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Title: Investigation of Nosocomial SARS-CoV-2 Transmission from Two Patients to Health Care Workers Identifies Close Contact but not Airborne Transmission Events

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ABSTRACT

OBJECTIVE

To describe the pattern of transmission of SARS-CoV-2 during 2 nosocomial outbreaks of COVID-19 with regard to the possibility of airborne transmission.

DESIGN

Contact investigations with active case finding were used to assess the pattern of spread from 2 COVID-19 index patients.

SETTING


PATIENTS

Two index patients and 421 exposed health care workers.

METHODS

Exposed staff were identified by analyzing the EMR and conducting active case finding in combination with structured interviews. Staff were tested for COVID-19 by obtaining oropharyngeal/nasopharyngeal specimens, with RT-PCR testing to detect SARS-CoV-2.

RESULTS

Two separate index patients were admitted in February and March 2020, without initial suspicion for COVID-19 and without contact or droplet precautions in place; both patients underwent several aerosol generating procedures in this context. A total of 421 health care workers were exposed in total, and the results of the case contact investigations identified 8 secondary infections in health care workers. In all 8 cases, the staff had close contact with the index patients without sufficient personal protective equipment. Importantly, despite multiple aerosol generating procedures, there was no evidence of airborne transmission.

CONCLUSION

These observations suggest that, at least in a healthcare setting, a majority of SARS-CoV-2 transmission is likely to take place during close contact with infected patients through respiratory droplets, rather than by long-distance airborne transmission.
INTRODUCTION

Multiple routes of transmission have been postulated for SARS-CoV-2 including respiratory droplets, airborne particles, and fomites.\textsuperscript{1–4} In particular, the risk of acquiring SARS-CoV-2 infection through inhalation of airborne particles, capable of transmitting infection over long distances, is uncertain, and remains a matter of vigorous debate.\textsuperscript{2,5,6} Given the significant risks of transmission to healthcare workers (HCWs),\textsuperscript{7} defining the degree to which airborne transmission occurs is important for guiding hospital infection control procedures and informing public health policy.

The predominant mode of transmission for most respiratory viruses is via large respiratory droplets inoculating mucous membranes.\textsuperscript{8} Respiratory droplets greater than 5 microns travel less than 2 meters, remain suspended less than 20 minutes and are effectively blocked by surgical masks.\textsuperscript{8} In contrast, smaller droplets evaporate rapidly, and the remaining desiccated droplet nucleus can remain airborne for hours, travel long distances, and require N95 respirators for protection.\textsuperscript{8}

For SARS-CoV-2, several laboratory and environmental studies have suggested the possibility of airborne transmission.\textsuperscript{5,6,9} Artificially generated SARS-CoV2 aerosols were found to be stable, with a half-life of 1.5h, and viral RNA has been detected on surfaces throughout the rooms of COVID-19 patients, including the ventilation system. The uncertain routes of transmission have led to inconsistent recommendations for infection prevention and appropriate personal protective equipment (PPE) for healthcare workers. For routine patient care, the WHO recommends contact and droplet precautions\textsuperscript{4}, and only recommends airborne precautions with a respirator in the setting of aerosol generating procedures (AGPs).\textsuperscript{2} In contrast, the US Centers for Disease Control (CDC) expresses a preference for respirators as routine PPE, with droplet/contact precautions being considered an acceptable alternative in the context of supply shortages.\textsuperscript{3}
To assess the routes of transmission of SARS-CoV-2, it will be necessary to document the pattern of spread from well-defined exposures. Here, we describe the pattern of nosocomial SARS-CoV-2 transmission from two separate patients, who were not initially suspected as having COVID-19, and who were cared for without contact, droplet, or airborne precautions.

METHODS

Ethics Statement: Hospital B’s Institutional Review Board (IRB) deemed that IRB approval and informed consent were unnecessary due to the quality improvement origins of the work.

Contact investigations: Investigation 1A reviews the contact investigation for Patient 1 at Hospital A, a community hospital. HCWs wore neither surgical masks nor eye protection, and were risk stratified based on examination of the medical record and subsequent phone interviews as follows: high risk: nose or mouth exposed during intubation or bronchoscopy; moderate: nose or mouth exposed and for over 2 minutes; and low: nose or mouth exposed under 2 minutes.

Investigation 1B and investigation 2 were completed at Hospital B, a university medical center. In both instances, Hospital B undertook active case finding, with a combination of electronic medical record (EMR) tracing to identify all staff who entered the index patient’s record, as well as surveys conducted by each unit manager to identify any staff that may have entered the room without EMR contact. Exposed staff filled out structured surveys regarding PPE, and types of contact, including AGPs. In addition, any staff with an ILI underwent testing as per hospital policy, including staff not directly involved in the patient’s clinical care. A number of asymptomatic staff were also tested because they were deemed higher risk for transmitting to patients, including respiratory therapists and all members of the oncology team.
Exposed HCWs Hospital B were risk-stratified with the following designations: patient source controlled with mask or intubation (Con+/−), and PPE with surgical mask (M+/−) and eye protection (E+/−). Risk level was defined as: high: (Con-M-E−), moderate (Con-M-E+ or Con-M+E−) and low (Con-M+E+ or Con+M+E−). No asymptomatic patients were tested, and no patients developed an ILI that triggered SARS-CoV-2 testing. Of note, using the criteria of Hospital B, all exposures at Hospital A would have been considered high-risk since no staff wore masks, eye protection or gowns. For Case 1, testing relied on oropharyngeal or nasopharyngeal swabs, with RT-PCR performed at the California Department of Public Health (CADPH). For Case 2, only nasopharyngeal swabs were used, and specimens were tested on-site by Hospital B using a validated assay on an ABI StepOnePlus instrument.

Statistical analysis: The Fisher’s exact test was used to assess the association between specific high-risk procedures and a positive SARS-CoV-2 RT-PCR.

CASE 1

Clinical Course at Hospital A

A previously healthy woman in her 40’s, who would later be deemed the first case of community-acquired COVID-19 diagnosed in the United States, presented to a local hospital with 48 hours of subjective fever, dry cough, nausea and vomiting.10 Upon presentation she was febrile, tachycardic, and hypotensive, and her chest x-ray showed a focal consolidation. The patient was admitted to the general medical/surgical ward with a diagnosis of community acquired pneumonia, and started on intravenous antibiotics. Over two days, she became increasingly hypoxic requiring oxygen through high-flow nasal canula and chest x-ray showed progressive disease. By day 3, she required non-invasive mechanical ventilation and was eventually transferred to the intensive care unit (ICU) and endotracheally intubated. The patient underwent an initial abbreviated bronchoscopy followed by a second longer
diagnostic bronchoscopy that showed only bloody secretions. The patient’s hypoxemia worsened, and she was subsequently transferred on day 4 to Hospital B for consideration of extracorporeal membrane oxygenation (ECMO).

Clinical Course After Transfer to Hospital B

Extensive additional evaluation for the etiology of ARDS was completed and unrevealing. Despite broad spectrum antimicrobials, she had persistent fever and hypoxemic respiratory failure, although she did not require ECMO. At the time of her illness, SARS-CoV-2 testing was only available through the CDC. Although she had no travel history that qualified her for SARS-CoV-2 testing, her severe presentation and unrevealing diagnostic evaluation suggested the possibility of COVID-19. On day 5 of her course at Hospital B, a nasopharyngeal swab for SARS-CoV-2 was sent to the CDC, which returned positive. Remdesivir was obtained through a compassionate use authorization, the patient slowly improved, and ultimately was discharged home after approximately 1 month.

Case 1 Contact Investigation – Hospital A

As COVID-19 was not initially suspected, a large number of staff were exposed to the index case at Hospital A without PPE; many of the details of this contact investigation have been recently reported in a CDC-issued MMWR bulletin.11 No contact, droplet, or airborne precautions were used. The patient initially spent time on the combined medical/surgical ward with 29 beds and staffed by 8 RNs, several physicians, and ancillary staff. She was then transferred to the ICU which has 6 rooms. The patient’s room for intubation and bronchoscopy measures 245 square feet, was not negative pressure, and has net air exchange of 100 cubic feet/minute.

The contact investigation at Hospital A determined that in total, 126 HCW were exposed, of which 28 staff were deemed high risk, 67 moderate risk, and 31 low risk. Of 126 staff, 43 developed an ILI. These 43 HCWs were tested, and 3 tested positive (Figure 1). All
3 had provided direct patient care with close contact for several days, and were present for AGPs without masks or eye protection. Two were direct providers on the ward and were present while the patient received oxygen by high flow nasal cannula or non-invasive positive-pressure ventilation, the third staff provided care both on the medical ward and the ICU and was present for the intubation and bronchoscopies (Figure 2). In summary, although a total 43 HCWs underwent testing, the infected staff all had prolonged direct contact with the patient, including during AGPs.

**Case 1 Contact Investigation – Hospital B**

Upon transfer, droplet and contact precautions were instituted and respiratory pathogen PCR testing was done. On hospital day 3, when the respiratory pathogen panel returned negative, droplet and contact precautions were discontinued. On hospital day 5, when it became possible to test for SARS-CoV-2 airborne precautions were instituted. Testing returned positive, and airborne precautions were continued until hospital day 23, when she had two negative SARS-CoV-2 nasopharyngeal swabs from consecutive days return negative, and airborne, droplet, and contact precautions were discontinued. Prior to the institution of airborne isolation, 147 HCWs at Hospital B were exposed to the patient (Figure 3). There were 15 high risk exposures, 73 medium risk exposures, and 59 low risk exposures. All of the high and medium risk HCWs (88 HCWs) were isolated from work for 14 days. 13 employees developed ILI symptoms, and were tested by for SARS CoV-2 RT-PCR, but all tested negative.

**CASE 2**

**Clinical Course:**

A previously healthy man in his 60’s presented to a local hospital with dyspnea. He was found to have a deep vein thrombosis with pulmonary emboli, and noted to have a leukocyte cell count of 69,000 cells/mm$^3$ with myeloblasts. He was transferred to Hospital B
and on day 2, where he developed progressive hypoxemic respiratory failure, and was intubated on day 3. Bone marrow biopsy confirmed AML, and his course was complicated by the presumed sequelae of leukostasis with disseminated intravascular coagulation, acute left middle cerebral artery infarct, subarachnoid hemorrhage, acute kidney injury, and splenic rupture. He remained persistently febrile and underwent an unrevealing diagnostic bronchoscopy, and on day 14 the Infectious Diseases service was consulted. A nasopharyngeal swab for SARS-CoV-2 testing was obtained, and droplet and contact precautions, with airborne precautions for AGPs were instituted. SARS-CoV2 testing returned positive on day 15 with a cycle-threshold (Ct) value of 25. The patient then developed central venous catheter-associated bloodstream infection with septic shock and despite IV antibiotics and catheter removal, he continued to decline. The family ultimately opted to pursue comfort-focused care and the patient died on hospital day 30.

Case 2 Contact Investigation:

The patient was originally admitted to the oncology unit which consists of 25 neutral-pressure rooms with 35 beds, and is staffed by 13 nurses per shift and 5-6 physicians on the oncology team. He was transferred to the medical ICU, which consists of 16 single room beds, each with an assigned nurse, as well as two teams with 6-7 physicians each and a variable number of respiratory therapists. The room in which the patient was intubated measures 165 square feet and has 15 air-exchanges per hour but is not negative pressure relative to the unit. Between hospital day 3 and day 15, there was some degree of source control, as his ventilator was fitted with closed-circuit suctioning an in-line high-efficiency particulate air (HEPA) filter.

145 staff were identified as having exposure to the index patient, with 5 confirmed infections, and 2 possible infections (Figure 4). 7 of the 145 HCWs developed ILI symptoms and all were at bedside for AGPs without adequate PPE. The patient underwent two
significant aerosol generating procedures: endotracheal intubation on day 3 and bronchoscopy on day 11, with neither airborne nor droplet precautions in place. Most transmission events were associated with the endotracheal intubation, as 4 of the 7 staff present for the procedure tested positive for SARS-CoV-2 (p<0.001; Figure 5). The individual performing the procedure wore a surgical mask without eye protection, and the remaining HCWs wore neither masks nor eye protection (Table 1). A fifth HCW, who was at neither the bronchoscopy nor intubation also developed symptoms, but had direct patient contact for several days without PPE, and assisted in transferring the patient between ventilators which necessitated a break in the closed ventilation circuit. All staff who tested positive developed symptoms within a 72-hour window. Two additional staff, who had direct patient contact without PPE during AGPs, whom we consider possible cases, developed high fevers and cough, but tested negative for SARS-CoV-2 twice each. Interestingly, we identified no transmission during the bronchoscopy when all staff wore surgical masks and eye protection. Seven staff were present; the two providers performing the bronchoscopy wore surgical masks with eye protection, a gown, and gloves. Everyone else wore a surgical mask with eye protection (Table 1). Thus, in summary, though a number of staff became infected by the index case, they all had direct contact with the patient and were present during aerosol-generating procedures without sufficient PPE.

DISCUSSION

The cases described here, and the pattern of spread to exposed staff, provide important insight into the transmissibility of SARS-CoV-2 in a healthcare setting. Both patients were in the hospital for several days before COVID-19 was suspected, without contact, droplet, or airborne precautions in place, and both patients underwent multiple AGPs without negative-pressure isolation rooms. The hypothesis that SARS-CoV-2 is airborne-transmissible would predict wide-
spread infection of staff or other patients during this time, unconstrained by the 2-meter radius that large respiratory droplets travel. Indeed, this is precisely the pattern seen with well-established airborne-transmitted agents such as tuberculosis and measles, where patients cared for without negative-pressure isolation have triggered multiple outbreaks, with infection spreading to staff and other patients throughout a unit who had no direct contact with the index case.\textsuperscript{13–15}

For the cases described here, this did not occur. While a total of eight hospital staff were infected, transmission occurred exclusively amongst staff that were at the patient’s bedside without contact and droplet PPE. There was no apparent transmission to staff or patients elsewhere on the units, including an oncology ward housing a large number of immunocompromised patients. These findings are much more consistent with transmission by respiratory droplets rather than airborne transmission.\textsuperscript{16,17} This idea is further supported by three other recent reports, each of individual patients with unsuspected COVID-19 that similarly documented an absence of airborne transmission.\textsuperscript{18–20}

Several possibilities exist to reconcile the theoretical concern for airborne transmission raised by other studies\textsuperscript{5,6,21} with our contact investigations showing no apparent airborne transmission. Though artificially-generated SARS-CoV-2 airborne particles are quite stable, and SARS-CoV-2 RNA can be detected throughout COVID-19 patient rooms, it is notable that no infectious virus could be recovered from the rooms, suggesting that the viral RNA might be from replication intermediates or non-infectious virions. However, it is impossible to exclude the possibility that virions isolated off surfaces were initially infectious but had degraded prior to sample collection. An alternative explanation may lie in the dose of SARS-CoV-2 necessary to establish infection. The minimum infectious dose varies dramatically between respiratory pathogens, with $<10$ bacilli needed to establish \textit{M. tuberculosis} infection, but $>500$ virions needed for echovirus.\textsuperscript{20} The minimum infectious dose for SARS-CoV-2 in humans is unknown, but a likely
explanation for a failure of SARS-CoV-2 airborne particles to efficiently transmit infection over long distances may simply be that the number of inhaled virions is insufficient to establish infection.

Of note, our observations do not discriminate between close-range transmission by large respiratory droplets that can be effectively blocked by surgical masks and eye protection, versus close-range transmission by small droplets and droplet nuclei that penetrate surgical masks. The potential importance of these small particles was highlighted during the 2003 SARS outbreak, when high-risk AGPs such as intubation and cardiopulmonary resuscitation were analyzed. During these procedures, HCWs with close patient contact became infected, even when droplet precautions were in place, with endotracheal intubation having an odds ratio of 13.\textsuperscript{21} Since the staff who became infected in our study wore neither droplet nor airborne protective equipment, we cannot assess the relative degree of protection that would have been provided by droplet precautions relative to N95 respirators.

Our report has several limitations. Most importantly, while there were a large number of exposed staff, with 421 individuals identified by contact tracing, we were limited by having only two index cases, and only had viral load information for one case. This patient had a Ct value of 25, approximating the median value of other studies.\textsuperscript{24} It is possible that patients with higher viral loads might more readily transmit infection via airborne particles. In addition, at the time these hospital outbreaks occurred, in February and March 2020, testing infrastructure was still very limited, and systematic testing of all asymptomatic staff or patients on each unit was not possible. Given the likelihood of asymptomatic COVID-19 cases,\textsuperscript{25} we cannot exclude occult transmission leading to asymptomatic secondary cases. However, we note that no additional cases were detected amongst the 35 asymptomatic staff who were able to be tested, and that all hospital staff developing ILI symptoms were tested for SARS-CoV-2, regardless of whether they had contact with an index patient. Finally, the sensitivity of a single nasopharyngeal test has been reported at 63%,\textsuperscript{22} and so some staff with
COVID-19 may have gone undetected. However, limitations in test sensitivity would apply to staff both with and without direct contact, and would not be expected to bias the overall distribution of cases. In summary, our findings suggest that, at least in a healthcare setting, a majority of SARS-CoV-2 transmission is likely to take place during close contact with infected patients rather than by long-distance airborne transmission.

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**Table 1.** Summary of PPE and SARS-CoV-2 testing for Case 2 procedures. Mask indicates surgical mask; * denotes staff performing the procedure. PCR +/(-) denotes SARS-CoV-2 test result.
FIGURE LEGENDS

Figure 1. Stratification of exposed HCWs for Case 1 at Hospital
Figure 2. Description of staff at endotracheal intubation for Case 1 at Hospital A. Abbreviations; Sx+, symptomatic; Sx (-) asymptomatic; PCR +/- denotes SARS-CoV-2 test result.
Figure 3. Stratification of exposed HCWs for Case 1 at Hospital B.
Figure 4. Stratification of exposed HCWs for Case 2.
Figure 5. Description of staff present during intubation of Case 2. Abbreviations; Sx+, symptomatic; Sx(-) asymptomatic; PCR +/- denotes SARS-CoV-2 test result.
REFERENCES


