Diagnostic Test Kinetics, Infectivity, and Immunological Responses Among Unvaccinated Adults During Acute SARS-CoV-2 Infection

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BACKGROUND

> Implementation of diagnostic testing for acute SARS-CoV-2 infection has been critical to identify COVID-19 cases, reduce transmission, and inform public health measures.

> Guidelines for SARS-CoV-2 have relied on limited data about duration of viral infectiousness and correlation with COVID-19 symptoms and diagnostic testing.

> Current public health guidance suggest a range of 5—20+ days of isolation for SARS-CoV-2-infected individuals.

> To determine the duration of viral infectiousness with replication-competent virus, we characterize the kinetics and variations of the following during and after an acute SARS-CoV-2 infection

- > Viral RNA
- > Viral antigens
- > Replication-competent virus
- > Isolation and viral growth assessment of several variants of interest/concern (VOI/VOC)

METHODS

> Prospective cohort study with serial measurements among adults with first SARS-CoV-2 infection.

> Participants were seen at baseline and for 5 follow-up visits with pre-defined windows. At each encounter we collected:

- > Anterior nasal (AN) swab (Puritan™ PurFlock™ Ultra Sterile Flocked Swabs 253806U)
- > Nasopharyngeal (NP) swab (VWR Flocked Nasopharyngeal Specimen Swabs 97-2012)
- > Venous blood

> AN swabs tested for nucleocapsid (N) and spike (S) antigens using electrochemiluminescence assay.

> Serum samples were tested for total (IgG +IgM +IgA) SARS-CoV-2 anti-spike antibody titers.

> Serum LOESS curve fit to quantitative data for each testing modality by days of symptom onset.

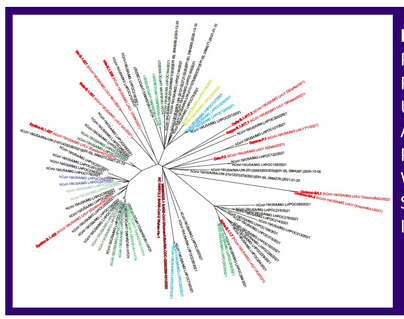


FIGURE 1. VIRAL PHYLOGRAM FOR UNVACCINATED ADULTS PRESENTING WITH ACUTE SARS-COV-2 INFECTION

FIGURE 2. TRAJECTORY OF (A) CLINICAL SYMPTOMS, (B) REPLICATION-COMPETENT VIRAL GROWTH, (C/D) VIRAL LOAD BY RT-PCR, (E) NUCLEOCAPSID AND (F) SPIKE ANTIGEN CONCENTRATIONS, AND (G/H) ANTIBODY TITERS, BY DAYS SINCE SYMPTOM ONSET.

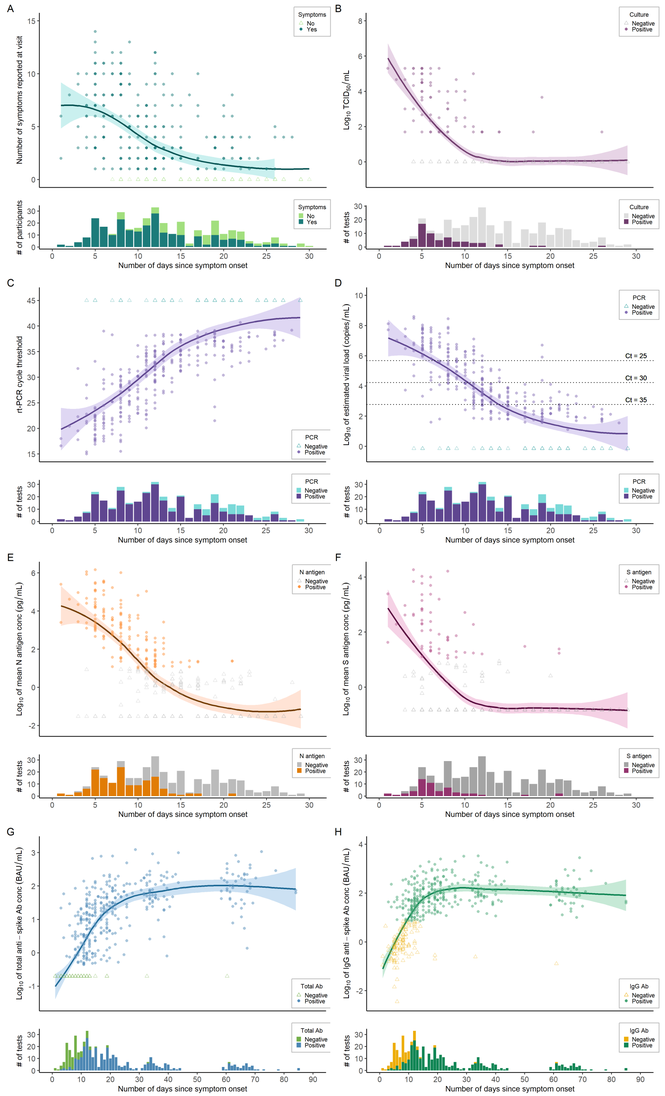


TABLE 1. ESTIMATES OF RELATIVE RISK OF INFECTIOUSNESS BASED ON SYMPTOMS, NUCLEOCAPSID (N) ANTIGEN OR RT-PCR TEST RESULT, AND COMBINATIONS, STRATIFIED BY DAYS SINCE SYMPTOM ONSET

	Relative Risk of Infectiousness (viral culture positive)		
	Days from Onset of Symptom		
	0-5 Days (N=110)	6-10 Days (N=138)	0-14 Days (N=306)
Symptoms Alone			
Presence of loss of smell/taste	1.07 (0.70-1.63)	0.48 (0.27-0.88)	0.67 (0.45-0.99)
Presence of fever	1.45 (0.84-2.52)	1.09 (0.50-2.42)	1.18 (0.71-1.93)
Presence of respiratory symptoms	2.16 (0.74-6.31)	1.61 (0.55-4.73)	1.48 (0.66-3.29)
Testing Alone			
N antigen test positive	**8.60 (3.50-21.14)**	**7.61 (3.01-19.22)**	**7.61 (4.33-13.35)**
RT-PCR test positive	—[b]	3.35 (0.65-17.3)	**7.14 (2.09-24.43)**
Combined Antigen Test and Symptoms			
N Ag test positive *among those* with loss of smell/taste	**11.57 (3.06-43.78)**	**7.25 (2.09-25.13)**	**8.21 (3.76-17.94)**
N Ag test positive *among those* with fever	**8.20 (2.89-23.32)**	**6.89 (2.22-21.38)**	**6.92 (3.66-13.10)**
N Ag test positive *among those* with respiratory symptoms	**6.13 (2.56-14.65)**	**7.14 (2.88-17.70)**	**6.67 (3.83-11.64)**
Combined RT-PCR Test and Symptoms			
RT-PCR test positive *among those* with loss of smell/taste	—[b]	1.97 (0.36-10.74)	**3.46 (1.06-11.32)**
RT-PCR test positive *among those* with fever	—[b]	2.37 (0.41-13.77)	**5.90 (1.64-21.22)**
RT-PCR test positive *among those* with respiratory symptoms	—[b]	3.32 (0.66-16.81)	**5.54 (1.67-18.37)**

FIGURE 3. MEDIAN DAYS FROM SYMPTOM ONSET TO FIRST NEGATIVE TEST AMONG SPIKE (S) ANTIGEN, VIRAL CULTURE, NUCLEOCAPSID (N) ANTIGEN, AND RT-PCR FOR VIRAL DNA

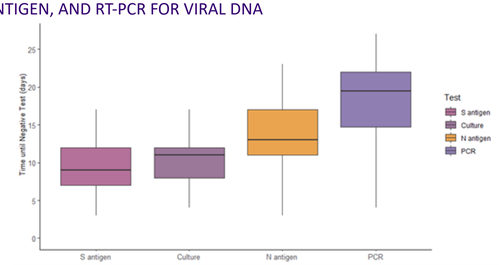
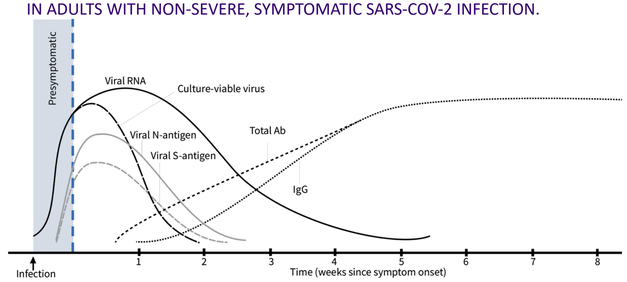


TABLE 2. ESTIMATES OF ADJUSTED RELATIVE RISK OF INFECTIOUSNESS BASED ON NUCLEOCAPSID (N) ANTIGEN OR RT-PCR TEST RESULT BETWEEN 0-14 DAYS SINCE SYMPTOM ONSET, AND STRATIFIED BY SYMPTOMS

	Adjusted Relative Risk of Infectiousness (viral culture positive)			
	Regardless of symptoms (N=306)	**Persons with loss of smell/taste** (N=198)	**Persons with fever** (N=226)	**Persons with respiratory symptoms** (N=268)
N antigen test positive	**7.66 (3.96-14.82)**	**7.33 (3.30-16.32)**	**4.77 (2.56-8.89)**	**5.11 (2.92-8.94)**
RT-PCR test positive	2.74 (0.81-9.25)	2.57 (0.75-8.79)	**4.12 (1.00-15.91)**	**4.25 (1.15-15.66)**

FIGURE 4. DIAGNOSTIC TEST KINETICS AND IMMUNOLOGICAL RESPONSES IN ADULTS WITH NON-SEVERE, SYMPTOMATIC SARS-COV-2 INFECTION.



DISCUSSION

> Among ambulatory adults with community-acquired SARS-CoV-2 infection, the Period of infectiousness averaged 11 days after onset of symptoms and extended to 15 days for several individuals.

> N antigen testing was the strongest predictor of the risk of infectiousness and was superior to COVID-19 symptom monitoring and molecular testing.

> Strengths of the study include high retention rates; repeated and consistent invasive sampling procedures; relatively young and healthy cohort more representative of general population.

> Limitations include exclusion of asymptomatic patients, who may be capable of transmitting infection; study design precluded ability to compare diagnostic results across variant sub-types.

CONCLUSIONS

> Most adults have replication-competent SARS-CoV-2 for 10-14 days after symptom onset.

> N antigen testing is a strong predictor of viral infectiousness.

> Within two weeks from symptom onset, N antigen testing, rather than absence of symptoms or viral RNA, should be used to safely discontinue isolation.

> These results can inform public health guidance and strengthen infection control to reduce SARS-CoV-2 transmission and accelerate ending the COVID-10 pandemic.

ACKNOWLEDGMENTS

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