Letters

RESEARCH LETTER

Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens

As of April 3, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had caused 972 303 cases of coronavirus disease 2019 (COVID-19) and 50 322 deaths worldwide.[1] Early reports from China suggested that co-infection with other respiratory pathogens was rare.[2] If this were the case, patients positive for other pathogens might be assumed unlikely to have SARS-CoV-2. The Centers for Disease Control and Prevention endorsed testing for other respiratory pathogens, suggesting that evidence of another infection could aid the evaluation of patients with potential COVID-19 in the absence of widely available rapid testing for SARS-CoV-2.[3] Here we report on co-infection rates between SARS-CoV-2 and other respiratory pathogens in Northern California.

Viewpoint

Methods | From March 3 through 25, 2020, we performed real-time reverse transcriptase–polymerase chain reaction tests for SARS-CoV-2 and other respiratory pathogens on nasopharyngeal swabs of symptomatic patients (eg, cough, fever, dyspnea). Our laboratory (Stanford Health Care) tested specimens from multiple sites in northern California. At some sites, specimens were simultaneously tested for a panel of non-SARS-CoV-2 respiratory pathogens (influenza A/B, respiratory syncytial virus, non-SARS-CoV-2 Coronaviridae, adenovirus, parainfluenza 1-4, human metapneumovirus, rhinovirus/enterovirus, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*). We included only specimens from sites that tested for this panel in addition to SARS-CoV-2.

We calculated the proportions of specimens positive for SARS-CoV-2 and for each non-SARS-CoV-2 pathogen, stratified by SARS-CoV-2 infection status. We evaluated differences in proportions with χ^2 tests with continuity correction (significance threshold, $P < .05$). We calculated mean ages of patients for all subgroups and compared means with 2-sided *t* tests. Analyses were conducted in R version 3.6.0 (R Foundation for Statistical Computing).

The analysis was performed as a quality assessment of a new diagnostic test, and the study was deemed exempt from human participants protection by the Stanford University institutional review board.

Results | We studied 1217 specimens tested for SARS-CoV-2 and other respiratory pathogens, from 1206 unique patients; 116 of the 1217 specimens (9.5%) were positive for SARS-CoV-2 and 318 (26.1%) were positive for 1 or more non–SARS-CoV-2 pathogens. **Table 1** reports patient demographics and location of testing, stratified by presence of SARS-CoV-2 and non–SARS-CoV-2 pathogens.

Of the 116 specimens positive for SARS-CoV-2, 24 (20.7%) were positive for 1 or more additional pathogens, compared with 294 of the 1101 specimens (26.7%) negative for SARS-CoV-2 (Table 1) (difference, 6.0% [95% CI, -2.3% to 14.3%]). The most common co-infections were rhinovirus/enterovirus (6.9%), respiratory syncytial virus (5.2%), and non–SARS-CoV-2 Coronaviridae (4.3%) (**Table 2**). None of the differences in rates of non–SARS-CoV-2 pathogens between specimens positive and negative for SARS-CoV-2 were statistically significant at $P < .05$.

Of 318 specimens positive for 1 or more non–SARS-CoV-2 pathogens, 24 (7.5%) were also positive for SARS-CoV-2. Among 899 specimens negative for other pathogens, 92 (10.2%) were positive for SARS-CoV-2 (difference, 2.7% [95% CI, -1.0% to 6.4%]).

Results were not substantially changed by restricting the analysis to 1 specimen per patient (defaulting to the second specimen when results conflicted): of 115 patients positive for SARS-CoV-2, 23 (20.0%) were positive for other pathogens, compared with 292 of 1091 patients (26.8%) negative for SARS-CoV-2

Table 1. Patient Characteristics and Sites of Specimen Collection, by SARS-CoV-2 and Non–SARS-CoV-2 Pathogen Status

Characteristic	SARS-CoV-2 status, No. (%)			
	Negative (n = 1101)		Positive (n = 116)	
	Positive for other respiratory pathogen	Negative for other respiratory pathogen	Positive for other respiratory pathogen	Negative for other respiratory pathogen
No. of samples	294	807	24	92
No. of patients[a]	292	800	23	92
Age, mean (range), y[b]	48.8 (7-82)	43.8 (1-100)	50.8 (9-88)	43.3 (1-98)
Female, No./total (%)[b]	161/292 (55.1)	443/800 (55.4)	12/23 (52.2)	52/92 (56.5)
Site of specimen collection, No./total (%)[c]				
Outpatient clinic	115/294 (39.1)	347/807 (43.0)	11/24 (45.8)	39/92 (42.4)
Emergency department				
Discharged	122/294 (41.5)	301/807 (37.3)	12/24 (50.0)	38/92 (41.3)
Admitted[d]	28/294 (9.5)	109/807 (13.5)	1/24 (4.2)	15/92 (16.3)
Inpatient	29/294 (9.9)	50/807 (6.2)	0/24	0/92

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Row sum (1207) is greater than the total number of unique patients (1206) because 1 patient was tested twice, 11 days apart, with different results for non–SARS-CoV-2 pathogens, and so appears in the first 2 columns.

[b] Mean age and proportion female are calculated with respect to unique patients.

[c] Proportions of samples collected at different sites are calculated with respect to numbers of samples.

[d] Denotes patients tested in the emergency department and admitted to an inpatient ward from the emergency department.

Table 2. Proportions of Specimens Positive for Non–SARS-CoV-2 Respiratory Pathogens and Mean Patient Ages for Each Subgroup, by SARS-CoV-2 Result[a,b]

	SARS-CoV-2 status			
	Negative (n = 1101)		Positive (n = 116)	
Pathogen	Proportion positive for other respiratory pathogen, No. (%)[b]	Mean age of positive patients, y	Proportion positive for other respiratory pathogen, No. (%)[b]	Mean age of positive patients, y
Influenza				
A	29/1101 (2.6)	45.9	1/116 (0.9)	74.0
B	8/1101 (0.7)	21.6	0/116 (0)	
RSV	32/1101 (2.9)	26.0	6/116 (5.2)	52.3
Parainfluenza				
1	1/1101 (0.1)	71.0	1/116 (0.9)	43.0
2	0/1101 (0)		0/116 (0)	
3	2/1101 (0.2)	40.0	1/116 (0.9)	45.0
4	5/1101 (0.5)	26.6	1/116 (0.9)	36.0
Metapneumovirus	47/1101 (4.3)	41.1	2/116 (1.7)	67.0
Rhinovirus/enterovirus	133/1101 (12.1)	32.6	8/116 (6.9)	42.1
Adenovirus	10/1101 (0.9)	14.1	0/116 (0)	
Other Coronaviridae	39/1101 (3.5)	42.2	5/116 (4.3)	40.8
Chlamydia pneumoniae	0/1060 (0)		0/116 (0)	
Mycoplasma pneumoniae	6/1101 (0.5)	14.8	0/116 (0)	

Abbreviations: RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Positive results for non–SARS-CoV-2 pathogens may in some cases represent the detection of residual virus in resolved cases, rather than clinical co-infection as such.

[b] None of the differences in proportions positive between patients positive and negative for SARS-CoV-2 are statistically significant at $P < .05$ (χ^2 tests with continuity correction).

(difference, 6.8% [95% CI, -1.5% to 15.0%]). Of 315 patients positive for other pathogens, 23 (7.3%) were positive for SARS-CoV-2, compared with 92 of 891 patients (10.3%) negative for other pathogens (difference, 3.0% [95% CI, -0.7% to 6.7%]).

Patients with co-infections did not differ significantly in age (mean, 46.9 years) from those infected with SARS-CoV-2 only (mean, 51.1 years) (4.2-year difference [95% CI, -4.8 to 13.2]).

Discussion | These results suggest higher rates of co-infection between SARS-CoV-2 and other respiratory pathogens than previously reported, with no significant difference in rates of SARS-CoV-2 infection in patients with and without other pathogens. The presence of a non–SARS-CoV-2 pathogen may not provide reassurance that a patient does not also have SARS-CoV-2.

The study is limited to a single region. Given limited sample size, restriction to multiply tested specimens, and spatiotemporal variation in viral epidemiology, the analysis is limited in the detection of specific co-infection patterns potentially predictive of SARS-CoV-2. Nonetheless, these results suggest that routine testing for non–SARS-CoV-2 respiratory pathogens during the COVID-19 pandemic is unlikely to provide clinical benefit unless a positive result would change disease management (eg, neuraminidase inhibitors for influenza in appropriate patients).

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Published Online: April 15, 2020. doi:10.1001/jama.2020.6266

Author Contributions: Drs Kim and Brown had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Drafting of the manuscript: Kim, Quinn.
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Conflict of Interest Disclosures: None reported.

1. Coronavirus Disease 2019 (COVID-19) Situation Report–74. World Health Organization. Published April 3, 2020. Accessed April 5, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200403-sitrep-74-covid-19-mp.pdf

2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7

3. Evaluating and Testing Persons for Coronavirus Disease. 2019 (COVID-19). Centers for Disease Control and Prevention. Published March 14, 2020. Accessed March 20, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html