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MAJOR ARTICLE

Genomic Investigation to Identify Sources of Severe Acute Respiratory Syndrome Coronavirus 2 Infection Among Healthcare Personnel in an Acute Care Hospital

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Background. Identifying the source of healthcare personnel (HCP) coronavirus disease 2019 (COVID-19) is important to guide occupational safety efforts. We used a combined whole genome sequencing (WGS) and epidemiologic approach to investigate the source of HCP COVID-19 at a tertiary-care center early in the COVID-19 pandemic.

Methods. Remnant nasopharyngeal swab samples from HCP and patients with polymerase chain reaction–proven COVID-19 from a period with complete sample retention (14 March 2020 to 10 April 2020) at Rush University Medical Center in Chicago, Illinois, underwent viral RNA extraction and WGS. Genomes with >90% coverage underwent cluster detection using a 2 single-nucleotide variant genetic distance cutoff. Genomic clusters were evaluated for epidemiologic linkages, with strong linkages defined by evidence of time/location overlap.

Results. We analyzed 1031 sequences, identifying 49 clusters that included ≥1 HCP (265 patients, 115 HCP). Most HCP infections were not healthcare associated (88/115 [76.5%]). We did not identify any strong epidemiologic linkages for patient-to-HCP transmission. Thirteen HCP cases (11.3%) were attributed to a potential patient source (weak evidence involving nonclinical staff that lacked location data to prove or disprove contact with patients in same cluster). Fourteen HCP cases (12.2%) were attributed to HCP source (11 with strong evidence).

Conclusions. Using genomic and epidemiologic data, we found that most HCP severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections were not healthcare associated. We did not find strong evidence of patient-to-HCP transmission of SARS-CoV-2.

Keywords. COVID-19; SARS-CoV-2; acute care hospital; healthcare personnel; whole genome sequencing.

Coronavirus disease 2019 (COVID-19) among healthcare personnel (HCP) has negative impacts on individual health, on the healthcare system (eg, staffing shortages leading to decreased quality of care), and in the community (eg, spread to household contacts). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections among HCP have been widely reported [1–5]. Investigation of nosocomial SARS-CoV-2 clusters is often complex, revealing multiple possible sources of acquisition. Outbreak investigation for HCP infection using contact tracing alone may be inadequate when COVID-19 is widespread in the community. Improved understanding of the sources of HCP COVID-19 would allow hospitals to prioritize efforts to prevent HCP infections.

We observed that some HCP in our facility were becoming sick with COVID-19 during the initial SARS-CoV-2 surge but the source of their infections was unclear. Our study period included the acceleration phase and peak of the first wave, with citywide incident COVID-19 hospitalizations reaching up to 200 per day [6, 7]. We were concerned that HCP may have been acquiring SARS-CoV-2 during encounters with infected patients. Most SARS-CoV-2 outbreak investigations in the healthcare setting start with evaluation for epidemiologic linkages, followed by whole genome sequencing (WGS), if available, to support likely transmission. We suspected that this approach may overestimate nosocomial spread when SARS-CoV-2 genetic diversity is low and may also miss transmission events that are not easily identified by epidemiologic data. In this study, we screened for nosocomial SARS-CoV-2 transmission events using a "sequence first" approach [8] to remove bias in the identification of putative transmission pairs. We hypothesized that HCP may be acquiring

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SARS-CoV-2 from patients. Remnant patient and HCP SARS-CoV-2 nasopharyngeal swab samples underwent WGS to identify possible transmission events involving HCP during the first wave of the pandemic in Chicago, Illinois. Genomic clusters were then evaluated for epidemiologic linkages to support potential nosocomial transmission.

METHODS

Study Design

We conducted an analysis of remnant nasopharyngeal SARS-CoV-2 samples from 14 March 2020 to 10 April 2020 (28 days) at Rush University Medical Center (RUMC), a 676-bed tertiary-care medical center in Chicago, Illinois, during the exponential growth phase of the first COVID-19 wave. Remnant viral transport medium from nasopharyngeal swab samples from all SARS-CoV-2 polymerase chain reaction (PCR)–positive specimens from symptomatic individuals (including HCP and patients) presenting to RUMC for testing were available for analysis; asymptomatic persons were not tested during this time. HCP was defined as any hospital staff member, including both clinical and nonclinical personnel. The circulating SARS-CoV-2 lineage was the Wuhan lineage (including Nextclade [9] clades 20A, B, C, G) with the d614G mutation. Samples were processed in the RUMC Clinical Microbiology laboratory and tested for SARS-CoV-2 virus by real-time reverse-transcription PCR (RT-PCR; CDC 2019-nCoV real-time RT-PCR assay or RealTime SARS-CoV-2 assay [Abbott Molecular, Des Plaines, Illinois]) [10]. Relevant patient and HCP data were collected from the electronic medical record (EMR). These records included date of positive SARS-CoV-2 diagnostic test, patient locations within the hospital, HCP job category, and assigned department. To ascertain HCP locations and patient-related interactions, we obtained time and location-stamped records of HCP-driven documentation within the EMR, including charting of medical history, writing notes, recording vitals, and cosigning notes and/or orders.

SARS CoV-2 Library Preparation, Sequencing, Genome Assembly, and Cluster Identification

Viral RNA was extracted from all SARS-CoV-2–positive remnant nasopharyngeal swab samples in M4RT viral transport medium (Remel) using the Quick-RNA Viral kit according to manufacturer's instructions (Zymo Research, Irvine, California). Complementary DNA was synthesized using SuperScript IV First-Strand Synthesis System (Thermo Fisher Scientific, Waltham, Massachusetts), with an increased reverse-transcription incubation step of 50°C for 30 minutes and 55°C for 15 minutes, and without RNase H treatment. SARS-CoV-2 whole genomes were amplified, and libraries were prepared using Swift Normalase Amplicon Panels for SARS-CoV-2 (Swift Biosciences, Ann Arbor, Michigan) according to manufacturer's instructions, using the modified multiplex PCR protocol for low viral input samples. Libraries were quality checked via TapeStation (Agilent Technologies, Santa Clara, California), quantified via real-time PCR, and then sequenced via NovaSeq (Illumina, San Diego, California), multiplexing a maximum of 384 samples.

Sequence-specific amplicon primer trimming and quality trimming were performed on demultiplexed sequencing reads using BBDuk2 [11], discarding short reads <75 bp in length and trimming ends with a Q score <30. Trimmed reads were mapped to a reference sequence (GenBank accession MN908947) using Geneious Prime [12] software, iterating 3 times. Consensus genomes were generated in Geneious Prime [12] using the highest quality consensus setting and requiring a minimum read coverage of 5. Genomes with >90% genome coverage were selected for downstream analysis. To enhance confidence in genomic linkages, the following genomic regions were masked: (1) the first and last 20 bp of the genome; (2) regions with high variant density (likely due to incomplete primer and/or quality trimming; manual investigation confirmed that these were sequence artefacts and were often found near gaps in coverage), defined as 5 or more differences from the reference genome in a 10 bp window; and (3) regions proximate to poly-N tracts, defined as being within 5 bp from a poly-N tract of 10 N's or longer. Sequences were submitted to GISAID [13] (Supplementary Table 1).

Cluster detection was performed by grouping together individuals where all members of a cluster were within a 2-variant genetic distance cutoff. These 2-variant clusters were detected by performing complete linkage agglomerative hierarchical clustering and splitting neighboring clusters if any pair of isolates between the clusters had >2 variants. We then analyzed clusters that contained at least 1 HCP.

Epidemiologic Analysis of Genomic Clusters

Clusters identified by initial genomic analysis were independently evaluated by 2 infectious diseases physicians with infection control expertise to categorize sources of infection among HCP. A third infectious diseases physician acted as an adjudicator if the initial reviewers did not agree. The date of the first positive SARS-CoV-2 test and EMR data were used to evaluate for location and time overlap between individuals in a genomic cluster. The infectious exposure period was defined as up to 14 days prior to test positivity, to account for possible SARS-CoV-2 incubation time. Approach to evaluation is outlined in Figure 1. The source of each HCP infection was classified into 1 of 3 categories: (1) healthcare associated: patient source (further subclassified as strong or weak linkage); (2) healthcare associated: HCP source (further subclassified as strong or weak linkage); and (3) not healthcare associated. Linkages were classified as *strong* if (1) there was documentation in the EMR of a contact between the HCP and a patient in the genomic cluster, or if (2) the HCP worked on the same

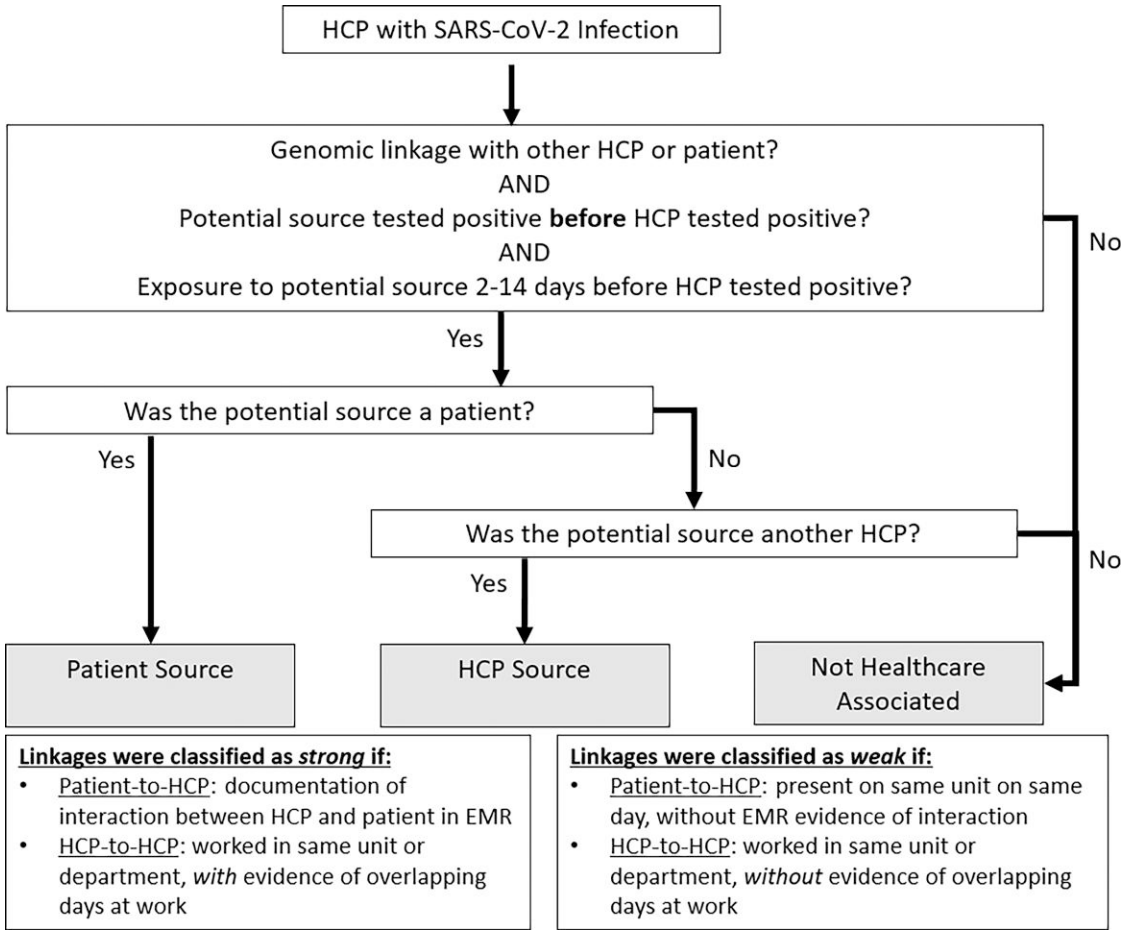

Figure 1. Epidemiologic criteria for classification of source of severe acute respiratory syndrome coronavirus 2 infections in healthcare personnel. Decision tree to judge likely epidemiologic source of healthcare personnel coronavirus disease 2019. Abbreviations: EMR, electronic medical record; HCP, healthcare personnel; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

unit on the same day with another HCP in the genomic cluster. Linkages were classified as *weak* if (1) the HCP and a patient in the same genomic cluster were on the same unit on the same day, without EMR evidence of interaction, or if (2) the HCP worked in the same unit or department as another HCP in the genomic cluster, without evidence of overlapping days at work. Being present in the same location on the same day was considered strong evidence of exposure for HCP because of our observations that HCPs congregated together in common areas such as breakrooms. This criterion was considered weak evidence for interactions between HCP and patients because HCP did not usually interact with every patient in a location. Patient was prioritized above another HCP when assessing the likely source of HCP infection. Agreement between the 2 reviewer assessments was calculated by Cohen kappa coefficient (κ).

Infection Control Measures During the Study Period

Symptom-based patient and HCP testing for COVID-19 occurred during the study period; routine asymptomatic testing for patients and HCP was not performed. All admitted SARS-CoV-2–positive patients were cared for in single-occupancy rooms. HCP were required to perform daily symptom self-monitoring and underwent daily temperature checks prior to facility entry. HCP providing direct patient care were fully trained in use of appropriate personal protective equipment (PPE) and there was adequate PPE availability at our hospital for HCP to follow prevailing PPE guidance. SARS-CoV-2 testing was available to any symptomatic HCP through the employee health department; during the study period, HCP had limited community (nonhospital) testing options.

PPE use recommendations evolved with local and national public health guidance. Hand hygiene, gowns, and gloves were required for care of patients with COVID-19 throughout the study period, and N95 respirators/equivalent were required for all aerosol-generating procedures. Patients with confirmed COVID-19 were encouraged to mask during healthcare interactions. For routine care of patients with COVID-19, HCP respiratory protection requirements evolved during the study

period: N95 respirator or equivalent (study days 1–5), medical facemask only (study days 6–19), and either medical facemask or N95 respirator/equivalent (study days 20–28). HCP universal face masking (including both clinical and nonclinical settings) was required beginning on day 20 of the study period.

Statistical Analysis

Nonparametric and parametric descriptive statistics were used for patient demographics, as appropriate. The data analysis for this work was generated using SAS software (version 9.4) and Microsoft Excel for Office 365 (2022).

RESULTS

We performed WGS on 1031 SARS-CoV-2–positive remnant samples. Samples with inadequate sequencing quality (<90% genome coverage, n = 94), from facilities other than the study hospital (n = 306), and duplicate samples from the same person (n = 9) were excluded from the cluster analysis. Generation of clusters where all members of a cluster were within 2 variants yielded a total of 153 clusters containing 664 individuals. Restricting to clusters that contained at least 1 HCP reduced the set to 68 clusters, including 365 patients and 169 HCPs. Of these 68 clusters, 18 were singletons, only including an individual HCP, and were excluded from further analysis. An additional cluster included 133 individuals and was also excluded as the large size of the cluster indicated that the genetic data were not informative of potential transmission in the hospital. Thus, our cluster analysis data set included 49 genomic clusters containing HCP and involving 383 individuals (118 HCP and 265 patients) (Supplementary Figure). Genomic clusters had a median of 4 members, ranging from 2 to 42 members per cluster (Figure 2). Although employed at the study hospital, 3 HCP were present only at outside affiliated healthcare facilities during the study period (clusters 12, 23, and 26), and thus these individuals were excluded from the final analytic data set (115 HCP and 265 patients).

Clinical characteristics among the 115 HCP evaluated for epidemiologic linkages are highlighted in Table 1. Most HCP were patient-facing clinical and support staff, that is, they had direct patient contact. Nurses were the most common patient-facing HCP category in our cohort. Administrative and accounting staff were the most common non-patient-facing HCP category.

There were 20 190 EMR activities documented for cohort HCP and patient interactions during the study period, including 2 weeks prior to the first identified case. These activities represented 4005 unique interactions between cohort COVID-19 patients and any HCP (with or without symptomatic COVID-19) during the study period. Fifty-three cohort HCP (46%) accessed or recorded data in the EMR, whereas the remaining HCP were either not patient-facing or had duties that did not generate identifiable data in the EMR (eg, environmental services technician, transport specialist, food service worker, security officer). There were 686 unique interactions where a cohort HCP entered information into a cohort patient's chart.

Most HCP infections were judged as not healthcare associated (88/115 [77%]) (Table 2). We found no instances of a strong linkage between an HCP case and a source patient. All 13 HCP cases (11%, including 8 genomic clusters) that were attributed to a potential patient exposure were categorized as weak linkage; specifically, we did not identify evidence in the EMR that the HCP had directly cared for the potential source patient within the same genomic cluster. Fourteen HCP cases (12%, including 5 genomic clusters) were attributed to another HCP as a source (11 strong and 3 weak linkages). One large cluster in the inpatient rehabilitation unit of our hospital included 10 of these HCP cases, with the remaining 4 clusters each containing 2 HCP, 1 of whom was deemed the likely source. Agreement between the 2 physician reviewers was high ($\kappa = 0.91$ [95% confidence interval, .82–.99]). Three cases (2.6%) required adjudication by a third infectious disease physician. A line list of HCP with additional information regarding each cluster and source adjudication is provided in the Supplementary Table 2.

Our combined genomic/epidemiologic approach identified a large HCP cluster in the inpatient rehabilitation unit of our hospital, which was independently identified by our infection control department (Cluster 21, see Supplementary Table 2). The original epidemiologic outbreak investigation identified 13 potential HCP cases within this cluster, including 1 index case and 12 additional HCP cases. Our genomic analysis identified the same HCP as the index case, with an additional 10 HCP within the cluster with strong HCP-HCP linkage. Thus, there were 2 HCP infections identified by epidemiologic outbreak investigation that were temporally associated, but our genomic analysis found that they were unrelated to the rest of the cluster. We did not find any evidence of patient-to-HCP transmission in this cluster. These findings provided additional confidence in the accuracy of our combined genomic/epidemiologic approach.

DISCUSSION

In a single-center study of HCP with symptomatic COVID-19, we did not identify strong evidence of patient-to-HCP transmission, despite many interactions (>4000 unique encounters) between patients with COVID-19 and HCP during the study period. We found only weak evidence to support symptomatic patients as a potential source of HCP infection, and stronger evidence implicating HCP-to-HCP transmission or HCP infection acquired in nonhealthcare settings (eg, the community). These results suggest that the hierarchy of controls used to protect HCP during the initial COVID-19 pandemic response (ie,

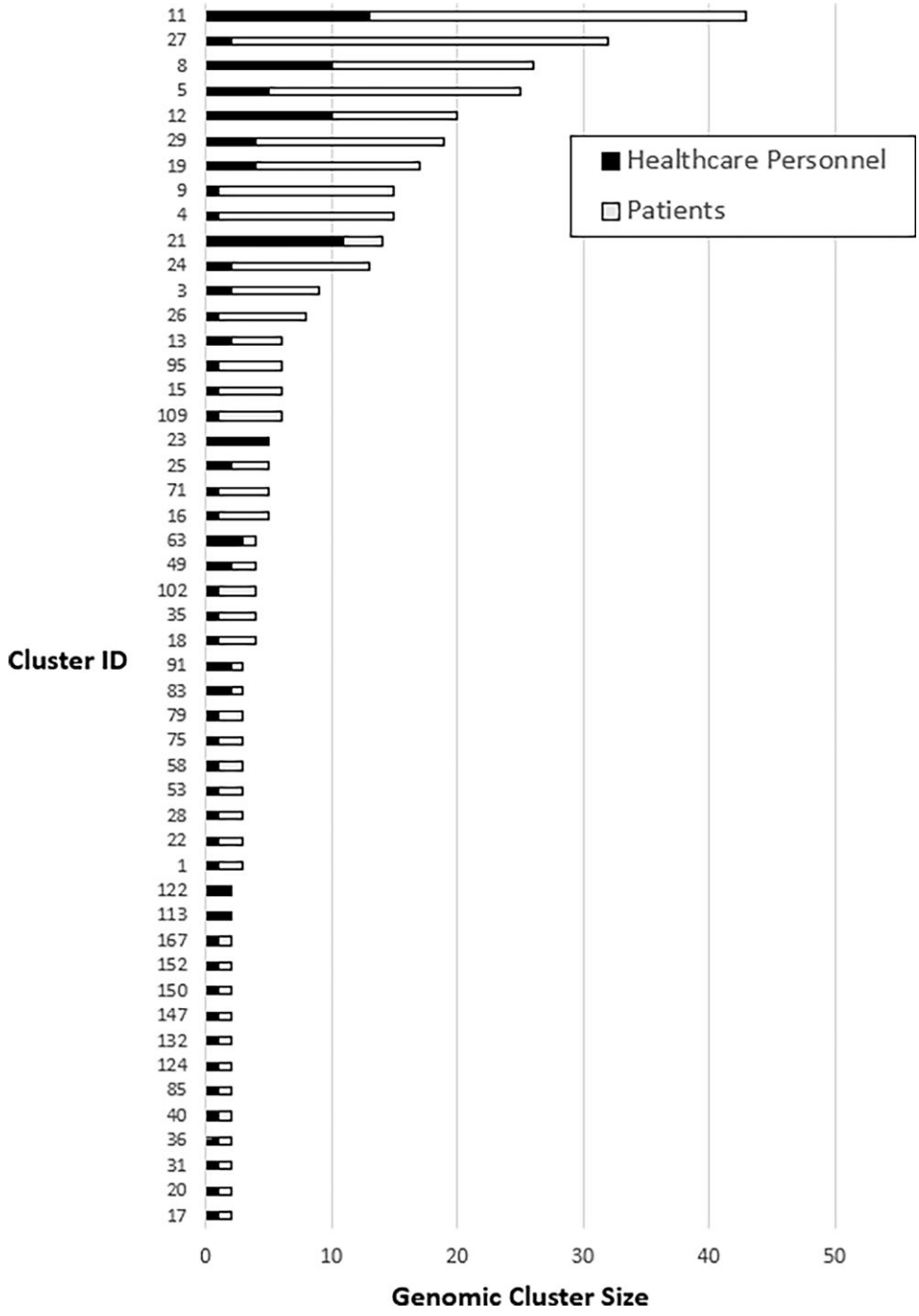

Figure 2. Severe acute respiratory syndrome coronavirus 2 genomic cluster size and composition, ordered by cluster size. Each bar represents an individual cluster. The number of healthcare personnel and patients within each cluster are represented by the bar size.

engineering, administrative, and PPE) [14] were effective at protecting HCP during care of COVID-19 patients.

Our study approach was particularly strong in evaluating potential transmission events among front-line HCP providing routine hands-on care for COVID-19 patients, such as nurses and physicians, due to its emphasis on using EMR charting as an indicator of HCP-patient interaction. Even with detailed interaction data, we did not identify any strong linkages for patient-to-HCP SARS-CoV-2 transmission. Our findings are consistent with previously reported studies that suggest that HCP SARS-CoV-2 acquisition risk is low (<5%), even with "high-risk" exposures and before vaccination was available

Table 1. Healthcare Personnel Demographics and Job Description (N = 115)

Variable	Healthcare Personnel
Demographics	
Age, y, mean (SD)	40 (29–49)
Female sex	82 (71)
HCP position category	
Patient-facing HCP	80 (70)
Nurse	24 (21)
Environmental services technician	15 (13)
Physician	12 (10)
Resident physician	8 (7)
Attending physician	3 (3)
Fellow physician	1 (<1)
Nursing or medical assistant	9 (8)
Physical or occupational therapist/rehabilitation aide	4 (3)
Clinical technician (EEG, surgical, radiological)	4 (3)
Food service worker	3 (3)
Peer counselor or health educator	2 (2)
Transport specialist	2 (2)
Audiologist	2 (2)
Physician assistant	1 (<1)
Case manager	1 (<1)
Security officer	1 (<1)
Non-patient-facing HCP	35 (30)
Administrative or accounting staff	21 (18)
Outpatient support staff	4 (3)
Pharmacy staff	3 (3)
Research staff	3 (3)
Training consultant	2 (2)
Supply chain technician	1 (<1)
Unknown	1 (<1)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: EEG, electroencephalography; HCP, healthcare personnel; SD, standard deviation.

Table 2. Epidemiologic Linkages Supporting Coronavirus Disease 2019 Transmission to Healthcare Personnel (N = 115)

Suspected Source of HCP COVID-19	Strength of Evidence for Epidemiologic Linkage	Frequency, No. (%)
Healthcare associated: patient source	Strong	0 (0)
	Weak	13 (11)
Healthcare associated: HCP source	Strong	11 (9)
	Weak	3 (3)
Not healthcare associated	Not applicable	88 (77)

Abbreviations: COVID-19, coronavirus disease 2019; HCP, healthcare personnel.

[15–19]. There is strong evidence that occupational safety measures protect HCP caring for patients with COVID-19 [1, 3, 20]. Notably, our study included periods of time with varying institutional respiratory PPE recommendations (including half of the study period when medical facemasks rather than N95 respirators were required for routine COVID-19 patient care, in part to ensure adequate N95 respiratory supply). Our study suggests that community exposures are the most common source of COVID-19 among HCP [21, 22]. SARS-CoV-2 seropositivity has been associated with community exposures, but not with healthcare occupational exposures (ie, caring for patients with COVID-19, exposure to aerosol-generating procedures) [18, 23–25]. In 1 study, the incidence of COVID-19 among nurses was the same in COVID-19 vs non–COVID-19 units after implementation of universal masking and eye protection [26].

For other HCP who did not interact with the EMR (eg, environmental services staff, transport technicians), we had no information about staff location, and our categorization erred on assuming possible work location overlap whenever there was genomic linkage. For example, Cluster 27 was a large genomic cluster including 30 patients and 2 HCP that was spread out over 1 month. EMR data were available that allowed us to exclude nosocomial transmission to a nurse because there was no time/place overlap with patients in this cluster. However, a transport technician without EMR data was judged as "healthcare-associated patient source" with weak evidence because we could not rule out patient exposure. We suspect that these results are an overestimation of transmission events, especially in large genomic clusters that were a consequence of low genetic variability of SARS-CoV-2 early in the pandemic. Capture of these potentially vulnerable groups during outbreak investigations that leverage electronic location remains limited. Incorporation of location monitoring for HCP (eg, radiofrequency identification systems) may be useful to overcome these challenges.

We did observe strong epidemiologic evidence to support HCP-to-HCP transmission. Occupational transmission between HCP has been well described [27–30]. Investigation of SARS-CoV-2 transmission in outpatient and inpatient facilities of a regional Veterans Affairs healthcare system [27] revealed that the index case for most genomic clusters was an HCP who acquired COVID-19 in the community, followed by transmission to coworkers. Among 14 clusters, they found support for HCP-to-HCP and HCP-to-patient transmission, but no evidence of patient-to-HCP transmission. Similar to our current findings, WGS confirmed some clusters but also demonstrated that some individuals linked by contact tracing were infected with distinct viral strains. Others have found WGS useful to identify routes of transmission between HCP, including shared break/lunch rooms [21, 29]. Thus, efforts to mitigate HCP infections should include focus not only on PPE when caring for patients, but also on interventions to reduce transmission between staff members (ie, universal masking, social distancing, education on use of shared workspaces, and additional break spaces).

Rapid transmission and limited pathogen evolution in early emergence of an infectious agent limit the value of WGS when

not combined with epidemiologic evaluation [22, 31]. This is especially challenging during periods of low viral diversity, such as the emergence and expansion of a new SARS-CoV-2 variant [32]. In this study, we chose a 2 single-nucleotide variant cutoff to maximize sensitivity of detecting genomic clusters based on prior published investigations [28, 33], with a potential tradeoff of reduced specificity. Although use of WGS for outbreak investigation during regional emergence of a novel pathogen may have limited utility, at least at the scale of a single healthcare facility [3], we anticipate that specificity will improve during periods of higher genomic variation.

This study has several strengths. Our comprehensive sequencing approach included all isolates from symptomatic HCP and patients at our medical center, which provided an opportunity for comprehensive investigation of possible transmission events among symptomatic individuals. Second, inclusion of HCP and patients was not filtered by preexisting epidemiologic criteria; we included all clinical and nonclinical HCP who were diagnosed with COVID-19. This allowed evaluation of the transmission risk to all staff members, including those who were not patient facing, allowing a more complete picture of COVID-19 transmission in the healthcare workforce. Third, we incorporated comprehensive clinical metadata from the EMR for HCP location and interactions with patients. Electronic abstraction of data could be operationalized for use in future outbreak investigations, which may reduce the burden on infection control staff members. The use of EMR data was particularly helpful in ascertaining patient contact for nurses and nursing assistants, who represent the group with the highest intensity of patient interactions. However, epidemiologic data by this approach were not available for nonclinical staff members.

There are several limitations to this study. First, we did not screen asymptomatic patients or HCP for SARS-CoV-2. Although the hospital testing guidance promoted a low symptom threshold for testing, HCP and patients with atypical or mild symptoms may not have sought COVID-19 testing. Additionally, 246 samples had inadequate genome coverage (ie, <90%) during WGS, which may also have contributed to missed linkages. Thus, we may have missed some index and linked cases for potential clusters. Second, this study included HCP from 1 hospital and was conducted very early in the pandemic, which may limit generalizability of our findings. Estimates of transmission during this first wave in Chicago, Illinois, may be inaccurate because (1) we had limited knowledge for how to prevent transmission, potentially resulting in higher estimates, or (2) HCP compliance with PPE may change over time (eg, HCP may have been more meticulous in PPE compliance earlier in the pandemic compared to now). Dynamics of nosocomial transmission may differ by facility type (eg, acute care vs long-term care facilities), possibly driven by staff role or level of training [34]. Third, our study was not designed to evaluate for transmission between patients [35] or from HCP to patient [27]. Fourth, this study was conducted before widespread vaccination or emergence of variants of concern with higher potential for transmissibility; both factors could influence dynamics of SARS-CoV-2 transmission.

In summary, through combined genomic and epidemiologic analysis, we found that risk of infection among HCP was primarily from sources other than direct patient care, specifically from community sources and from other sick HCP. We did not find strong evidence of patient-to-HCP transmission of SARS-CoV-2. Such knowledge is critical to evaluate prevailing safety measures for patient care, to target effective prevention measures for HCP, and to keep the HCP workforce safe.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent. This study does not include factors necessitating patient consent. The design of the work has been reviewed by the Rush University Medical Center Institutional Review Board (IRB) and was granted exemption from IRB review.

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Potential conflicts of interest. The authors: No potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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