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**SARS-CoV-2 Exposure Investigations Using Genomic Sequencing Among Healthcare Workers and Patients in A Large Academic Center**

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Abstract

SARS-CoV-2 transmissions among healthcare personnel (HCP) and hospitalized patients are challenging to confirm. Investigation of infected persons often reveals multiple potential risk factors for viral acquisition. We combined exposure investigation with genomic analysis confirming two hospital-based clusters. Prolonged close contact with unmasked, unrecognized infectious, individuals was a common risk.
Background

Implementation of infection prevention policies reduces the risk of SARS-CoV-2 transmission between patients and healthcare personnel (HCP). While a cross-sectional study of US HCP found an association between community exposure and SARS-CoV-2 seropositivity, no such association was found for hospital workplace factors, including contact with patients with known COVID-19. While hospital transmissions are likely infrequent, in the absence of genomic sequencing, exposure investigations alone may misclassify HCP or patient co- incidental temporally related infections as the same transmission cluster, or conversely, transmissions may go unrecognized if exposure investigations do not reveal a common exposure between positive persons.

Here we describe two clusters of cases in which genomic sequencing of SARS-CoV-2 isolates and epidemiological links clarified transmission events.

Methods

Between November 2020 and February 2021 at The Johns Hopkins Hospital (JHH), a 1095 bed academic tertiary center in Baltimore, MD, the following infection prevention precautions were followed: 1) respirator, eye protection, gown, gloves for patients with known, or suspected, COVID-19; 2) respirator, eye protection, gown, gloves, for all patients undergoing aerosol-generating procedures; and 3) surgical mask and face shield for all other patients. Patients were encouraged to mask during clinical interactions and underwent SARS-CoV-2 testing at hospital admission, pre-procedure and from December 17th, 2020 weekly intervals while in-patient. Contact tracing was conducted for all HCP and exposure investigations were performed for inpatients with an unexpected, positive SARS-CoV-2 test result.

If an exposure investigation suggested in-hospital transmission, available isolates underwent genomic sequencing, using previously published methods. Phylogenetic trees were created with ClustalW2.1, NJ Clustering algorithm, and visualized with interactive Tree of Life (ITOL).
Results

2% of patients had a negative admission test followed by a positive surveillance test. 2 clusters were confirmed as linked through sequencing and are included below.

Cluster One
Patient A was admitted with end-stage liver disease complications, undergoing transplant evaluation, and had negative SARS-CoV-2 tests one day pre-admission, and on hospital days 8 and 12 (routine asymptomatic testing). Hospital day 23 the patient developed dyspnea and routine pre-procedure test day 24 was positive with a cycle threshold (Ct) value of 12.

Patient A, their visitor, and five HCP with prolonged close contact with Patient A, developed symptomatic SARS-CoV-2 infection within 1-2 days of each other (Figure 1). Genomic sequencing of three isolates from patient A, and two HCP, matched to lineage B.1.2 and showed a characteristic P2685T substitution in ORF1a corresponding to P1867T in viral protease NSP3 (Figure 2). There were no other samples with that NSP3 substitution from over 5,000 samples sequenced at the JHH laboratory, and no complete genotypic matches in over 2.1 million genomes on GISAID, at that time. The other three HCPs, and the visitor, underwent testing at outside laboratories and their isolates were unavailable for sequencing.

Regarding potential transmission risks, while in patient A’s room, the five HCP reported consistently wearing masks, however, patient A and the visitor did not; two of the HCP did not consistently wear eye protection. Four HCP noted socializing unmasked in the community. The patient had high dependency nursing care.

Cluster Two
Patient B was admitted with delirium and joint pain with a history of neurogenic bladder and recurrent urinary tract infections (UTIs) with multidrug-resistant organisms (MDROs). His admission SARS-CoV-2 test was negative. He was treated for a suspected UTI and placed on contact precautions for the MDRO. On day 8 of admission, his routine weekly asymptomatic SARS-CoV-2 test was positive (Ct value 21). On focused questioning, he endorsed a mild cough and noted that a household contact, who had not visited patient B in hospital, had also been diagnosed with symptomatic COVID-19.

Three HCP, who cared for patient B during the first seven days of admission, developed symptomatic COVID-19 within two days of each other (Figure 1). The three HCP and patient
B’s isolates were highly similar (Figure 2); lineage B.1.2, with a I2663L substitution within ORF1a, corresponding to I1845L in viral protease NSP3. This I1845L substitution of NSP3 was not in any other samples sequenced at the JHH laboratory, and as of July 2021, in less than 70 samples in GISAID.

The HCP caring for patient B reported consistently wearing face masks and eye protection while in his room, although patient B did not wear a face mask. One HCP noted socializing unmasked in the community. Two HCP had prolonged contact with Patient B while providing high dependency nursing care. One was partially vaccinated.

Discussion

Using findings from exposure investigations coupled with genomic sequencing, we identified two hospital-related clusters of SARS-CoV-2 infections when the 7-day moving average was greater than 25 per 100K in Maryland.

For Cluster One, exposure investigation linked seven COVID-19 cases, three of these were most likely true transmissions, confirmed by genomic sequencing; four samples were unavailable for sequencing. Given the strong epidemiological risk factors, including close contact of the visitor and HCP with Patient A, it is probable that all seven are part of the same transmission pathway, although the identification of the index case and onward transmission pathways are unclear given close timing of symptom onset of all involved.

Cluster Two linked 4 cases; patient B and three HCP. Patient B was likely the index case, having acquired COVID-19 either from his household member or other community exposure prior to admission. It is unclear if patient B’s symptoms on admission were caused by SARS-CoV-2 infection, with a false negative admission SARS-CoV-2 test, or if the admitting symptoms were caused by another etiology, and it was too early in the incubation period for a positive test. Three HCP were likely subsequently infected.

SARS-CoV-2 transmissions are more likely when there is a constellation of factors conducive to spread. Both clusters involved patients who were unmasked while HCP were providing care during their hospital stay. For patient A, this unmasking may have contributed to both acquiring COVID-19, and transmitting onward to HCP caring for him. For patient B, who was likely in a highly infectious pre-symptomatic phase, lack of masking contributed to onward spread. This
reinforces the importance of patient masking to protect themselves and HCP. Both patients had high dependency needs, particularly nursing care, and therefore HCP had close interactions of lengthy duration while caring for them. These findings are consistent with previous studies that found increasing risk as length of time in the same room as a positive index case increases\(^8,9\), and that risk is increased further if either person is unmasked.\(^{10}\)

Limitations to our findings include inability to prove transmission directionality, including if transmissions occurred between HCP, rather than from patients. Not all samples were available for genomic sequencing, so, despite strong epidemiology supporting evidence, we could not confirm all cases were related, particularly when high community incidence. This study was pre-Delta and before widespread vaccinations. Exposure investigation is inherently subject to recall bias, and HCP may have over- or under-estimated their personal protective equipment (PPE) compliance. Asymptomatic employees or employees not identified through exposure investigations may not have been included in these clusters. In conclusion, SARS-CoV-2 transmission between HCP and patients is infrequent, but exposure investigations coupled with genomic sequencing can be informative. Risk factors may include prolonged close contact with unmasked patients during high dependency care tasks.
References


**Figure 1:** COVID-19 clusters involving healthcare workers, patients and visitor: Relative timing of symptom onset, testing and viral burden
Cluster Two

Patient admitted for presumed urinary tract infection. Risk factors: Unidentified positive household member.

**Lineage B.1.2, Clade 20G**
- Ct 21, tested positive Day 8

HCW  Risk Factors: No outside risk factors, took care of patient.

**Lineage B.1.2, Clade 20G**
- Ct 21, tested positive 11 days after patient’s symptom onset

HCW  Risk Factors: Outside risk factors, took care of patient.

**Lineage B.1.2, Clade 20G**
- Ct 14, tested positive 8 days after patient’s symptom onset

HCW  Risk Factors: Outside risk factors, took care of patient.

**Lineage B.1.2, Clade 20G**
- Ct 16, tested positive 9 days after patient’s symptom onset

**Figure 2:** Phylogenetic representation of relationships of sequences from Cluster One (Red) and Cluster Two (Blue) to all sequences from Clade 20G at JHH.