,24] A recent UK study shows that the vaccine effectiveness against symptomatic COVID-19 caused by the omicron variant was approximately 30% lower than that of the delta variant.[23] Furthermore, the vaccine effectiveness against the omicron variant declines more significantly with time than that against the delta variant. The effectiveness against the omicron variant was measured to be less than 10% from 20 weeks after completion of two doses, while that against the delta variant was 50–60%.[23]

As the vaccination prevents household transmission of SARS-CoV-2 by protecting contacts from infection, the vaccine effectiveness against household SAR is less prominent in the omicron variant than in the delta variant.[25,26] Nonetheless, the booster dose is more effective in preventing symptomatic omicron variant infection than that of the primary dose; therefore, it can reduce household transmission of the omicron variant.[25-27] Furthermore, the vaccine effectiveness against symptomatic COVID-19 was similar among groups using the same type of booster vaccine, regardless of the type of primary course of vaccination.[23] People recruited in this study had received either one of the four types of the primary dose with ChAdOx1 nCov-19 (Oxford–AstraZeneca), BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), or Ad26.COV2.S (Johnson and Johnson). Among booster-vaccinated individuals, most of them selected BNT162b2 as the booster dose (data not shown). We showed the decreased household transmission among booster-vaccinated contacts in households exposed to the omicron variant. However, the booster dose of contacts did not reduce the household transmission by the delta variant in the cohort of this study. The discordant result might be due to the small sample size of booster-vaccinated contacts exposed to the delta variant. Further studies with a large population sample size are required to clarify this issue.

An increase in antibody titres, including anti-RBD antibodies and neutralising antibodies, in the vaccinated index cases was associated with a decrease in the estimated probability of household transmission. There is a possible explanation for this result in the present study. A higher vaccine-induced antibody level might affect a faster rate of viral load decline in vaccinated index cases, resulting in reduced transmission.[8,10,16] Our hypothesis should be verified by a study investigating the viral load kinetics of SARS-CoV-2 in vaccinated individuals according to antibody levels. We also found that the association between antibody levels in vaccinated index cases and transmission was more prominent in the omicron variant, although the entire probability of transmission was lower in the delta variant. This finding might result from attenuated vaccine effectiveness against the omicron variant. The omicron variant more efficiently evades neutralising antibodies elicited from the vaccine than

the delta variant.[15] Therefore, we postulate that higher antibody levels would be needed for omicron variant neutralisation and transmission prevention compared to lower levels needed for delta variant neutralisation. Increased immunity from boosters with mRNA vaccines or heterologous vaccination (e.g., ChAdOx1 nCov-19 followed by BNT162b2) could improve the vaccine effect on omicron variant neutralisation.[22,28,29] These data suggest that robust humoral immunity (largely by the booster vaccine) may reduce the household SAR.

There are several potential limitations in the present study. First, some significant findings related to household SAR might have been missed due to the relatively small sample size of participants. For example, exposure time to the index patient, mode or frequency of contact, composition of the household, including the presence of children within the household, were not considered when considering the reasons for variations in the household SAR in this study. Furthermore, meticulous analyses with adequately controlled possible confounders such as age and sex were not performed. These variables could affect the probability of household transmission. Second, there was a change in the quarantine policy of COVID-19 for household contacts during the study period. Due to the surge in omicron variant infection cases, the vaccinated individuals were moved out of the national quarantine management program for household contacts since February 7, 2022.[30] Therefore, some household contacts enrolled at the end of the study period might have been infected by other people, not by index cases. Third, recall bias might exist because some data were collected only by interview. To minimise this, we cross-checked the answers from index cases with those from the contacts. Finally, only hospitalised patients were recruited as index cases. In fact, hospitalised patients tended to present more severe clinical symptoms of COVID-19 or have a greater number of underlying comorbidities than non-hospitalised patients with COVID-19. Therefore, the results cannot be generalised to all patients with COVID-19.

In conclusion, although findings of this study indicate the decreased vaccine effectiveness on the transmission of the omicron variant in households, we suggest that enhancing the immunity of all household members through vaccination may help mitigate the current pandemic.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1

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Supplementary Table 1

Characteristics of index patients stratified by variant type

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Supplementary Table 2

Comparison of unvaccinated and vaccinated index patients

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Supplementary Table 3

Characteristics of household contacts stratified by variant type of index cases

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Supplementary Table 4

Comparison of unvaccinated and vaccinated household contacts

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Supplementary Table 5

Comparison of booster-unvaccinated and booster-vaccinated household contacts

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Supplementary Table 6

Comparison of booster-unvaccinated and booster-vaccinated index patients

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Supplementary Fig. 1

Confirmed SARS-CoV-2 infection cases in South Korea. Since the omicron variant was first confirmed on December 1, 2021, the number of confirmed SARS-CoV-2 infection cases has increased rapidly in South Korea.

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Supplementary Fig. 2

The proportion of the omicron variant identified by the surveillance system in South Korea. The omicron variant overtook the delta variant in domestic severe acute respiratory syndrome coronavirus 2 cases from the third week of January 2022, and its detection rate exceeded 90% in the first week of February 2022.

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Supplementary Fig. 3

The association of antibody levels in vaccinated index cases and household transmission (sensitivity analysis using 5-day threshold). In a model with an adjustment for factors that could affect the household transmission, the estimated probabilities of severe acute respiratory syndrome coronavirus 2 infection among 129 contacts according to the levels of anti-RBD antibodies (**A**) and neutralising antibodies (**B**) of 60 index cases. Serum samples for antibody tests were collected within 5 days of symptom onset or diagnosis, whichever was earlier, in vaccinated index cases. Shaded areas indicate 95% confidence intervals.

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Supplementary Fig. 4

The association of antibody levels in vaccinated index cases and household transmission (sensitivity analysis using 3-day threshold). In a model with an adjustment for factors that could affect the household transmission, the estimated probabilities of severe acute respiratory syndrome coronavirus 2 infection among 105 contacts according to the levels of anti-RBD antibodies (**A**) and neutralising antibodies (**B**) of 49 index cases. Serum samples for antibody tests were collected within 3 days of symptom onset or diagnosis, whichever was earlier, in vaccinated index cases. Shaded areas indicate 95% confidence intervals.

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