Nosocomial severe acute respiratory coronavirus virus 2 (SARS-CoV-2) transmission arising from a case of N-gene dropout on reverse-transcription polymerase chain reaction (RT-PCR) testing

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To the Editor—During the coronavirus-disease-2019 (COVID-19) pandemic, in-hospital surveillance via serial severe acute respiratory coronavirus virus 2 (SARS-CoV-2) testing has repeatedly demonstrated its utility in early detection, isolation, and interruption of nosocomial transmission.1 However, analytical sensitivity of real-time, reverse-transcriptase, polymerase chain reaction (rRT-PCR) testing for SARS-CoV-2 is crucial in ensuring accurate results and early detection of COVID-19 cases and, thus, to mitigate nosocomial COVID-19 outbreaks. The emergence of SARS-CoV-2 variants has been demonstrated to negatively affect analytical sensitivity of rRT-PCR assays. For instance, failure of the N-gene assay has occurred with certain SARS-CoV-2 variants.2

N-gene point mutations have been reported in the literature; however, analytical sensitivity of rRT-PCR assays. For instance, failure of the N-gene assay has occurred with certain SARS-CoV-2 variants.2 N-gene point mutations have been reported in the literature, resulting in cases of diagnostic escapes.3 To date, however, no confirmed case of nosocomial transmission arising from N-gene dropout has been reported in the literature. We highlight here a case of nosocomial SARS-CoV-2 transmission arising from a case of N-gene dropout, which illustrates the importance of proper interpretation when discrepant results are encountered on different gene-targets utilized in SARS-CoV-2 diagnostic testing. This study was conducted as part of an outbreak investigation, and ethics approval was not required under our institutional review board guidelines.

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to isolation. Also, 5 other patients in the shared cubicle were exposed. The fully vaccinated patient in the adjacent bed (patient B), with an exposure time of 12 hours, subsequently tested positive on day 4 after exposure (ie, day 14 of admission), with a similar pattern of N-gene dropout on testing (Fig. 1). Previously, our institution reported 2 cases of N-gene dropout arising from a point mutation in G29195T; however, these cases were submitted from an outpatient ambulatory clinic in October 2021 and did not overlap with this cluster of cases in space or time.5

The nasopharyngeal swab samples of patient A and patient B were subjected to whole-genome sequence analysis. A point mutation, C29200T, was detected in the consensus sequences of both samples. G29200T is a synonymous mutation that was previously reported to cause N-gene detection failure.4 Whole-genome similarity analysis was performed using previously published workflows utilizing the ARTIC protocol on Oxford Nanopore miniION sequencers.8 The SARS-CoV-2 genomes from patient A and patient B were identical (0 SNP difference). The identical genomes and epidemiological link support the hypothesis of nosocomial transmission. No additional cases of N-gene dropout were detected amongst inpatients or healthcare workers (HCWs) despite intensive surveillance including weekly, rostered, routine testing.7 This result is likely due to enhanced infection prevention measures in place during the study period, including universal N95 usage by HCWs and high vaccination-uptake rates (∼80%) among inpatients and HCWs.9

The potential of nosocomial SARS-CoV-2 transmission from cases of N-gene dropout is not purely theoretical. Clinicians and diagnostic laboratories need to be vigilant for such cases because emergence of novel SARS-CoV-2 variants with the potential to escape existing diagnostic tests remains inevitable. Test interpretation is critical. According to the manufacturer instructions for the Cepheid GeneXpert-Xpert-Xpress test kit, cases with discrepant results (negative on the N2-gene target but positive on the E-gene target) should have been reported as presumptively positive with a recommendation for repeated testing.10 Had this interpretation been used, the patient would have been isolated upon admission and the additional period of transmission risk would not have occurred, despite the N-gene dropout. SARS-CoV-2 diagnostic assays should ideally be based on ≥2 gene targets, and healthcare institutions need to maintain a robust molecular surveillance system to detect emergent diagnostic escapes. Reliable diagnostic detection of SARS-CoV-2 is crucial for containment of COVID-19 and prevention of spread within healthcare facilities.

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References

Lack of severe acute respiratory coronavirus virus 2 (SARS-CoV-2) transmission from a healthcare worker to a cohort of immunosuppressed patients during the SARS-CoV-2 omicron variant surge, California, 2022

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To the Editor—During the coronavirus disease 2019 (COVID-19) surge in January 2022 caused by the severe acute respiratory coronavirus virus 2 (SARS-CoV-2) o (omicron) variant, more infections among healthcare workers (HCWs) were documented than at any other point in the COVID-19 pandemic. Transmission from infected HCWs to other HCWs and patients is a noteworthy concern. The risk of an HCW acquiring COVID-19 from another HCW is reportedly 3 times higher than contracting it from patients.1 Given that not all infections are detected, it is critically important that during surges, all infection controls (administrative, engineering, and personal protective equipment [PPE]) are optimized to protect patients and HCW colleagues.2 We report a case in which a highly infectious HCW working with profoundly immunosuppressed patients did not transmit SARS-CoV-2 to patients despite multiple close interactions. Our data analysis was approved under the Stanford University Institutional Review Board (IRB) through expedited review.

The index HCW was vaccinated with BNT162b2 in December 2020 and January 2021 and received a booster vaccination in October 2021. The HCW was in their usual state of health and had a negative routine screening rtPCR anterior nares swab (self-collected; Color Health, Inc) on Monday of the week of infection; medical school personnel were required to test weekly regardless of symptoms or exposure history. The following day, the HCW felt mild fatigue in the morning, which resolved soon after awakening. The HCW proceeded to work and performed physical exams on 7 patients over the course of the day. The patients were moderately to severely immunocompromised. All but 1 patient had undergone solid-organ transplantation, and 1 patient had undergone heart transplantation on day 1 following the interaction with the infectious HCW. The HCW began to feel symptoms while on the wards, including severe fatigue, diffuse sweating, and chills, which prompted the HCW to leave the wards and proceed with rapid rtPCR testing via a nasopharyngeal sample. The HCW went home to isolate. The rtPCR returned positive within 2 hours (cycle threshold value [CT], 15.9). The HCW had also examined 7 patients the day before symptom onset. Of these patients, 3 were examined both days. The HCW worked closely with another HCW for ∼8 hours the day before onset of symptoms and for ∼6 hours on the day of symptom onset.

The index HCW reported wearing an N95 respirator during all patient encounters and during all other activities during the workday. Both HCWs wore fit-tested N95 respirators in the presence of patients, 3 were examined both days. The HCW worked closely with another HCW for ∼8 hours the day before onset of symptoms and for ∼6 hours on the day of symptom onset.

The index HCW reported wearing an N95 respirator during all patient encounters and during all other activities during the workday. Both HCWs wore fit-tested N95 respirators in the presence of patients. Patients were not masked during encounters, except one who was wearing both an N95 respirator and a surgical mask. Patient encounters were reported as being 2 m distant but <15 minutes in duration. None of the patients were in airborne isolation because they had not reported any recent COVID-19 symptoms or known exposures. Although the index HCW’s sample was not subjected to whole-genome sequencing, most samples were SARS-CoV-2 omicron variant during this period. We tested all patients except for 2 who had been discharged. All available SARS-CoV-2 tests returned negative (Table 1). The second HCW who was exposed also tested negative on multiple follow-up tests.

This report is important for several reasons. First, the HCW had a negative weekly screening test on Monday with only mild fatigue that resolved upon awakening on the next day. This type of symptomatology would not be accurately picked up on a screening symptom survey given high frequency of fatigue among HCWs at baseline.3 Second, the patients themselves were not adequately masked, which emphasizes the need for HCWs themselves to wear high-quality masks as PPE and source control, such as N95 respirators. Third, these patients were immunocompromised, putting them at higher risk of severe infection and death (as high as 13%–20%) if they were to contract SARS-CoV-2.4,5

We hypothesize many possible reasons why the index case did not transmit to patients or other HCWs. First, the index case was wearing an N95 respirator, which may have provided superior source control compared to surgical masks.6 Both HCWs who were in close contact for 2 days were wearing N95 respirators during all encounters. Some have argued that the universal use of N95 respirators during COVID-19 surges is an important measure to reduce in-hospital transmission.1,2

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