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BRIEF REPORT

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SARS-CoV-2 antibody detection in skilled nursing facility residents

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Abstract

Objective: To describe the frequency and timing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody detection in a convenience sample of skilled nursing facility (SNF) residents with and without confirmed SARS-CoV-2 infection.

Design: Retrospective analysis of SNF electronic health records.

Setting: Qualitative SARS-CoV-2 antibody test results were available from 81 SNFs in 16 states.

Participants: Six hundred and sixty nine SNF residents who underwent both polymerase chain reaction (PCR) and antibody testing for SARS-CoV-2.

Measurements: Presence of SARS-CoV-2 antibodies following the first positive PCR test for confirmed cases, or first PCR test for non-cases.

Results: Among 397 residents with PCR-confirmed infection, antibodies were detected in 4 of 7 (57.1%) tested within 7–14 days of their first positive PCR test; in 44 of 47 (93.6%) tested within 15–30 days; in 182 of 219 (83.1%) tested within 31–60 days; and in 110 of 124 (88.7%) tested after 60 days. Among 272 PCR negative residents, antibodies were detected in 2 of 9 (22.2%) tested within 7–14 days of their first PCR test; in 41 of 81 (50.6%) tested within 15–30 days; in 65 of 148 (43.9%) tested within 31–60 days; and in 9 of 34 (26.5%) tested after 60 days. No significant differences in baseline resident characteristics or symptoms were observed between those with versus without antibodies.

See related editorial by Ann R. Falsey in this issue.

Conclusions: These findings suggest that vulnerable older adults can mount an antibody response to SARS-CoV-2, and that antibodies are most likely to be detected within 15–30 days of diagnosis. That antibodies were detected in a large proportion of residents with no confirmed SARS-CoV-2 infection highlights the complexity of identifying who is infected in real time. Frequent surveillance and diagnostic testing based on low thresholds of clinical suspicion for symptoms and/or exposure will remain critical to inform strategies designed to mitigate outbreaks in SNFs while community SARS-CoV-2 prevalence remains high.

KEYWORDS

COVID19, nursing home, SARS-CoV-2, serology, skilled nursing facility

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection escalated into a pandemic in 2020, with the greatest mortality affecting individuals who live in skilled nursing facilities (SNFs).[1,2] Few data exist to describe the relationship of symptoms, testing and serology in a vulnerable, largely immunosenescent nursing home population. We describe SARS-CoV-2 infection, symptoms, and antibody assessment in a cohort of SNF residents, who, due to advanced age, frailty, and multiple comorbidities may have altered presentation and response from other non-SNF populations.

Key Point

- In a convenience sample of 669 SNF residents who had SARS-CoV-2 PCR and antibody testing, antibodies were detected in 86% of PCR positive residents and 43% of PCR negative residents.

Why Does this Paper Matter?

Vulnerable older adults appear able to mount an antibody response to SARS-CoV-2, but infections can be difficult to identify in real-time.

METHODS

We used clinical data from Genesis Healthcare, a large multistate long-term care provider to identify a cohort of SNF residents who underwent both reverse transcriptase polymerase chain reaction (PCR) and antibody testing for SARS-CoV-2 as of August 1, 2020. Data sources included the electronic health record, Minimum Data Set (MDS), and infection logs maintained by infection control teams at each SNF to track testing and cases. Whereas PCR testing was largely driven by standardized organizational testing protocols, antibody testing was subject to the clinical judgment of individual primary care providers. As such, the population of residents who underwent antibody testing represents a convenience sample and is not random.

Antibody and PCR test dates and results were queried from both the facility infection logs and electronic health record. Antibody testing data were available from 81 SNFs in 16 states and represented a mix of labs and testing manufacturers which were not consistently identified in the data. Antibody tests could be specified as IgG or IgM, or recorded generically as "antibody tests." Results were reported qualitatively as "positive" or "negative." Quantitative titers were unavailable for most of the reported results and thus were not included in the analysis.

We limited the sample to residents who underwent antibody testing at least 1 week after a first positive PCR test for cases, or first PCR test for non-cases (hereafter referred to as their reference PCR test). Baseline resident demographics, chronic conditions, and measures of cognition, physical function, and frailty were captured from the last MDS assessment prior to the reference PCR test. Cognition was measured with the Cognitive Function Scale (1 = intact to 4 = severe impairment),[3] while physical function was measured with the Activities of Daily Living (ADL) score (0 = completely independent to 28 = completely dependent).[4] Frailty was assessed using the Changes in Health, End-Stage Disease and Symptoms and Signs Scale (0 = most stable to 5 = least stable) which incorporates severe cognitive impairment, cognitive decline, behaviors, ADL dependency, and other clinical signs and symptoms of advanced illness.[5]

Nurses assess residents at least twice daily and document any changes in condition in a structured form in the electronic health record. From this documentation, we flagged the following symptoms: fever, hypoxia, cough, shortness of breath, chest congestion, gastrointestinal symptoms, rhinorrhea, nasal congestion, sore throat, tachycardia, and altered mental status. We classified residents as symptomatic, pre-symptomatic, or asymptomatic at the time of their reference PCR test. They were considered symptomatic if they had new symptoms in the 5 days prior to the test, pre-symptomatic if they developed new symptoms in the 14 days post-test, and asymptomatic if they had no symptoms from 5 days pre-test to 14 days post-test.

We report the proportion of SARS-CoV-2 PCR positive and PCR negative residents with antibodies detected, stratified by the number of days between the reference PCR test and antibody test (7–14 days, 15–30 days, 31–60 days, more than 60 days). We then report the frequency of symptoms by resident SARS-CoV-2 PCR and antibody status. All analyses are descriptive, relying on Pearson's chi-square tests for categorical variables and ANOVA or Wilcoxon rank-sum tests for continuous variables. Data were analyzed using Stata MP 16.0 (StataCorp, College Station, TX) and Python v.3.8 (Python Software Foundation, Beaverton, OR). The Brown University Institutional Review Board approved this study.

RESULTS

Table 1 summarizes characteristics of the 669 residents who underwent both PCR and antibody testing for SARS-CoV-2 as of August 1, 2020. Compared to PCR negative residents, a higher proportion of PCR positive residents in the sample were female (74.1% vs. 66.9%) and White (83.1% vs. 76.1%). There were no significant differences in

TABLE 1 Characteristics of 669 residents who underwent both PCR and antibody testing for SARS-CoV-2

Resident characteristics	PCR positive ($n = 397$)	PCR negative ($n = 272$)	p
Female, *n* (%)	294 (74.1)	182 (66.9)	0.05
Age, median (IQR)	81.0 (71.0, 89.0)	80.0 (70.5, 88.0)	0.65
Race/ethnicity, *n* (%)			
Black	37 (9.3)	33 (12.1)	0.24
Hispanic/Latino	12 (3.0)	22 (8.1)	0.003
White	330 (83.1)	207 (76.1)	0.03
Other	4 (1.0)	7 (2.6)	0.12
CFS score, mean (SD)	2.2 (1.0)	2.2 (1.0)	0.97
ADL score, mean (SD)	15.9 (6.9)	16.1 (7.2)	0.72
CHESS score, mean (SD)	0.7 (0.9)	0.7 (0.9)	0.37
Diagnoses, *n* (%)			
Coronary artery disease	91 (23.0)	59 (21.9)	0.73
Heart failure	91 (23.0)	61 (22.6)	0.91
COPD	78 (19.7)	55 (20.4)	0.83
Diabetes	137 (34.6)	86 (31.9)	0.46
Hypertension	309 (78.0)	205 (75.9)	0.53
Chronic kidney disease	99 (25.0)	60 (22.2)	0.41

Note: Sample limited to residents who underwent antibody testing at least 1 week after first positive PCR test for cases, or first PCR test for non-cases. Some antibody tests were recorded generically as "antibody tests" while others were specified as IgG or IgM. CFS ranges 1 (intact) to 4 (severe impairment). ADL score ranges from 0 (completely independent) to 28 (completely dependent). CHESS scale ranges from 0 (most stable) to 5 (least stable), and incorporates the following indicators: life expectancy less than 6 months, CFS score 4, acute mental status change, aggressive behavior score ≥ 3, impaired daily decision making, ADL score ≥ 21, dehydration, pressure ulcers, swallowing disorder, respiratory failure, shortness of breath, and heart failure. Data as of August 1, 2020. P-values shown for Pearson's chi-square for categorical variables, and ANOVA or Wilcoxon rank-sum for continuous variables.

Abbreviations: ADL, activities of daily living; CFS, Cognitive Function Scale; CHESS, Changes in Health, End-stage Disease Symptoms and Signs; IQR, interquartile range; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNF, skilled nursing facility.

baseline clinical or functional characteristics between PCR positive and PCR negative residents. We also observed no statistically significant differences in demographic, clinical, or functional characteristics between residents with and without SARS-CoV-2 antibodies (data not shown).

The proportion of residents with SARS-CoV-2 antibodies detected varied based on the number of days between the reference PCR test and antibody test (Figure 1). Among PCR positive residents, antibodies were detected in 4 of 7 (57.1%) tested within 7–14 days of their first positive PCR test; in 44 of 47 (93.6%) tested within 15–30 days; in 182 of 219 (83.1%) tested within 31–60 days; and in 110 of 124 (88.7%) tested after 60 days (Table S1). Among PCR negative residents, antibodies were detected in 2 of 9 (22.2%) tested within 7–14 days of their first PCR test; in 41 of 81 (50.6%) tested within 15–30 days; in 65 of 148 (43.9%) tested within 31–60 days; and in 9 of 34 (26.5%) tested after 60 days (Table S1).

Table 2 summarizes resident symptom presentation at the time of the reference PCR test. Among the 397 SARS-CoV-2 PCR positive residents, rates of asymptomatic presentation were similar for those with and without SARS-CoV-2 antibodies (49.4% vs. 49.1%, $p = 0.97$). Among PCR positive residents, those with antibodies more often had fever, hypoxia, cough, shortness of breath, and gastrointestinal symptoms than those without antibodies, although none of these differences reached statistical significance. Among the 272 PCR negative residents, 117 (43%) had SARS-CoV-2 antibodies present. Of those, 96 (82.1%) were asymptomatic and 21 (17.9%) had symptoms.

DISCUSSION

Findings from this convenience sample of SNF residents who underwent both PCR and antibody testing for SARS-CoV-2 illustrate two key points. First, vulnerable older adults with SARS-CoV-2 infection appear capable of mounting an antibody response. Anti-SARS-CoV-2 antibodies were detected in 94% of residents with PCR-confirmed infection who underwent serologic testing within 15–30 days of their diagnosis. The proportion of PCR positive residents who had antibodies was lower for those tested after 30 days, consistent with data from other populations that have demonstrated a waning of SARS-CoV-2 antibodies in the weeks after acute infection.[6] Still, among residents with PCR-confirmed infection, 89% of those who underwent serologic testing more than 60 days after diagnosis still had antibodies detected.

Secondly, anti-SARS-CoV-2 antibodies were detected in almost half (43%) of the residents in whom PCR did not detect SARS-CoV-2 infection. This suggests either (1) the PCR test missed the moment of SARS-CoV-2 RNA shedding in the upper airways, if it occurred at all; (2) poor technique in sampling or specimen handling for PCR testing; or (3) prior non-SARS-CoV-2 coronavirus infection producing cross-reactive antibodies resulting in positive serology results. Regarding the latter possibility, prior studies have observed CD8+ T cells responding to SARS-CoV-2 peptide pools in 20–50% of unexposed individuals, indicating pre-existing cross-reactive T cell memory most likely due to exposure to "common cold" coronaviruses.[7-9] This evidence also suggests the possibility for the existence of cross-reactive antibodies between these other coronaviruses and SARS-CoV-2. A small but

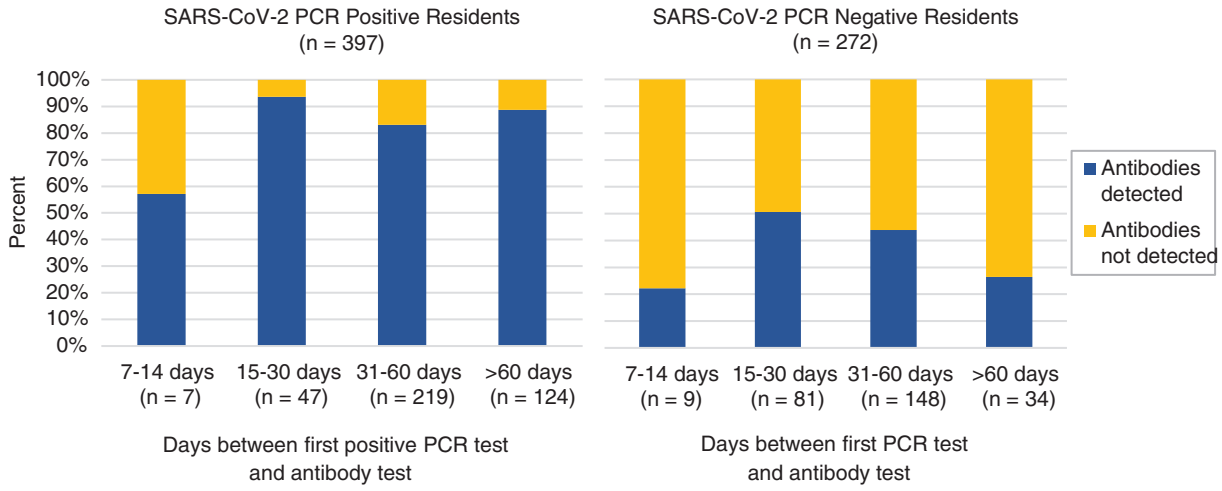

FIGURE 1 Percent of residents with and without PCR-confirmed SARS-CoV-2 infection who have SARS-CoV-2 antibodies, by days lapsed between PCR and antibody test ($n = 669$). Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

TABLE 2 Antibody status of 397 SARS-CoV-2 PCR positive residents and 272 SARS-CoV-2 PCR negative residents by symptom presentation at time of PCR testing

	PCR positive ($n = 397$)			PCR negative ($n = 272$)		
Symptoms	**Antibody present ($n = 340$, 85.6%)**	**Antibody absent ($n = 57$, 14.4%)**	***p***	**Antibody present ($n = 117$, 43.0%)**	**Antibody absent ($n = 155$, 57.0%)**	***p***
Symptom status at time of first positive PCR test, *n* (%)						
Symptomatic or presymptomatic	172 (50.6)	29 (50.9)	0.97	21 (17.9)	52 (33.5)	0.004**
Asymptomatic	168 (49.4)	28 (49.1)	0.97	96 (82.1)	103 (66.5)	0.004**
Symptoms present, *n* (%)						
Fever	92 (27.1)	9 (15.8)	0.07	9 (7.7)	17 (11.0)	0.36
Hypoxia	23 (6.8)	2 (3.5)	0.35	6 (5.1)	6 (3.9)	0.62
Cough	52 (15.3)	5 (8.8)	0.19	6 (5.1)	9 (5.8)	0.81
Shortness of breath	8 (2.4)	1 (1.8)	0.78	1 (0.9)	1 (0.6)	0.84
Chest congestion	3 (0.9)	0 (0.0)	0.48	1 (0.9)	0 (0.0)	0.25
Gastrointestinal symptoms	34 (10.0)	5 (8.8)	0.77	4 (3.4)	13 (8.4)	0.09
Rhinorrhea, nasal congestion, or sore throat	7 (2.1)	2 (3.5)	0.50	1 (0.9)	3 (1.9)	0.46
Tachycardia	6 (1.8)	1 (1.8)	1.00	0 (0.0)	4 (2.6)	0.08
Altered mental status	11 (3.2)	2 (3.5)	0.91	0 (0.0)	4 (2.6)	0.08

Note: Symptom status is classified as of the date of the reference PCR test which is the first positive PCR test for PCR positive residents, or the first PCR test for PCR negative residents. Residents are classified as symptomatic if they had symptoms in the 5 days before the reference PCR test; pre-symptomatic if they had no symptoms in the 5 days pre-test, but developed new symptoms in the 14 days post-test; and asymptomatic if they had no new symptoms from 5 days pre-test to 14 days post-test. Gastrointestinal symptoms include nausea, vomiting, diarrhea, or loss of appetite. Data as of August 1, 2020.
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

significant proportion (14%) of residents in our sample in whom PCR confirmed a SARS-CoV-2 infection did not have antibodies, likely either due to timing relative to development of an antibody response or, less likely, a false negative serology test.

An important consideration for interpreting these observations is that antibody testing was not random in this cohort, but rather was driven largely by certain primary care providers who aimed to better understand the impact of SARS-CoV-2 infections in their SNFs. For example, the medical directors of two facilities in Connecticut that had significant outbreaks conducted whole house serology testing to understand whether their residents who remained PCR negative had indeed been exposed. Thus, residents in those SNFs had a high baseline risk for infection. In much of the rest of the sample, the reason why antibody testing was done was not known.

Accurate identification of resident and staff SARS-CoV-2 infections in SNFs is critical for managing outbreaks. These findings highlight the complexity of identifying those infected with SARS-CoV-2 in real time, even in a population with systematic surveillance and frequent diagnostic PCR testing conducted based on low thresholds of suspicion for infection or exposure. That 43% of residents in whom PCR failed to detect SARS-CoV-2 infection developed antibodies anyway speaks to the shortcomings of a PCR testing strategy to confidently discern who may be infected and transmitting virus, particularly given the wide variation in testing availability in March and April, and in test turnaround time throughout the pandemic. Conversely, that 11–17% did not have specific SARS-CoV-2 antibodies more than a month after PCR-confirmed infection produces concerns about the extent to which herd immunity from natural infection can develop or remain sustained, if not also adding to questions about the role of antibodies in SARS-CoV-2 infection recovery.

There are some limitations to the study. First, our data come from a convenience sample of SNF residents who were predominantly female, White, and located in the Northeast, meaning that these findings may not be generalizable to other populations of SNF residents. Second, antibody and PCR results were from a range of labs and vendors which were not consistently identified in the data. Third, we were limited to a single antibody test per

resident, preventing trending of antibody detection in individuals over time. Fourth, we did not assess neutralizing antibody and quantitative titers, limiting our understanding of the clinical significance of declining antibody levels over time.[10] Finally, we cannot determine how survival skews sampling bias; it is possible that those who succumbed to disease may have had less (inadequate protection) or more (hyperimmune response) antibody.

CONCLUSIONS

Our data suggest that vulnerable older adults with PCR-confirmed SARS-CoV-2 infection are capable of mounting an antibody response that appears to peak 2 to 4 weeks from initial diagnosis, before waning in subsequent weeks. Declining antibodies, also demonstrated in other populations, may presage vulnerability to future or seasonal outbreaks in SNFs, and suggest the critical need for vaccination and other strategies to promote more durable immunity from recurrent infection in this population. The detection of antibodies in a substantial proportion of residents in whom PCR failed to identify SARS-CoV-2 infection highlights the complex challenges of identifying in real time who is infected to inform quarantine and cohorting decisions. Frequent surveillance and diagnostic testing based on low thresholds of clinical suspicion for symptoms and/or exposure will remain critical to inform strategies designed to mitigate SARS-CoV-2 outbreaks in SNFs while community virus prevalence remains high.

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CONFLICT OF INTEREST

Elie Saade reports investigator-initiated grants from Sanofi Pasteur and Janssen Pharmaceuticals; speaker fees from Sanofi Pasteur; and advisory board fees from Pfizer. David Canaday reports investigator-initiated grants to Case Western Reserve University to study influenza and pneumococcal vaccines from Seqirus, Sanofi Pasteur, and Pfizer; and for advisory work with Seqirus on vaccines. Vincent Mor is Chair of the Scientific Advisory Board at NaviHealth, Inc., former Chair of the Independent Quality Committee at HCR ManorCare, and former Director of PointRight, Inc., where he holds less than 1% equity. Stefan Gravenstein reports grants and personal fees from Sanofi Pasteur, Seqirus, Pfizer; and consulting or speaker fees from Healthcentric Advisors, Janssen, Merck, Novartis, Pfizer, and Longeveron related to vaccines or nursing home care quality. The other authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Study design: Elizabeth M. White, Xiaofei Yang, Carolyn Blackman, Richard A. Feifer, Vincent Mor, Stefan Gravenstein. Data acquisition: Elizabeth M. White, Carolyn Blackman, Christopher M. Santostefano, Vincent Mor. Data Analysis: Elizabeth M. White, Xiaofei Yang. Data Interpretation: all authors. Writing and critical revision of the manuscript: all authors.

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The National Institute on Aging and the National Institute of Allergy and Infectious Disease had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Table S1 Antibody status of 669 residents by days lapsed between initial SARS-CoV-2 PCR test and antibody test.

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