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Title: Molecular Epidemiology of Large COVID-19 Clusters before and after the Implementation of Routine Serial Testing at an Academic Medical Center — Iowa, 2020

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Introduction:

Coronavirus disease 2019 (COVID-19) is a multisystemic illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Preventing COVID-19 transmission in healthcare settings is challenging. Several strategies for early identification and isolation have been implemented, including COVID-19 screening of patients on admission.\textsuperscript{1} However, because COVID-19 has a median incubation period of ~5 days, infected patients may have negative results at the time of admission. Undetected cases during hospital admission may contribute to nosocomial transmission and outbreaks.\textsuperscript{2,3}

Investigating hospital COVID-19 outbreaks is challenging because of the multitude of patient interactions and the high incidence in the community. Viral genome sequencing data can help discern healthcare-associated from community-associated infections. We describe two large COVID-19 clusters identified in our hospital before and after the implementation of serial testing and apply molecular epidemiology to confirm nosocomial transmission.

Methods:

The University of Iowa Hospitals & Clinics is an 811-bed Academic Medical Center. We identified large clusters involving patients with hospital onset COVID-19 detected during March–October 2020. Large clusters were defined as including $\geq$10 individuals: patients, visitors, or healthcare personnel (HCP) with a laboratory-confirmed
COVID-19 diagnosis (RT-PCR) and an epidemiologic link. Epidemiologic links were defined as hospitalization, working, or visiting in the same hospital unit during the incubation or infectious period of a hospital-onset case. Hospital-onset was defined as a COVID-19 diagnosis ≥14 days from the admission date. Medical grade mask and eye protection requirements were in place for patient care at the time of the first outbreak and the requirement was expanded to all hospital areas (e.g., break rooms) soon after the first outbreak. Symptom screening and testing for symptomatic HCP was in place throughout the study period. Visitors were screened for symptoms and only allowed in if asymptomatic. Patient admission screening (nasopharyngeal RT-PCR) was started in May 2020 and serial testing for all inpatients (RT-PCR every five days) in July 2020. Nasopharyngeal swab specimens were retrieved for whole genome sequencing (WGS). WGS was performed using a MinION sequencer from Oxford Nanopore Technology and protocols from the ARTIC network. Phylogenetic classification was based on GISAID clades and Pango lineages (version: 2021-04-23). A cutoff for genetic diversity was not defined beforehand but assumed to increase with the number of single nucleotide polymorphisms (SNPs).

**Results:**

The first cluster occurred in June 2020. Two hospital-onset cases were identified in adjacent rooms in a non-COVID-19 medical-surgical unit. Contact tracing and testing of patients and unit staff revealed four additional patients (three shared a room with another case), one visitor, and thirteen HCP (eight took care of a patient who was part of this cluster), for a total of twenty infected individuals. Seventeen samples (six
patients, one visitor, and ten HCP) were sequenced. All samples belonged to clade GH and lineage B.1 and were 0–5 SNPs different from each other (Figure 1). In July 2020, after this cluster was identified, routine serial testing every five days was started for hospitalized patients.

In September 2020, a hospital-onset case was identified as part of routine serial testing in a non-COVID-19 intensive care unit. Contact tracing and serial testing revealed three additional patients (two shared a room with another case) and eight HCP (four cared for a patient who was part of this cluster), for a total of twelve individuals. One HCP also had a household exposure. Eleven samples (four patients and seven HCP) were sequenced. Most samples belonged to clade G and lineage B.1.565. The sample from the HCP with a household exposure belonged to clade GH and lineage B.1.582, and it was 20–21 SNPs different from other samples in the cluster. Therefore, this infection was not considered to be the result of in-hospital transmission. The remaining samples were 0–3 SNPs different from each other, showing less diversity compared to the first cluster (Figure 1).

Discussion:

Two hospital COVID-19 outbreaks were confirmed using WGS. WGS helped differentiate in-hospital from community acquisition. Serial testing in all hospitalized patients may have contributed to reduce outbreak size and genetic diversity during the second outbreak.

Hospital outbreaks are traditionally investigated using contact tracing. However, COVID-19 transmission routes remain controversial and there is a limit to what we can
learn from contact tracing. Transmission networks are often complex, involving patients, HCP, and visitors. WGS can confirm hospital COVID-19 outbreaks, suggest possible transmission routes, and inform subsequent infection control measures.\(^\text{2,5,6}\) In this study, an HCP with a household exposure had a distinctly different viral genomic sequence from others and was not considered part of the cluster of in-hospital transmission. Understanding SARS-CoV-2 transmission in a healthcare setting is critical to manage hospital-associated COVID-19.

Serial SARS-CoV-2 testing is known to be effective in identifying hospital-associated COVID-19 early or detecting COVID-19 that might have been in the incubation period upon admission screening.\(^\text{3}\) In addition, when COVID-19 outbreaks occur, serial testing of patients and HCP, until no new cases are detected after 14 days, can be used to control outbreaks.\(^\text{7}\) However, there is limited data assessing the impact of serial testing on prevention or reduction of COVID-19 clusters. In our hospital, the first cluster (before the implementation of serial testing) was bigger than the second cluster (after the implementation of serial testing). Serial testing leads to early identification and isolation, therefore preventing COVID-19 spread to other inpatients or HCPs within a hospital. Interestingly, WGS results in this study also showed less genetic diversity in the second cluster, after implementation of serial testing for hospitalized patients.

This study has limitations. This is a retrospective single center study with a small number of subjects. We could not perform WGS for all individuals identified in each cluster because some samples were not available.
In conclusion, WGS is a powerful tool in hospital cluster investigations. Routine serial testing led to earlier cluster detection, which may have decreased outbreak size and genetic diversity.

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Conflicts of interest: All authors report no conflicts of interest relevant to this article.
References:


Figure legends:

**Figure 1:** Phylogenetic tree of COVID-19 clusters. Clusters are denoted with brackets and separated by a dashed line. Pango lineages (version: 2021-04-23) are labeled in different colors. Sample numbers represent the order of sample collection. The root of the tree is the SARS-CoV-2 reference genome (NC_045512.2).