Good morning. First and foremost, I hope all of you in the current severe winter situation are safe and warm. So many are still without power, water, and internet. I am very fortunate to have a generator. This has truly turned out to be a catastrophic event for so many.

For today under COVID-19 News the CDC has added new evidence and recommendations for duration of isolation and precautions for severely immunocompromised adults. The UK has updated findings on the B.1.1.7 variant.

Under journal reviews the first article is an analysis which may provide additional evidence to explain why B.1.1.7 may be transmitting more rapidly. The next two articles are from J Infect Dis looking at who may be superspreaders. The last article is from the Surviving Sepsis group. The committee decided on 13 priorities for COVID-2019 research.

Everyone please be safe

Ed

COVID-19 News

Interim Guidance on Duration of Isolation and Precautions for Adults with COVID-19
February 13, 2021
Added new evidence and recommendations for duration of isolation and precautions for severely immunocompromised adults. Severely immunocompromised adults with COVID-19 require additional testing and consultation with infectious disease specialists before ending their isolation period, in updated guidance. Studies have found that they can produce replication-competent virus beyond 20 days after symptom onset. For these purposes, severely immunocompromised patients include those who have cancer and are being treated with chemotherapy, untreated HIV infection with CD4 count of less than 200, combined primary immunodeficiency disorder, and receipt of prednisone of more than 20 mg per day for more than 14 days. A test-based strategy could be considered for determining when severely immunocompromised patients can end their isolation period.

Key other findings:

1. Concentrations of SARS-CoV-2 RNA in upper respiratory specimens decline after onset of symptoms. The likelihood of recovering replication-competent virus also declines after onset of symptoms. For patients with mild to moderate COVID-19, replication-competent virus has not been recovered after 10 days following symptom onset. In a large contact tracing study, no contacts at high risk of exposure developed infection if their exposure to a case patient started 6 days or more after the case patient's infection onset.
2. Recovery of replication-competent virus between 10 and 20 days after symptom onset has been reported in some adults with severe COVID-19; some of these cases were immunocompromised. However, in this series of patients, it was estimated that 88% and 95% of their specimens no longer yielded replication-competent virus after 10 and 15 days, respectively, following symptom onset.
3. Recovered patients can continue to have SARS-CoV-2 RNA detected in their upper respiratory specimens for up to 12 weeks after symptom onset. Investigation of 285 "persistently positive" adults, which included 126 adults who had developed recurrent symptoms, found no secondary

infections among 790 contacts to these case patients. Efforts to isolate replication-competent virus from 108 of these 285 case patients were unsuccessful.

UK Update on B.1.1.7

The UK scientists said last month that there was a "realistic possibility" that the UK variant (B.1.1.7) was not only more contagious than others, but also may be more lethal. Now, they say in a new document released last Friday that it is "likely" that the variant is linked to an increased risk of hospitalization and death. Some evidence cited suggested that people infected with the variant may have higher viral loads, a feature that could not only make the virus more contagious but also potentially more lethal. The variant has spread to at least 82 countries, and is being transmitted 35 to 45 percent more easily than other variants in the United States, scientists recently estimated. American officials have suggested that the variant could be the dominant source of infection there by March. See below

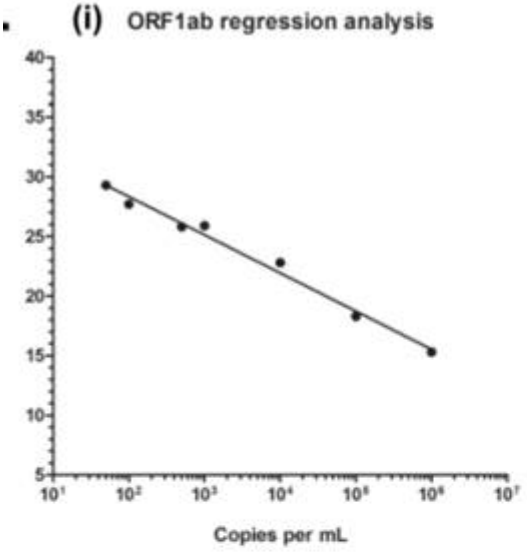
Journal Reviews

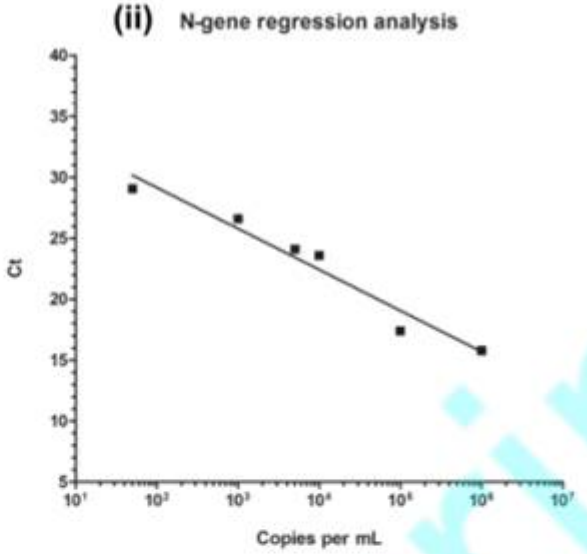
S-Variant SARS-CoV-2 Lineage B.1.1.7 is Associated with Significantly Higher Viral Loads in Samples Tested by ThermoFisher TaqPath RT-qPC

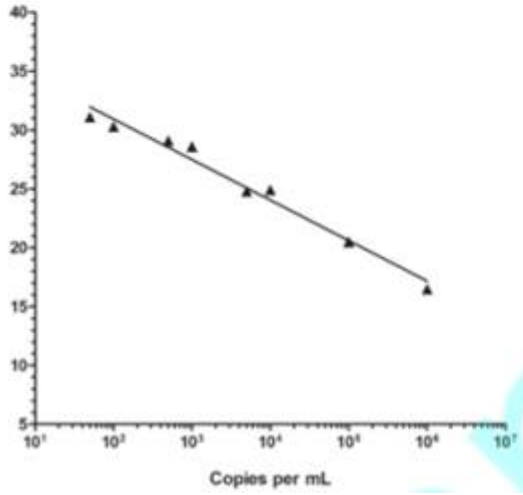
J Infect Dis published online February 13, 2021

Doi/10.1093/infdis/jicb082/6134354

A SARS-CoV-2 variant B1.1.7 contains a mutation Δ69/70 which is spreading rapidly in the UK. Recent published evidence shows that the presence of the Δ69/70 mutation in the viral genome, causes the SGTF phenomenon in TaqPath RT-qPCR tests, strongly correlates with presence of the VOC / B1.1.7 in clinical samples as determined by sequencing, and is now used as an epidemiological proxy for presence of the variant. The ThermoFisher 'TaqPath' test co-amplifies three SARS-CoV-2 viral gene targets from a single clinical sample (ORF1ab, N, and S). The variant shows an identifiable profile in ThermoFisher TaqPath RTqPCR (S-gene target failure; SGTF). The investigators analyzed recent test data for trends and significance of this SARS-CoV-2 lineage. They linked Ct values for respiratory samples which showed that a low Ct for ORF1ab and N were clearly associated with SGTF. Significantly more SGTF samples had higher inferred viral loads between $1x10^7$ and $1x10^8$. They conclude that patients whose samples exhibit the SGTF profile are more likely to have high viral loads, which may explain higher infectivity and rapidity of spread. Bottom line, samples collected from COVID-19 patients for B.1.1.7 viral loads found that those infected with the variant had up to 10,000-fold higher viral loads than those infected with other virus strains.







(iv)

	Viral gene target		
	ORF	N	S
Slope:	-3.20	-3.365	-3.439
Y-intercept:	34.74	35.89	37.8
1/slope:	-0.31	-0.2972	-0.2908
R square:	0.9868	0.9526	0.9783
P value:	< 0.0001	0.0009	< 0.0001
Efficiency:	1.05	0.98	0.95

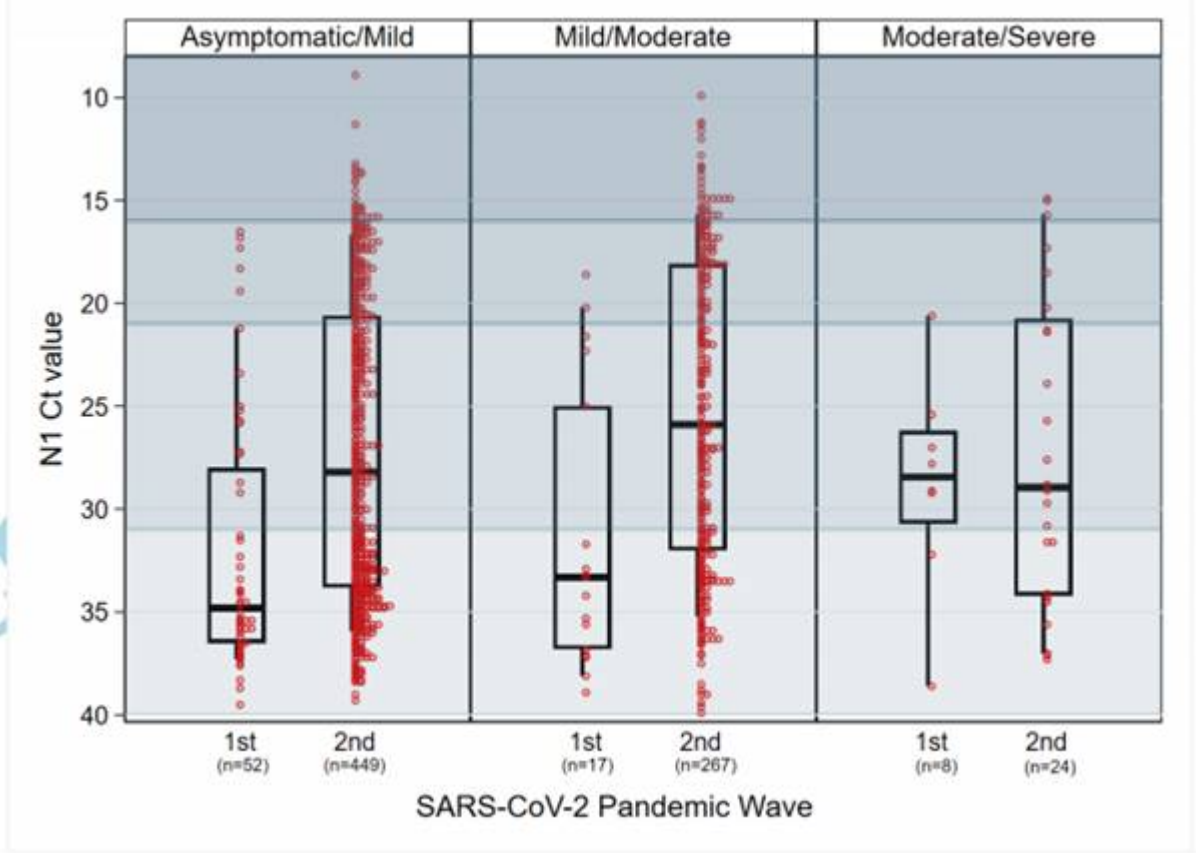
Comment: Their analysis may provide additional evidence to explain why B.1.1.7 may be transmitting more rapidly amongst populations, but it does not provide an explanation of how an increased viral load could occur. If verified by others, the biological plausibility of its higher infectivity, whether through evolutionary viral replication advantages or evasion of the host immune system, is yet to be determined.

Viral Load of SARS-CoV-2 in Adults During the First and Second Wave of COVID-19 Pandemic in Houston, TX: The Potential of the Super-Spreader

J Infect Dis published online February 15, 2021

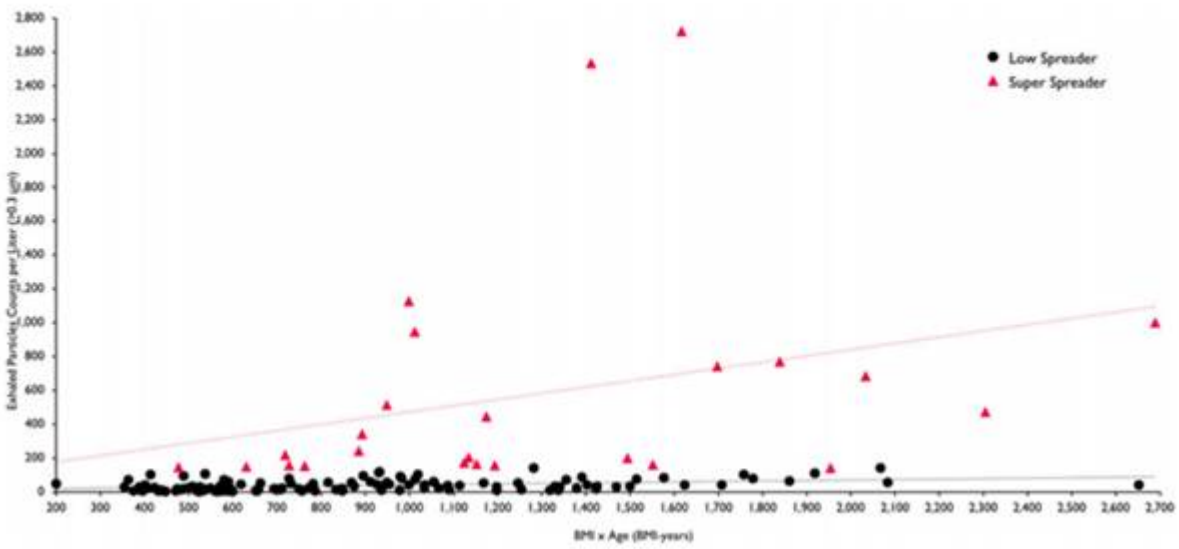
doi/10.1093/infdis/jiab097/6135117

Researchers at Baylor College of Medicine compared SARS-CoV-2 loads in 1,319 COVID-19 patients from Mar 18 to Aug 15, 2020, in Houston. In the second pandemic wave, a small number of patients had extremely high average viral loads, meaning that they could have been super-spreaders, even though they are not sick or only mildly ill. The potential super-spreaders were most likely to be otherwise healthy women who did not require hospitalization. The length of viral shedding was similar in patients with no symptoms and those with mild to moderate illness.



Comment: The finding that many were asymptomatic or had mild illness indicates the challenge. Without appropriate viral detection, social distancing and quarantine, individuals who have extremely high viral load may be able to spread SARS-CoV-2 and sustain transmission. Could these individuals be consistent with the super-spreader phenomenon [like we saw in SARS] and that greater awareness of the social dynamics of these individuals is needed to understand the spread of SARS-CoV-2 in our community. This finding clearly supports universal masking and social distancing.

Exhaled Aerosol Increases with COVID-19 Infection, Age, and Obesity
PNAS published online February 2021
doi.org/10.1073/pnas.2021830118
The investigators studied respiratory droplet generation and exhalation in human and nonhuman primate subjects with and without COVID-19 infection to explore whether SARS-CoV-2 infection, and other changes in physiological state, translate into observable evolution of numbers and sizes of exhaled respiratory droplets in healthy and diseased subjects. In this observational cohort study of the exhaled breath particles of 194 healthy human subjects, and in their experimental infection study of eight nonhuman primates infected, by aerosol, with SARS-CoV-2, they found that exhaled aerosol particles vary between subjects by three orders of magnitude, with exhaled respiratory droplet number increasing with degree of COVID-19 infection and elevated BMI-years. They observed that 18% of human subjects accounted for 80% of the exhaled bioaerosol of the group, reflecting a superspreader distribution of bioaerosol analogous to a classical 20:80 superspreader of infection distribution.



Comment: These findings suggest that quantitative assessment and control of exhaled aerosol may be critical to slowing the airborne spread of COVID-19 until we reach herd immunity including use of masks and social distancing. These findings indicate that the capacity of airway lining mucus to resist breakup on breathing varies significantly between individuals, with a trend to increasing with more severe COVID-19 infection and body mass index multiplied by age (i.e., BMI-years).

Surviving Sepsis Campaign: Research Priorities for Coronavirus Disease 2019 in Critical Illness
Crit Care Med published online February 12, 2021
DOI: 10.1097/CCM.0000000000004895
The Surviving Sepsis Research Committee, a multiprofessional group of 17 international experts representing the European Society of Intensive Care Medicine and Society of Critical Care Medicine came up with the most important priorities for COVID-2019 research. The entire committee voted on 58 submitted questions to determine top priorities for COVID-2019 research.

The Committee decided on 13 priorities for COVID-2019. Of these, the top six priorities were identified and include the following questions:

1. Should the approach to ventilator management differ from the standard approach in patients with acute hypoxic respiratory failure?
2. Can the host response be modulated for therapeutic benefit?
3. What specific cells are directly targeted by SARS-CoV-2 and how do these cells respond?
4. Can early data be used to predict outcomes of COVID-2019 and, by extension, to guide therapies?
5. What is the role of prone positioning and noninvasive ventilation in nonventilated patients with COVID-19?
6. Which interventions are best to use for viral load modulation and when should they be given?

Below is the entire list.

Top Ranked Research Questions Developed by the Surviving Sepsis Campaign Research Committee

Should the approach to ventilator management differ from the standard approach in patients with acute hypoxic respiratory failure?
Can the host response be modulated for therapeutic benefit?
What specific cells are directly targeted by SARS-CoV-2 and how do these cells respond?
Can early data be used to predict outcomes of COVID-19 and, by extension, to guide therapies?
What is the role of prone positioning and noninvasive ventilation in nonventilated patients with COVID-19?
Which interventions are best to use for viral load modulation and when should they be given?
Do endothelial cells play a central role in driving and/or potentiating COVID-19 disease?
What is the best approach to anticoagulation in patients with COVID-19?
What are mechanisms of vascular dysfunction and thrombosis in COVID-19 and why are thrombotic manifestations more common in SARS-CoV-2 infection compared with other infections or causes of critical illness?
How can quality research be performed and assessed during a pandemic?
Do the long-term sequelae of severe COVID-19 disease differ from sequelae of sepsis/acute respiratory distress syndrome?
How does SARS-CoV-2 impair immune function?
What are the predictors of ICU admission in COVID-19?

Comment: I think we would all agree this is a particularly good list. One question really caught my eye: How can quality research be performed and assessed during a pandemic? Perhaps the UK/Oxford RECOVERY Project should be examined as a model for the future. This would mean developing research networks and datasets across health care systems to enroll and analyze important research questions in a pragmatic, but scientific way.