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BRIEF REPORT

Characteristics of Persons With Secondary Detection of Severe Acute Respiratory Syndrome Coronavirus 2 ≥90 days After First Detection, New Mexico 2020

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The New Mexico Department of Health (NMDOH) conducted a matched case-control study to compare 315 persons (cases) with and 945 persons (controls) without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) secondary detection (ie, positive SARS-CoV-2 test ≥90 days after first detection as of December 10, 2020). Compared with controls, cases had greater odds of higher SARS-CoV-2 testing frequency (adjusted odds ratio [aOR] = 1.2), being female (aOR = 1.6), being non-Hispanic American Indian/Alaska Native (aOR = 2.3), having diabetes mellitus (aOR = 1.8), and residing and/or working in detention and/or correctional facilities (aOR = 4.7). Diagnostic tools evaluating infectiousness at secondary detection are urgently needed to inform infection control practices.

Keywords. American Indian/Alaska Native; detention/correctional facilities; reinfection; SARS-CoV-2.

Reinfection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has been documented [1] but appears to occur infrequently. In a Danish cohort study of 11 068 persons positive for SARS-CoV-2 during Denmark's first surge (before June 1, 2020), only 72 (0.65%) people also tested positive during the second surge (September 1–December 31, 2020) [2]. The Centers for Disease Control and Prevention (CDC) has provided a common protocol for investigating suspected SARS-CoV-2 reinfection, prioritizing individuals with detected SARS-CoV-2 ribonucleic acid (RNA) ≥90 days since their first SARS-CoV-2 infection (see https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html). Reinfection confirmation requires molecular analysis of paired specimens from each infection episode, which can be difficult due to lack of long-term specimen storage, limited jurisdictional resources for molecular analysis, and delayed confirmation preventing effective public health response. For this reason, some health jurisdictions treat SARS-CoV-2 secondary detections (ie, SARS-CoV-2 detection ≥90 days after an initial positive test) as reinfection, recommending patient isolation and exposed contact quarantine. Although reinfection has been described, risk factors for SARS-CoV-2 secondary detection have not been fully established. To assess characteristics and testing frequency of persons with SARS-CoV-2 secondary detection, the New Mexico Department of Health (NMDOH) conducted a matched case-control study to compare 315 persons (cases) with and 945 persons (controls) without a positive SARS-CoV-2 test ≥90 days after first detection as of December 10, 2020.

METHODS

Using NMDOH COVID-19 surveillance data among all persons with COVID-19 extracted on December 10, 2020, a matched case-control study was performed to evaluate epidemiologic differences between persons with SARS-CoV-2 secondary detection ≥90 days after first infection and other persons with COVID-19. (Persons with COVID-19 were defined as New Mexico residents with an upper respiratory specimen positive for SARS-CoV-2 RNA or antigen by a US Food and Drug Administration-approved molecular test.) Cases were defined as persons for whom SARS-CoV-2 RNA or antigen was detected ≥90 days after first symptom onset or first positive SARS-CoV-2 test collection date (secondary detection). Controls were defined as persons without SARS-CoV-2 RNA or antigen detection ≥90 days after first symptom onset or first positive SARS-CoV-2 test collection date. This included individuals with a negative SARS-CoV-2 test or with no SARS-CoV-2 testing ≥90 days after first infection to provide a representative sample of New Mexico COVID-19 cases and account for testing practice effects on secondary detection. Although SARS-CoV-2 RNA and antigen tests have different sensitivities, both were included to more accurately reflect the burden of secondary detections in New Mexico. Controls were randomly selected in a 3:1 ratio, matching on region (New Mexico Department of Health Regions: https://ibis.health.state.nm.us/view/docs/HealthRegions2012_RegionLabels.pdf) and first positive SARS-CoV-2 specimen collection date, using an automated matching program in SAS (SAS Institute) [3]. Of 27 005 eligible COVID-19 cases, 315 (1%) secondary detection

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cases were identified and matched to 945 controls. First positive SARS-CoV-2 specimens were collected between March 15, 2020 and August 27, 2020 allowing for at least 90 days follow-up for both cases and controls as of data extraction on December 10, 2020.

Comparisons between cases and controls were made by median age, median number of SARS-CoV-2 tests since first positive (ie, SARS-CoV-2 test frequency), and by sex, race/ethnicity, hospitalization, symptoms, comorbidities (chronic lung disease, type I or II diabetes mellitus, cardiovascular disease, chronic renal disease, chronic liver disease, immunocompromised condition, neurologic/neurodevelopmental/intellectual disability, and other chronic disease), and working or living in healthcare or detention/correctional settings. For cases, SARS-CoV-2 test frequency was counted between specimen collection date of a patient's first positive test and up to, but not including, the positive specimen collection date ≥90 days later. Because controls had no positive SARS-CoV-2 tests ≥90 days after first infection as of December 10, 2020, a control's test frequency was counted over the time period determined by the control's matched case. Race/ethnicity was categorized as Hispanic/Latino, non-Hispanic White, non-Hispanic American Indian/Alaska Native (AI/AN), and non-Hispanic other race. Working or living in healthcare or detention/correctional settings was categorized as none, healthcare workers, residents of long-term care facilities, and staff or residents of detention/correctional facilities. Because SARS-CoV-2 vaccines were not yet authorized, vaccination status was not assessed. Covariates with $P < .2$ according to a univariate conditional logistic regression model were considered for inclusion in a multivariable model to compare the odds of secondary detection between cases and controls. Purposeful model selection was performed on the remaining covariates using complete case analysis (cases, n = 197; controls, n = 582) [4]. In the final model including SARS-CoV-2 test frequency, sex, race/ethnicity, diabetes mellitus status, and healthcare or congregate living status, adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated, and statistical significance ($P < .05$) was determined using Wald χ^2 tests.

Among cases, hospitalization and symptoms were compared between first and secondary SARS-CoV-2 detection. *ORF1ab* (n = 29), *N* (n = 36), and *S* (n = 29) gene target cycle threshold (Ct) values—the ThermoFisher TaqPath COVID-19 real-time polymerase chain reaction (RT-PCR) test targets 3 SARS-CoV-2 genes (*ORF1ab*, *N*, and *S* genes); during RT-PCR, the gene targets are replicated repeatedly; the Ct value is the number of replication cycles it takes for a gene target to reach a detectable level—were compared in a subset of first and secondary detection specimens that were tested at NMDOH using ThermoFisher TaqPath COVID-19 RT-PCR. Differences were tested using McNemar's test and paired Student *t* test with a significance threshold of $P < .05$. The SARS-CoV-2 sequencing was performed using the ARTIC v.3 LoCost protocol [5, 6] modified for use with the Illumina DNA Flex Library Prep Kit (Illumina, San Diego, CA) on the Illumina MiSeq platform (Illumina), and consensus sequences were generated and classified by Pango lineage (version 2.4.2, https://github.com/cov-lineages/pangolin) with the Cecret analysis pipeline (version 202110119, https://github.com/UPHL-BioNGS/Cecret.git). All statistical analyses were performed in SAS (version 9.4; SAS Institute). This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy (see, eg, 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

RESULTS

The median time from first to secondary detection was 117 days (interquartile range [IQR], 103–141)—207 (66%) secondary detection cases had at least 1 intervening negative SARS-CoV-2 test, 35 (11%) had only positive intervening tests, and 73 (23%) had no intervening tests; among the secondary detection cases with an intervening negative specimen, all intervening negative SARS-CoV-2 tests were conducted by RT-PCR. Secondary detection cases had 313 (99%) first detections and 302 (96%) secondary detections by real-time reverse-transcription PCR as opposed to antigen testing. Univariate analysis showed secondary detection cases had higher median age and SARS-CoV-2 test frequency and larger proportions of chronic lung disease, diabetes mellitus, and working or living in healthcare or detention/correctional settings than controls (Table 1).

When adjusted in a multivariable model, cases had greater odds of having higher SARS-CoV-2 test frequency (aOR = 1.2; 95% CI, 1.1–1.3), being female (aOR = 1.6; 95% CI, 1.1–2.5), being AI/AN (aOR = 2.3; 95% CI, 1.03–5.3), having diabetes mellitus (aOR = 1.8; 95% CI, 1.1–3.0), and being staff or residents of detention/correctional facilities (aOR = 4.7; 95% CI, 1.8–12.1) (Table 2) compared with controls. Results of the multivariable model were not affected by the exclusion of positive antigen tests.

Among cases, being symptomatic was more likely at first detection compared with secondary detection (74% vs 45%, $P = .001$); however, there was no statistically significant difference in hospitalization between first and secondary detections (24% vs 32%, $P = .27$) (Supplementary Tables 1 and 2). Mean Ct value at secondary detection was higher than the first for all targets (*ORF1ab*: mean 33.6 vs 24.7, $P < .0001$) (Supplementary Table 1). Of the 39 individuals with paired specimens tested at NMDOH, 2 had both specimens available for viral genomic sequencing and passed quality control. Both cases had different lineages identified between the first and second detection (patient A: B.1 and B.1.567, collected 108 days apart; patient B: B.1 and B.1.1.416, collected 126 days apart), suggesting reinfection caused the secondary detection (Supplementary Table 3).

Table 1. Comparisons Between Persons With (Cases)[a] and Without (Controls) a Positive SARS-CoV-2 Test ≥90 Days After First Detection (N = 1260), by Demographics, New Mexico, March–December 2020

Characteristics	Cases (N = 315) No. (%)	Controls (N = 945) No. (%)	*P* Value[b]
Median age, years (IQR)	44 (29–56)	39 (25–54)	.001
Median number of SARS-CoV-2 tests since first positive test[c] (IQR)	2 (1–4)	0 (0–1)	<.0001
Sex			
Female	171 (54.3)	471 (49.8)	.18
Male	142 (45.1)	468 (49.5)	
Missing	2 (0.6)	6 (0.6)	
Race/Ethnicity			
Non-Hispanic American Indian/Alaska Native	140 (44)	365 (39)	.05
Hispanic or Latino	118 (37)	370 (39)	
Non-Hispanic White	42 (13)	138 (15)	
Non-Hispanic Other Race[d]	8 (3)	31 (3)	
Missing	7 (2)	41 (4)	
Hospitalized During First SARS-CoV-2 Infection			
Not hospitalized	262 (83)	832 (88)	.06
Hospitalized	37 (12)	85 (9)	
Intensive Care Unit	16 (3)	28 (5)	
Symptomatic During First SARS-CoV-2 Infection			
Yes	166 (53)	515 (55)	.09
No	75 (24)	175 (19)	
Missing	74 (23)	255 (27)	
Chronic Lung Disease[e]			
Yes	38 (34)	78 (8)	.04
No	171 (54)	546 (58)	
Missing	106 (34)	321 (34)	
Diabetes Mellitus			
Yes	62 (20)	96 (10)	.0004
No	147 (47)	534 (57)	
Missing	106 (34)	315 (33)	
Cardiovascular Disease			
Yes	40 (13)	80 (8)	.22
No	164 (52)	546 (58)	
Missing	111 (35)	319 (34)	
Chronic Renal Disease			
Yes	7 (2)	17 (2)	.74
No	194 (62)	597 (63)	
Missing	114 (36)	331 (35)	
Chronic liver disease			
Yes	6 (2)	24 (3)	.40
No	195 (62)	595 (63)	
Missing	114 (36)	326 (35)	
Immunocompromising Condition[f]			
Yes	8 (3)	14 (1)	.29
No	193 (61)	597 (63)	
Missing	114 (36)	334 (35)	
Neurologic/Neurodevelopmental/Intellectual Disability			
Yes	19 (6)	31 (3)	.22
No	179 (57)	569 (57)	
Missing	117 (37)	345 (37)	
Other Chronic Disease[g]			
Yes	54 (17)	114 (12)	.07
No	152 (48)	476 (50)	
Missing	109 (35)	355 (38)	
Working or Residing in Healthcare or Detention/Correctional Settings			
None	168 (53)	540 (57)	.0001
Healthcare worker	29 (9)	66 (7)	
Long-term care facility resident	31 (10)	44 (5)	
Staff or resident of detention/correctional facility	31 (10)	39 (4)	
Missing	56 (18)	256 (27)	

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome.

[a]Cases were defined as persons for whom SARS-CoV-2 was detected ≥90 days after first symptom onset or first positive SARS-CoV-2 test collection date. Controls were defined as persons without SARS-CoV-2 RNA or antigen detection ≥90 days after symptom onset or specimen collection date. Cases and controls were matched on region of residence and specimen collection date of first positive SARS-CoV-2 test.

[b]Difference in cases and controls compared with Wald χ^2 test in univariable conditional logistic regression.

[c]The number of SARS-CoV-2 tests were counted between the specimen collection date of a patient's first positive SARS-CoV-2 test and up to, but not including, the specimen collection date ≥90 days after first infection for cases. Because controls had no positive SARS-CoV-2 tests ≥90 days after first infection as of December 10, 2020, the number of tests for a control was determined using the time frame defined by a control's matched case.

[d]Non-Hispanic other race includes non-Hispanic individuals of Asian, Black, and Native Hawaiian or other Pacific Islander race.

[e]Includes asthma, emphysema, and chronic obstructive pulmonary disease.

[f]Does not include diabetes mellitus.

[g]The case investigation interview form provided a question for patients to report any other chronic disease not listed above.

DISCUSSION

Secondary SARS-CoV-2 detection ≥90 days after first infection was associated with higher SARS-CoV-2 testing frequency and working or residing in detention/correctional facilities. This result suggests secondary detection is a function of both infection rates and testing frequency within a population. Detention/correctional facilities exemplify both aspects: high transmission environments with intensive screening. Where feasible, the CDC recommends expanded screening to reduce SARS-CoV-2 transmission in priority settings including long-term care facilities and detention/correctional facilities (see https://www.cdc.gov/coronavirus/2019-ncov/php/open-america/expanded-screening-testing.html). Although healthcare workers and long-term care facility residents had higher odds of secondary detection in the unadjusted model, this association was attenuated when adjusted for SARS-CoV-2 testing frequency. This was not true for detention/correctional facilities, suggesting that secondary detections might be attributable to transmission events rather than prolonged shedding. These results emphasize the high transmission risk within congregate living settings, which might exacerbate health inequities among persons who are incarcerated or detained. Furthermore, due to appropriate, but stringent, criteria for reinfection confirmation, current literature might underestimate reinfection incidence.

Table 2. Unadjusted and Adjusted Odds of SARS-CoV-2 Secondary Detection Cases (N = 197) Compared With Controls (N = 582)[a], New Mexico, March–December 2020

Characteristics	Unadjusted OR (95% CI)	*P* Value[b]	Adjusted[c] OR (95% CI)	*P* Value[b]
Greater SARS-CoV-2 test frequency[d]	1.3 (1.2–1.4)	<.0001	1.2 (1.1–1.3)	<.0001
Sex				
Female	1.5 (1.01–2.2)	.02	1.6 (1.1–2.5)	.02
Male	Ref		Ref	
Race/Ethnicity				
Non-Hispanic American Indian/Alaska Native	2.1 (1.01–4.2)	.1	2.3 (1.03–5.3)	.12
Hispanic or Latino	1.1 (0.7–2.0)		1.3 (0.7–2.4)	
Non-Hispanic Other Race[e]	0.4 (0.1–2.2)		0.5 (0.08–2.5)	
Non-Hispanic White	Ref		Ref	
Diabetes Mellitus				
Yes	2.2 (1.4–3.4)	.0003	1.8 (1.1–3.0)	.01
No	Ref		Ref	
Working or Residing in Healthcare or Detention/Correctional Settings				
None	Ref	.001	Ref	.01
Healthcare worker	1.9 (1.1–3.3)		1.6 (0.9–3.0)	
Long-term care facility resident	2.1 (1.1–4.1)		1.1 (0.5–2.4)	
Staff or resident of detention/correctional facility	3.9 (1.7–9.1)		4.7 (1.8–12.1)	

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, referent group; SARS-CoV-2, severe acute respiratory syndrome.

[a]Cases were defined as persons for whom SARS-CoV-2 was detected ≥90 days after first symptom onset or first positive SARS-CoV-2 test collection date. Controls were defined as persons without SARS-CoV-2 RNA or antigen detection ≥90 days after symptom onset or specimen collection date. Cases and controls were matched on region of residence and specimen collection date of first positive SARS-CoV-2 test. Complete case analysis was used for both unadjusted and adjusted models.

[b]Wald χ^2 test.

[c]Adjusted for number of SARS-CoV-2 tests since first positive test, current sex, race/ethnicity, diabetes mellitus, and healthcare or congregate living setting status.

[d]The number of SARS-CoV-2 tests were counted between the specimen collection date of a patient's first positive SARS-CoV-2 test and up to, but not including, the specimen collection date ≥90 days after first infection for cases. Because controls had no positive SARS-CoV-2 tests ≥90 days after first infection as of December 10, 2020, the number of tests for a control was determined using the time frame defined by a control's matched case.

[e]Non-Hispanic other race includes non-Hispanic individuals of Asian, Black, and Native Hawaiian or other Pacific Islander race.

Secondary detection was also associated with characteristics previously linked to COVID-19 susceptibility, such as diabetes mellitus and AI/AN race [7, 8]. Although intensive screening of AI/AN communities might partly explain these findings, other socioeconomic health determinants that lead to greater exposure and susceptibility likely contributed [9]. The independent association of secondary detection with diabetes mellitus, an immunosuppressive condition, illustrates that certain underlying medical conditions might predispose individuals to secondary detection, due to either prolonged shedding or reinfection. Prolonged shedding of infectious virus has been reported in an immunocompromised patient [10]. Continued screening for reinfection in populations with high prevalence of comorbidities or documented health inequities is critical in unvaccinated individuals to protect communities at highest risk of SARS-CoV-2 infection.

Of the 315 secondary detection cases, 2 cases with sequenced paired specimens were both confirmed as reinfections. Due to the scarcity of available paired specimens with adequate Ct value, the overall proportion of secondary detections caused by reinfection cannot be estimated. A subset of cases were more likely to be asymptomatic, with higher Ct values at secondary detection compared with their first. Data suggest that SARS-CoV-2 RNA can remain detectable in respiratory specimens ≥90 days after first infection, even with intervening negative tests [11–13], but limited data have demonstrated prolonged shedding of SARS-CoV-2 antigen [14]. Although expanded screening might find prolonged shedding that could translate in false-positive RT-PCR tests, it might also detect reinfections, especially in high transmission settings. If secondary detections represent true infections, higher Ct values at secondary detection could represent reinfections with overall lower viral load or detection later in the infection's course. In addition, fewer symptoms might indicate a milder clinical presentation, potentially due to cross-protection from the first infection. However, our data also show similar hospitalization frequencies at first and secondary detection, suggesting that those with clinical disease at reinfection may have more severe disease progression. Further studies investigating secondary detection infectiousness would help clarify public health significance.

These findings are subject to limitations. First, genomic analysis and viral culture were limited or not performed; therefore, whether most cases represented reinfection or were infectious cannot be confirmed. Second, data were missing for some variables. For example, only 24% (n = 76) of secondary detection cases had any symptom information at both first and second detections. Third, the combined category of staff and residents of detention/correctional facilities prevents the independent assessment of these 2 populations. Fourth, testing practices might be biased by some of the evaluated factors, such as prioritization of symptomatic individuals early in the pandemic. Fifth, testing ≥90 days after first

infection was not required for controls. Although this might have included individuals with undetected potential reinfection, it allows comparison of epidemiologic factors between identified secondary detections and general COVID-19 cases, including the evaluation of current testing practices. Finally, Ct value comparisons excluded specimens tested by private laboratories. Furthermore, a standard curve was not used for RT-PCR, preventing the quantification of viral RNA load, which would have normalized the assay runs and controlled for testing variations [15].

CONCLUSIONS

Although common investigative criteria have been established (see https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html), a standard case definition for confirmed reinfection has not yet been developed. In addition, it is unclear how health jurisdictions should count suspected and confirmed reinfections in official case counts, which might lead to inconsistent methods across states. Lack of a standard case definition or reporting approach precludes national epidemiologic analysis to identify populations at highest risk for reinfection, a mounting issue with the continued emergence of SARS-CoV-2 variants of concern. Although the effect of vaccination on SARS-CoV-2 reinfection and secondary detection is not yet known, SARS-CoV-2 vaccination is recommended, including in those with previous SARS-CoV-2 infection. After recovery from SARS-CoV-2 infection, individuals who are not fully vaccinated should continue to follow all infection prevention measures such as wearing a well fitting mask. Individuals with SARS-CoV-2 secondary detection ≥90 days after first infection should be isolated, and their contacts who are not fully vaccinated should be quarantined (see https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html). Where paired specimens are available, suspected reinfection cases should be confirmed with genomic sequencing, viral culture, and/or subgenomic messenger RNA analysis (see https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html). Considering resource limitations, reinfection confirmation could be prioritized in high transmission and high-risk settings (see https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html), among symptomatic patients, or for detections long past the 90-day time threshold. Epidemiologic studies, such as household transmission studies or contact tracing data analysis, could also be used to assess the impact of suspected reinfection on COVID-19 health outcomes.

Supplementary Data

Supplementary materials are available at *The Journal of 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.

Supplementary Table 1. Hospitalizations, symptoms, and mean cycle threshold (Ct) values among the first and secondary SARS-CoV-2 detections[a], COVID-19 case-patients, New Mexico, March–December 2020.

Supplementary Table 2. Hospitalizations[a] among the first and secondary SARS-CoV-2 detections[b], COVID-19 case-patients, New Mexico, March–December 2020

Supplementary Table 3. Sequencing results and GISAID[a] accession numbers for 2 patients with confirmed SARS-CoV-2 reinfection.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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