COVID-19 symptoms and SARS-CoV-2 antibody positivity in a large survey of first responders and healthcare personnel, May-July 2020

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Abstract

A SARS-CoV-2 serosurvey among first responder/healthcare personnel showed that loss of taste/smell was most predictive of seropositivity; percent seropositivity increased with number of COVID-19 symptoms. However, 22.9% with nine symptoms were seronegative, and 8.3% with no symptoms were seropositive. These findings demonstrate limitations of symptom-based surveillance and importance of testing.

Keywords: SARS-CoV-2, COVID-19 symptom, seroprevalence, first responders, healthcare personnel

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Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has often relied on symptom-based screening when coronavirus disease 2019 (COVID-19) testing resources are limited.[1] As a result, presymptomatic or asymptomatic transmission occurred and uninfected persons unnecessarily self-isolated.[1, 2] While universal testing has been called for,[2] it has not been widely implemented. Evaluations of how well symptoms predict infection have focused on association with COVID-19 test positivity, mainly reverse transcriptase polymerase chain reaction (RT-PCR).[1, 3-6] However, RT-PCR accuracy is dependent on timing relative to infection—persons with asymptomatic infection may not present for testing, and symptomatic infections may not be identified if testing occurs too long after infection.[2, 3] Thus, the predictive power of symptoms could be under- or over-estimated when evaluated by RT-PCR positivity compared to seropositivity.

We assessed the association between seropositivity and prior COVID-19 symptoms in a large serologic survey[7, 8] to inform COVID-19 surveillance and testing strategies. Serologic testing (conducted >2 weeks after infection)[9-12] is a cumulative measure of infection over recent months and can more completely reveal the association between COVID-19 symptoms and infection.

METHODS

During May 17-July 2, serologic surveys were conducted among first responders and healthcare personnel in the Detroit, Michigan metropolitan area and in New York City.[7, 8, 12] Region 2 South Healthcare Coalition (Michigan Department of Health and Human Services) and the NYC Department of Health and Mental Hygiene distributed survey recruitment materials to hospitals and emergency medical and public service agencies who shared materials with employees. Participation was voluntarily initiated by accessing a web-based questionnaire that included informed consent and eligibility screening for COVID-19 symptoms and RT-PCR positivity in the prior two weeks.[9-11] The survey collected data on presence of any of nine COVID-19 symptoms since March 1 and other items (see Supplement). Upon survey completion, participants received information about providing a blood sample at or near their workplace within the next 1-7 days.

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Serologic testing was performed with the ORTHO Clinical Diagnostics VITROS® Immunodiagnostic Products Anti-SARS-CoV-2 IgG Test.[9] Individual results were not shared with employers. CDC did not have access to personal identifiers. This activity was reviewed by CDC and was conducted consistent with applicable federal law (45CFR6, 21CFR56; 42USC§241(d); 5USC§552a; 44USC§3501 et seq) and CDC policy.

After exclusions (invalid test results, n=88, and implausible self-reported weight and/or height, n=25), 40,938 participants were included. Unadjusted SARS-CoV-2 seropositivity rates were calculated with 95% confidence intervals (CI) using exact binomial models. Adjusted seropositivity rates were estimated using two logistic regression models with covariates shown in the **Supplemental Table 1** (a priori model),[1, 7, 12, 13] plus either non-mutually exclusive dichotomous variables for nine COVID-19 symptoms (model 1), or one variable for number of symptoms (model 2). There was no evidence of multicollinearity: variance inflation factors were <1.9. A classification and regression trees (CART) approach was used to identify symptom combinations predictive of seropositivity. There were no meaningful symptom combinations that directly predicted seroprevalence. Therefore, infection severity was used as a surrogate response variable: seeking healthcare for COVID-19 symptoms and/or being hospitalized (n=6,351, 15.5%) versus not. The nine COVID-19 symptoms were evaluated as risk predictors. The optimal binary tree resulted in a high predictive area under the curve (0.903) with a 5% error rate for predicting participants with less severe symptoms and a 50% error rate for predicting participants with more severe symptoms. Symptom combinations identified by CART predictive of ≥70% prevalence of more severe symptoms were then assessed for seropositivity prevalence. SAS 9.4 software (Research Triangle Institute) was used for all analyses.

RESULTS

Overall, 16.2% (95% CI 15.9%-16.6%) of participants and 8.3% (95% CI 7.9%-8.6%) of asymptomatic participants were seropositive. Seropositivity decreased with age, was higher among men versus women, lower among non-Hispanic White persons compared with other race/ethnic

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groups and increased with increasing weight status (**Supplemental Table 1)**. Asymptomatic participants (n=23,294) represented 56.9% of the study population and 28.9% of those who tested seropositive (n=1,921 out of 6,645). Participants reporting new loss of sense of taste or smell since March 1 (8.5% of participants) had the highest seropositivity (76.5%, 95% CI 75.1%-77.9%) (**Figure panel A**). Seropositivity ranged from 14.1% (95% CI 13.1%-15.1%) among participants reporting any one symptom to 77.1% (95% CI 72.0%-81.6%) for all nine symptoms (**Figure panel B**).

Seroprevalence by symptom type was attenuated after adjustment but the pattern of increasing seroprevalence with increasing number of symptoms did not appreciably change (**Figure panel B**). Loss of taste/smell had the strongest association with seropositivity (55.6% adjusted seroprevalence, 95% CI 53.5%-57.7%), followed by fever, chills, muscle aches and cough (18.6% to 26.0%). Adjusted seroprevalence among asymptomatic participants was 14.5% (95% CI 13.9%-15.1%), a level similar for sore throat (12.0%, 95% CI 11.5%-12.5%), diarrhea (14.4%, 95% CI 13.6%-15.1%), and headache (15.7%, 95% CI 15.1%-16.4%).

Seropositivity among participants reporting symptom combinations identified by CART analysis is shown in the **Figure (panel C)**. Seropositivity was 62.8% among participants reporting a combination of fever, shortness of breath (SOB) and chills, and 82.1% among participants with fever, shortness of breath and loss of taste/smell. The combination of fever, SOB, chills and headache had a seroprevalence similar to fever, SOB and chills (63.6% versus 62.8%).

DISCUSSION

New onset of loss of taste/smell had the strongest association with seropositivity and was more common among younger participants as seen in other studies.[1, 4, 13] Seropositivity increased with number of symptoms. However, ~25% of participants reporting either loss of taste/smell or all nine symptoms were seronegative. Seropositivity associated with symptom clusters was high, but seronegativity was 18% for the combination with the highest seropositivity (fever, SOB and loss of taste/smell). Moreover, prevalence of this combination was low, limiting usefulness in

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symptom screening. Asymptomatic participants had adjusted seroprevalence similar to those reporting each of several other non-specific symptoms commonly associated with other infections and/or conditions (sore throat, diarrhea, and headache). Asymptomatic participants represented more than half of the study population and nearly 30% of those who tested seropositive. Previous studies have found ~20% of persons with positive RT-PCR tests remain asymptomatic.[5]

These findings suggest that recalled presence or absence of symptoms is insufficient screening criteria to accurately predict infection status. Other studies have noted the strong association of new onset loss of taste/smell with RT-PCR positivity.[1, 4, 5] Loss of smell in the absence of blocked nasal passages (that may be more indicative of upper respiratory infection or allergies) has been noted to have higher predictive value for RT-PCR positivity.[14] This is one of the first reports showing a strong association with seropositivity.[15] While obtaining accurate RT-PCR test results is dependent on testing close to time of infection, serology indicates infection over the past few months,[12, 16] and may identify asymptomatic persons who did not present for RT-PCR testing. This study demonstrates that symptom association with seropositivity is consistent with earlier associations found with RT-PCR positivity. Yet with both types of diagnostic tests, a substantial percentage of those with symptoms suggestive of COVID-19 have negative results. Although it is possible that some are false negatives, findings from a previous analysis in a subsample of this serology survey with previously confirmed infections (2,547 participants with state health department-confirmed RT-PCR positive results >2 weeks prior to study participation) showed that seronegativity was very low: 3% among those with loss of taste/smell, and 1.8% among those with nine symptoms.[12] In addition, supplemental laboratory testing showed high agreement between the Ortho IgG assay used in this study and the Ortho pan IgG assay and CDC pan IgG assay. All three of these assays demonstrated increased sensitivity compared to a fourth assay, suggesting false negatives are not common with the assay used in this study.[12] Thus, in the current study among the entire study population where most did not have confirmed prior infection,

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seronegativity most likely represents lack of previous infection rather than false negatives or failure to produce antibody.

Limitations include biases inherent in analysis of first responders and healthcare personnel who were likely healthier and younger compared to the general adult population. Additionally, results from this convenience sample may not be generalizable. Recall bias likely impacted symptom reporting with a recall period starting March 1 for a survey administered in May through July. We are unable to differentiate between false negative results, loss of antibodies,[17] and failure to develop antibodies.[12] The contribution of these three patterns to observed seronegativity could vary by symptoms, especially if certain symptoms are more strongly associated with more severe illness.

Overall, our findings highlight the limitations of symptom-based screening. Increasing the number of specific symptoms to improve specificity for seropositivity results in a lower proportion of persons with those combinations and thus, lower utility for screening. The corollary--there were relatively large percentages of infected persons with less specific symptom combinations or no symptoms at all—implies that many infected persons will be missed by symptom-based screening. In addition to principal mitigation measures (e.g., physical distancing, etc.), regular RT-PCR or other viral testing of persons at high exposure risk or with continuing contact with patients or the community can augment symptom-based strategies used to prevent transmission.

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NOTES

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Figure. Crude and adjusted† percent seropositivity for SARS-CoV-2: A. by symptom type B. bynumber of symptoms, and C. crude seropositivity for specific symptom combinations

† Adjusted for age group, sex, race/ethnicity, weight status, jurisdiction, medical conditions, and exposure to a COVID-19 positive household member

* Symptom combinations identified using classified regression tree approach

Note: SOB=shortness of breath

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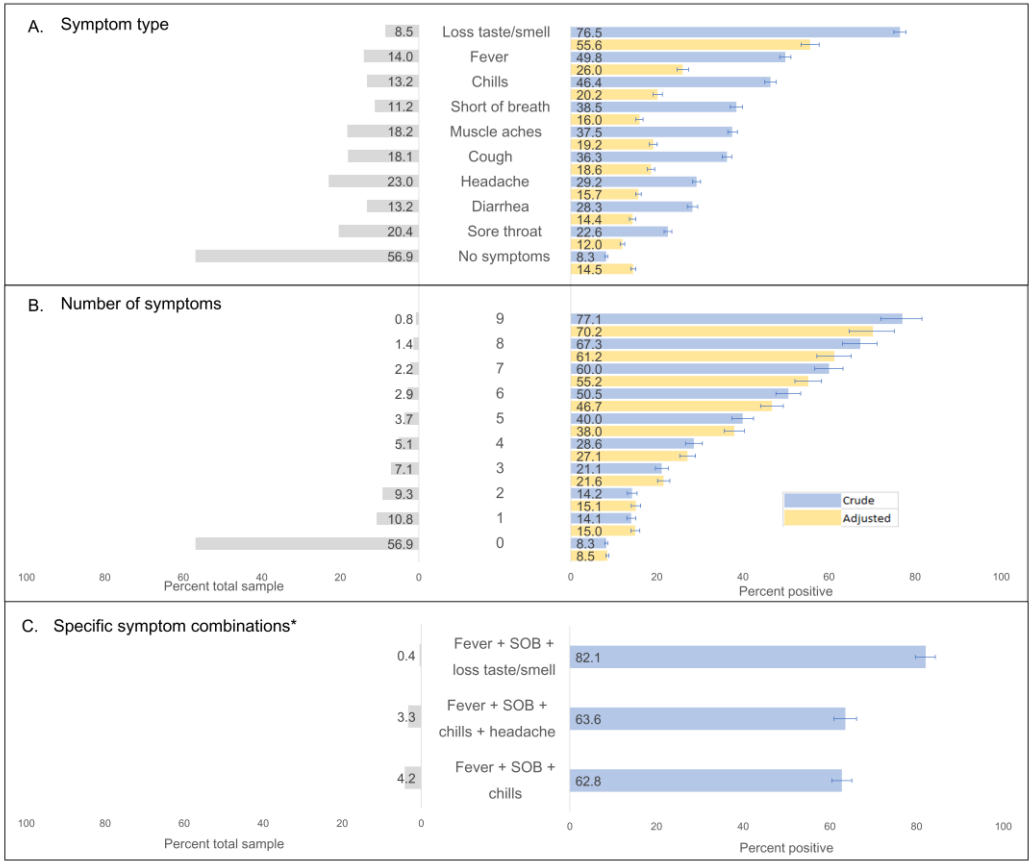
Figure 1


A. Symptom type
8.5
Loss taste/smell
76.5
55.6
14.0
Fever
49.8
26.0
13.2
Chills
46.4
20.2
11.2
Short of breath
38.5
16.0
18.2
Muscle aches
37.5
19.2
18.1
Cough
36.3
18.6
23.0
Headache
29.2
15.7
13.2
Diarrhea
28.3
14.4
20.4
Sore throat
22.6
12.0
56.9
No symptoms
8.3
14.5
B. Number of symptoms
0.8
9
77.1
70.2
1.4
8
67.3
61.2
2.2
7
60.0
55.2
2.9
6
50.5
46.7
3.7
5
40.0
38.0
5.1
4
28.6
27.1
7.1
3
21.1
21.6
9.3
2
14.2
15.1
10.8
1
14.1
15.0
56.9
0
8.3
8.5
Crude
Adjusted
100 80 60 40 20 0
Percent total sample
0 20 40 60 80 100
Percent positive
C. Specific symptom combinations*
0.4
Fever + SOB + loss taste/smell
82.1
3.3
Fever + SOB + chills + headache
63.6
4.2
Fever + SOB + chills
62.8
100 80 60 40 20 0
Percent total sample
0 20 40 60 80 100
Percent positive