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Risk of transmission of COVID-19 from healthcare workers returning to work after a 5-day isolation, and kinetics of shedding of viable SARS-CoV-2 variant B.1.1.529 (Omicron)

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SUMMARY

Background: There have been limited data on the risk of onward transmission from individuals with Omicron variant infections who return to work after a 5-day isolation.

Aim: To evaluate the risk of transmission from healthcare workers (HCWs) with Omicron variant who returned to work after a 5-day isolation and the viable-virus shedding kinetics.

Methods: This investigation was performed in a tertiary care hospital, Seoul, South Korea. In a secondary transmission study, we retrospectively reviewed the data of HCWs confirmed as COVID-19 from March 14th to April 3rd, 2022 in units with five or more COVID-19-infected HCWs per week. In the viral shedding kinetics study, HCWs with Omicron variant infection who agreed with daily saliva sampling were enrolled between February and March, 2022.

Findings: Of the 248 HCWs who were diagnosed with COVID-19 within 5 days of the return of an infected HCW, 18 (7%) had contact with the returned HCW within 1–5 days after their return. Of these, nine (4%) had an epidemiologic link other than with the returning HCW, and nine (4%) had contact with the returning HCW, without any other epidemiologic link. In the study of the kinetics of virus shedding (N = 32), the median time from symptom onset to negative conversion of viable virus was four days (95% confidence interval: 3–5).

Conclusion: Our data suggest that the residual risk of virus transmission after 5 days of isolation following diagnosis or symptom onset is low.

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Introduction

After the surge in Omicron cases, the US Centers for Disease Control and Prevention (CDC) shortened the isolation period for people with COVID-19 from 10 days after symptom onset or positive viral test to 5 days, and recommended wearing a well-fitting mask for 5 days after the 5-day isolation period [1]. Likewise, on January 26th, 2022 the Korea Disease Control and Prevention Agency (KDCA) changed the isolation period for the general population with mild disease from 10 days to 7 days after positive viral test [2]. They also announced that the isolation period for healthcare workers (HCWs) confirmed with COVID-19 and up-to-date with vaccination could be reduced to 3–5 days, and these HCWs could work wearing well-fitted masks after they returned [3].

A previous study has reported that no contacts developed SARS-CoV-2 infection after exposure to a COVID-19 patient ≥6 days after the onset of that patient’s symptoms, but there was a worry concerning the risk of transmission from HCWs who return earlier to healthcare facilities [4]. In this study, we used two cohorts to determine, respectively, the risk of onward transmission from HCWs with Omicron variant infections who return to work after a 5-day isolation, and the kinetics of shedding of viable virus from HCWs infected with the Omicron variant.

Methods

This cohort study included the epidemiologic investigation study on the risk of transmission from HCWs who returned to work after a 5-day isolation (cohort 1) and a viral kinetics shedding study (cohort 2).

Cohort 1: risk of transmission from HCWs who return to work after a 5-day isolation

This study was performed in Asan Medical Center, a 2700-bed tertiary care hospital, in Seoul, South Korea. During the study period, HCWs were recommended to wear universal masking (KF94 (FFP2-equivalent mask)) and eye protection (goggle or faceshield) regardless of whether they were caring for COVID-19 patients. Patients with COVID-19 were isolated in the single room with or without negative pressure. In a study carried out in units with five or more COVID-19-infected HCWs per week from March 14th to April 3rd, 2022 when the Omicron subvariant BA.2 was dominant, we evaluated the number of HCWs subsequently confirmed with COVID-19 occurring 1–5 days after the return of HCWs who had been diagnosed as having COVID-19 and had completed a 5-day isolation [5]. During the study period, all HCWs with COVID-19 were isolated in their homes from the day of a positive viral test (day 1) to day 5, and they filled out a mobile epidemiologic investigation form which was sent to the infection control team in our hospital. We investigated symptoms at diagnosis, history of exposure to returned HCWs, households, and patients with COVID-19. Exposure to a COVID-19 case (close contact) was defined as being within 2 m of that case for >3 min regardless of mask-wearing by the index and contact or as being more distant than 2 m if the HCW and COVID-19 case had taken off their mask to eat or drink in a narrow space. Confirmed SARS-CoV-2 infection was defined as a positive reverse transcription–polymerase chain reaction (RT–PCR) result from a nasopharyngeal swab or from a rapid antigen test performed by a trained healthcare professional. HCWs with mild illness or asymptomatic infections and a positive viral test, and who had received third-dose vaccinations with mRNA vaccine, were allowed to return after a 5-day isolation. These HCWs received guidance on behaviour for 2 days after returning; they were advised to always wear well-fitting KF94 (FFP2-equivalent) masks, dine and relax in a separate space, minimize non-essential contact with colleagues, and restrict face-to-face meetings.

The institutional review board of Asan Medical Center evaluated and approved the medical, scientific, and ethical aspects of the study protocol concerning cohort 1 (2021–0024).

Cohort 2: kinetics of shedding of the omicron variant

The study enrolled HCWs with SARS-CoV-2 infections confirmed as due to the Omicron variant and who agreed to undergo daily saliva sampling at Asan Medical Center, in February and March 2022. All enrolled HCWs were instructed to submit daily saliva samples. The institutional review board of Asan Medical Center evaluated and approved the medical, scientific, and ethical aspects of the study protocol concerning cohort 2 (2020–0297).

Saliva sample collection and laboratory procedures

During the isolation period, all HCWs were instructed to place ≥2 mL of saliva into airtight containers. They were advised not to eat or brush their teeth for ≥30 min before providing a sample, and the samples were immediately stored in a freezer at −80°C. Viral RNA was extracted from respiratory specimens using a QiAamp viral RNA Mini kit (Qiagen Inc., Hilden, Germany) followed by manufacturer’s instruction. To detect subgenomic RNA, the reaction mixture included 0.1 μL of 200× enzyme mix, 4 μL of 5× master mix, 1000 nM of leader primer, 500 nM of each S and N gene reverse primer, 250 nM of S and N gene probes, and internal control primers and probe (Supplementary Table S1). In each mixture, 5 μL of extracted RNA or in-vitro-synthesized control RNA were added. PCR amplification was performed with a LightCycler 96 system (Roche, Basel, Switzerland) in the following conditions: reverse transcription at 50°C for 10 min, initial denaturation at 95°C for 5 min, 45 cycles of two-step amplification, denaturation at 95°C for 10 s and annealing and elongation at 60°C for 30 s, and final extension at 60°C for 5 min. Viral copy numbers were determined by plotting the cycle threshold (Ct) values against \( \log_{10} \) copies/reaction. The determination of positives and measurement of viral loads were made according to the SARS-CoV-2 N gene. The Omicron variants were detected using a PowerChek SARS-CoV-2 S-gene mutation detection kit Ver.3.0 (Kogenbiotech Co., Ltd, Seoul, South Korea).

Definitions

The Omicron variant was defined as detection of the N501Y, K417N, E484A substitutions in the spike protein. If the T547
substitution was also present, the strain was defined as the Omicron BA.2 subvariant. We categorized vaccinated patients into two subgroups: completion of the primary vaccine series (two-dose) and three-dose vaccinated [6].

**Statistical analysis**

Kaplan–Meier survival analysis was performed based on three different methods of detecting Omicron: genomic RNA PCR, subgenomic RNA PCR, and virus culture. The cut-off value for genomic RNA PCR and subgenomic RNA PCR was 2.6 virus copies/mL, the 95% limit of detection. For the sake of logical validity, samples identified as culture- or PCR-negative before obtaining a positive sample were neglected in the survival analysis, and the duration of virus shedding was taken to be the period up to the last day that a culture- or PCR-positive sample was obtained. All statistical analyses were done using R for statistics (version 4.1.1).

**Results**

**Cohort 1: risk of transmission from HCWs who returned to work after a 5-day isolation**

During the study period, 65 hospital units had five or more COVID-19-infected HCWs per week with a total of 736 HCWs with COVID-19. Their median age was 32 years (interquartile range (IQR): 26–41), 550 (75%) were female, and the median days from symptom onset to diagnosis of SARS-CoV-2 infection in the 635 symptomatic HCWs was 0 (IQR: 0–1). In addition, 248 of the HCWs were diagnosed with COVID-19 within 5 days of the return of previously infected HCWs (median age of 32 years (IQR: 27–42); 175 (71%) of them female). All the HCWs were asymptomatic or had mild illness, and none were immunocompromised. Of the 248 HCWs, 240 (97%) received three-dose vaccination, and 18 (7%) had contact with returned HCWs from 1 to 5 days after their return. The study flowchart is shown in Supplementary Figure S1. Of these 18, nine (4%) also had epidemiologic links other than with returned HCWs (exposure to other HCWs during their infectious period before diagnosis (N = 3), household contacts (N = 3), or exposure to patients with COVID-19 (N = 1)), while eight (3%) had contact with returned HCWs without any epidemiological link from the known COVID-19 patients without appropriate personal protective equipment in the hospital or social and family contacts through interview or epidemiological investigations while wearing KF94 (FFP2-equivalent) masks, and the remaining HCWs (0.4%) ate a meal with a returned HCW. Detailed information concerning the exposure of the latter nine HCWs is given in Table I.

**Cohort 2: kinetics of shedding of the omicron variant**

A total of 32 HCWs were enrolled. All had received at least two doses of COVID-19 vaccines, and had no underlying illnesses. Baseline characteristics are shown in Table II. The median age was 28 years (IQR: 26–33) and 23 (72%) were female. More than half the HCWs (62%) had mild COVID-19; the remaining 12 HCWs (38%) were asymptomatic.

Viable virus was detected in 12 (10%) of the 116 samples (Figure 1A, B, Supplementary Table S2, and Supplementary Figures S2, S3). The median time from symptom onset to negative conversion of viable virus was 4 days (95% confidence interval (CI): 3–5 days) (Figure 1C), while median times from symptom onset to negative conversion exceeded 8 days (95% CI: 7 to >9) and 5 days (95% CI: 5–7 days) for genomic RNA and subgenomic RNA, respectively (Figure 1C). Survival analysis showed that 16% of the HCWs shed viable virus on symptom onset day 6, and none on day 8 (Figure 1C, Supplementary Figure S2). Based on the date of diagnosis, the median clearance time for culture-based virus detection was 3 days (95% CI: 3–4), one day less than the duration of symptoms

| Patient no. | Day of contact with returned HCW (return day defined as day 0) | Mask worn during contact | Days from return day of index to day of diagnosis of exposed HCW |
|-------------|---------------------------------------------------------------|--------------------------|----------------------------------------------------------------|
| 1           | 0, 1                                                          | +                        | 3                                                               |
| 2           | 0                                                             | +                        | 1                                                               |
| 3           | 1                                                             | +                        | 1                                                               |
| 4           | 0, 1                                                          | +                        | 3                                                               |
| 5           | 0, 1                                                          | +                        | 2                                                               |
| 6           | 0                                                             | +                        | 3                                                               |
| 7           | 0                                                             | +                        | 3                                                               |
| 8           | 1                                                             | +                        | 3                                                               |
| 9           | 0                                                             | –                        | 1                                                               |

HCW, healthcare worker; IQR, interquartile range.

**Table I** Characteristics of HCWs exposed to returned HCWs between 1 and 5 days after their return (cohort 1)

| Variable                                      | No. of HCWs with SARS-CoV-2 infection |
|-----------------------------------------------|---------------------------------------|
| Age (years), median (IQR)                     | 28 (26–33)                            |
| Female sex                                    | 23 (72%)                              |
| Initial severity                              |                                       |
| Asymptomatic                                  | 12 (38%)                              |
| Mild                                          | 20 (62%)                              |
| Type of COVID-19 vaccine                      |                                       |
| 2 doses of ChAdOx-nCoV-19                     | 3 (9%)                                |
| 2 doses of mRNA-1273                         | 1 (3%)                                |
| 2 doses of ChAdOx-nCoV-19, followed by BNT162b2| 28 (88%)                              |
| Vaccination status                            |                                       |
| 2-dose                                        | 4 (12%)                               |
| 3-dose                                        | 28 (88%)                              |
| Subvariants                                   |                                       |
| Omicron BA.1                                  | 14 (44%)                              |
| Omicron BA.2                                  | 18 (56%)                              |
| Symptoms                                      |                                       |
| Systemic                                      | 23 (77%)                              |
| Gastrointestinal                              | 13 (43%)                              |
| Respiratory                                   | 30 (100%)                             |
| Sensory                                       | 10 (33%)                              |
| Time from last vaccination to infection (days)| 97 (82–108)a                          |

HCW, healthcare worker; IQR, interquartile range.

* Including one HCW who did not remember the date of vaccination.
Figure 1. Timing of presence or absence of viable SARS-CoV-2 on viral culture, and viral copy numbers for 116 serial samples obtained from 32 consecutive healthcare workers with COVID-19. Viral loads were determined copy numbers of the SARS-CoV-2 N gene. Each circle represents a sample obtained on the specified day. (A) Genomic RNA PCR viral copy number and viral culture results. (B) Subgenomic RNA PCR viral copy number and viral copy results. (C) Kaplan–Meier curve for viral clearance.
Supplementary Figure S2). Nineteen percent (6/32) of the HCWs were culture positive on day 5 from diagnosis (Supplementary Figure S2).

Discussion

In this study, most of the HCWs who were diagnosed with COVID-19 within 5 days of the day another HCW returned to work had no history of contact with the returned HCW, and only about 4% had epidemiologic links with the returned HCW without any other epidemiologic link. In our study of viral kinetics, the median time from symptom onset to negative conversion of viable virus was median 4 days (95% CI: 3–5), and 16% of HCWs shed viable virus at symptom onset day 6, and none by day 8. In addition, the previous epidemiologic study reporting that no contacts developed SARS-CoV-2 infection after exposure to a COVID-19 patient 5 days or more after the symptom onset supports a 5-day isolation with additional 5 days of high-quality mask wearing by CDC [4]. In this context, our data build on the current evidence supporting the current CDC recommendation that HCWs should wear a high-quality mask after their end of isolation and keep it until day 10, depending on the infection control practice and duty arrangement.

Replication-competent virus has been recovered up to 10 days after symptom onset in patients with mild illness [7–9]. However, the recovery of replication-competent virus does not always imply transmissibility, considering the dose required for successful infection. The concentration of SARS-CoV-2 RNA declines after onset of symptoms [10,11]. Previous epidemiologic study has measured an attack rate of 1% (22 cases from 1818 contacts; 1.0%; 95% CI: 0.6–1.6%) among close contacts whose exposure to index cases started within 5 days of the index cases’ symptom onset, whereas for those who were exposed later it was zero (0 cases from 852 contacts; 0%; 95% CI: 0–0.4%) [4]. Another cohort study also found a higher risk of transmission if exposure occurred between 2 and 3 days from symptom onset in the index patients [12]. During our study, which was performed during a huge Omicron outbreak, multiple exposures were possible, so it was difficult to identify those infections that occurred specifically via epidemiologic links between HCWs. Therefore, our figure for the risk of transmission after a 5-day isolation may be overestimated. In contrast, it is possible that the frequency of transmission through epidemiologic links between close contacts is an underestimate because of the higher frequency of airborne transmission of the Omicron variant than of historical strains [13]. Despite these limitations, our study adds to the evidence for a low risk of onward transmission by 6 days after index case symptom onset in the era dominated by Omicron.

To estimate the kinetics of viable viral shedding of the Omicron variants, we performed culture-based virus isolation and subgenomic RNA detections of spike (S) and nucleocapsid (N) proteins which are surrogate markers of viral infectivity. These two subgenomic genes were chosen because S protein is essential for viral entry to target cells and N protein is an RNA-binding protein critical for viral replication and is the most abundant subgenomic RNA in infected cells [14,15]. Recently, Chen et al. reported that ORF7b gene was the first undetectable subgenomic RNA; thus it may be the most sensitive surrogate marker for viral activity [15]. However, Chen et al. did not assess the relationship between the subgenomic RNA genes and virus culture-isolation. This study evaluated the risk of transmission of Omicron variants, which is highly associated with culturable virus. Phuphuakrat et al. reported that detection of subgenomic N RNA can be a marker for isolation period [16]. Also, our previous study demonstrated that the duration of positive subgenomic N or S RNA appeared to closely reflect the duration of positive culture-isolation [17].

We previously showed that the median duration of negative conversion of viral culture in young patients with the Delta variant was 5 days (95% CI: 3–6) after symptom onset [18]. Therefore, viable viral shedding of the Omicron variant appears to last 1 day less than with the Delta variant, although direct comparison between studies is difficult due to differences in vaccination status and symptom severity. Boucau et al. reported that the median time from diagnosis day to culture conversion was 5 days (IQR: 3–9) in the Omicron group and 4 days (IQR: 3–5) in the Delta group, although there was no significant difference in viable viral shedding between two groups [19]. However, it is difficult to draw a firm conclusion on this issue due to small sample size, so further studies are needed.

Our study has several limitations. First, it was a single-center study over a short period, and the number of study participants was small. Second, we did not perform whole genome sequencing, and the epidemiologic investigation was based on self-report. Moreover the study was performed during a huge epidemic; therefore we could not rule out other sources of transmission in the HCWs in cohort 1 who were designated as having only epidemiologic associations with returned HCWs. Furthermore, epidemiologic investigations might miss the unrecognized contacts from multiple sources, so the source of infection might not be definite. Third, we evaluated how much the HCWs wearing a high-quality mask who returned to work after a 5-day isolation contributed to the transmission to other HCWs in the workplace. Thus we did not evaluate the transmission from the HCWs to the patients. Finally, in order to reduce public confusion over the isolation period in asymptomatic individuals with SARS-CoV-2 infection, the South Korean government has recommended that the reference day (day 1) for calculating the isolation period should be the day of diagnosis, because of the difficulty of defining the day of symptom onset. Most HCWs were diagnosed on the day of symptom onset or 1 day later, so the 5-day isolation period from diagnosis is essentially the same as the 5 days from symptom onset (with day 0 as symptom onset day), as currently recommended by the CDC.

In conclusion, shedding of viable Omicron virus lasted a median of 4 days from symptom onset, and less than 5% of the cases occurring over 5-day periods could have involved transmission from HCWs returning after 5 days of isolation. Therefore, it appears that the residual risk of transmission of Omicron by 5 days after diagnosis is low.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2022.11.012.

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