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COVID–19
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Seroprevalence data continues to emerge — latest numbers from CDC surveillance

The Centers for Disease Control and Prevention (CDC) tested 11,933 blood samples originally collected for purposes other than SARS-CoV-2 testing.[1] IgG antibodies were detected to the SARS-CoV-2 spike protein using an ELISA assay estimated at 96% sensitivity and 99.3% specificity. These samples were from two commercial laboratories, collected from individuals in six different states, collected at different times and not necessarily timed to the peak of the COVID-19 outbreak in any location. This is important to point out given the data for NYC reflects a prevalence rate of 6.93% on March 23, 2020, well before peak infection rates in NYC were reached. Test dates and seropositivity are reported in Table 1.

As the pandemic progresses, seroprevalence will increase in the geographies affected by local surges in COVID-19.

Table 1

Test results → State/region ↓	Sample date	IgG-positive % (95% confidence interval)	Estimated infections/ reported cases
Connecticut	4.26.20–5.3.20	4.94 (3.61, 6.52)	6.0
South Florida	4.6.20–4.10.20	1.85 (1.00, 3.23)	11.2
Missouri	4.20.20–4.26.20	1.85 (1.00, 3.23)	23.8
New York City (metro)	3.23.20–4.1.20	6.93 (5.02, 8.92)	11.9
Utah	4.20.20–5.3.20	1.85 (1.00, 3.23)	10.5
Washington State (Puget Sound area)	3.23.20–4.1.20	1.13 (0.70, 1.94)	11.2

The exact prevalence of COVID-19 in the general population is still a matter for considerable debate. This is likely the result of widespread prevalence variation even among similar populations. We have estimates of prevalence in the general population ranging from 4.5% in Los Angeles County, CA,[2] 14% in New York,[3] 31.5% in Boston[4] (Table 2). Disease transmissions were likely facilitated by population density, particularly early in the pandemic. Hence, major metro areas worldwide have early prevalence higher than rural areas. French researchers demonstrated this with a prevalence of 9.9% in Paris and 3.0% in Hauts-de-France.[5] Recent studies claim disease prevalence is underestimated by as much as 10- to 100-fold as the result of incomplete testing and extensive asymptomatic infection.[6,7] This most recent study confirms these earlier estimates, suggesting actual cases were at least 10 times greater than reported cases.

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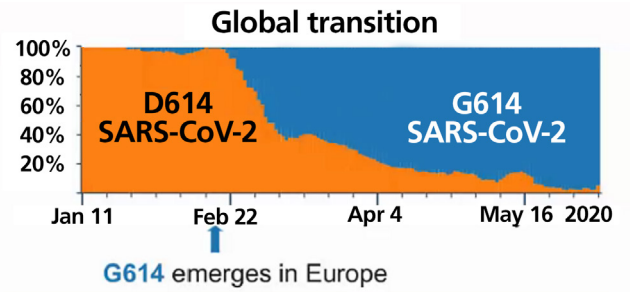
Table 2

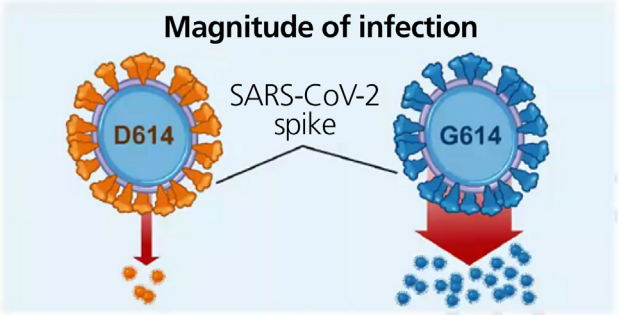
Location	% positive	Date of sample	Reference
Paris, France	9.9	5.11.20	Salje
Hauts-de-France, France	3.0	5.11.20	Salje
Boston	31.5	4.12.20	Vogel
Santa Clara	2.5–4	4.4.20	Bendavid
New York City	14	4.19.20–4.28.20	Rosenberg

It will continue to be important to follow local seroprevalence as the pandemic progresses. Despite widespread outbreaks, all surveys continue to demonstrate the majority of the population remains susceptible to infection and herd immunity, expected with a population seroprevalence of 60–70%, remains months away. The CDC plans to periodically restudy various geographies as the pandemic progresses.

SARS-CoV-2 spike protein changes — new strain now dominants worldwide

Researchers have reported changes in the genetic sequence of the spike protein of SARS-CoV-2.[8] The new strain, G614, produces more infectious virions, higher viral loads and an increased infectivity of the virus. As a result, this strain has become the predominant strain worldwide. G614 does not seem to have an increase in disease severity, as reflected by hospitalization status, despite the tendency that it produces higher viral loads. However, there have been some reports of higher mortality rates across countries associated with the G614 strain. These trends will need to be closely followed. The G614 strain continues to be neutralized by polyclonal antibody from the convalescent sera from previously infected individuals. This neutralization is equivalent to, or better than the original D614 strain.





Most of the vaccine candidates are targeting the spike protein as the primary target of immunity. The changes in the spike protein in G614 have not created enhanced resistance to neutralization by antibody in convalescent sera. However, it is not yet known if the G614 and D614 will be differentially neutralized by antibody generated by vaccination. It is also not known if the higher viral loads associated with G614 will require a more robust immune response to control, or if G614 continues to exhibit greater infectivity (higher R_o), then the percentage of immune individuals in the population needed to achieve herd immunity will also increase.

COVID-19-related rate of ischemic stroke[9]

Several lines of evidence point to an underlying hypercoagulability in COVID-19 infection. These include pathological evidence of widespread endothelial inflammation with in-situ thrombosis, marked elevation of D-dimer levels which correlate with increased COVID-19 related mortality, and evidence of increased rates of clotting in multiple arterial beds including the lungs, heart and brain. With respect to ischemic stroke, there have been small case studies of large vessel thrombotic stroke in younger patients with a paucity of risk factors. The actual rate of thrombotic stroke is unknown. A recent study in JAMA Neurology looked at the rate of thrombotic stroke in patients presenting to the hospital in the setting of COVID-19 infection and compared it to historical rates of thrombotic stroke in patients presenting with influenza from 2016–2018. Among over 1900 patients presenting to either the emergency room or hospitalized for COVID-19 infection at two academic hospitals in NYC, there were 31 cases of ischemic stroke, for an incidence of 1.6%. When compared with the incidence in patients presenting with influenza infections, this rate was over seven-fold higher. In the subset of patients with stroke, the median time from symptom onset to stroke symptoms was 16 days, suggesting that on average, this is a late COVID-19 complication.

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Eight patients presented with stroke, and in the other 23 patients stroke developed during the hospital stay. As might be expected, patients with stroke were significantly older and on average had more stroke risk factors, higher laboratory markers of inflammation, and more critical illness than patients without ischemic stroke. The youngest patient with ischemic stroke in the cohort was age 51 years. The median initial plasma D-dimer value was over three-fold higher in the patients who had stroke compared to those without stroke (P = .01). Although randomized controlled trials have not yet been published, the growing body of evidence of hypercoagulability in COVID-19 infection has prompted many institutions to develop anticoagulation protocols that vary the intensity of anticoagulation therapy to the magnitude of the D-dimer elevation. The above data confirm that ischemic stroke is a complication associated with COVID-19 infection.

Neurologic and psychiatric disorders reported among patients with COVID-19 — a surveillance study

Brain complications of COVID-19 have been increasingly recognized. A nationwide, cross-specialty surveillance study in the UK aimed to characterize the neurologic and psychiatric disorders related to COVID-19. Case contributors included clinicians in neurology, psychiatry, stroke and neuro intensive care. During a 3-week surveillance period, 125 patients were identified with neurologic or psychiatric complications associated with confirmed (91%), probable (5%), and possible (4%) SARS-CoV-2 infections.[10] The findings included:

Cerebrovascular events in 62% of the patients:

- Fifty-seven (74%) had ischemic stroke
- Nine (12%) had cerebral hemorrhage
- One (1%) had cerebral vasculitis

Altered mental status in 31% of the patients:

- Seven (18%) had encephalitis
- Nine (23%) had unspecified encephalopathy
- Twenty-three (59%) had some sort of neuropsychiatric disorder, including psychosis, neurocognitive impairment or other psychiatric disorder (depression, personality change, catatonia or mania)

Peripheral neurologic disorders in 5% of the patients:

- Four (67%) had Guillain–Barré
- Two (33%) had other peripheral disorders

Other neurologic disorders (opsoclonus–myoclonus syndrome, sixth nerve palsy, and seizures) were found in 2% of patients. Ischemic stroke and other cerebrovascular events were the most common neurologic complications in this cohort. The pathophysiologic mechanism(s) that lead to stroke among patients with COVID-19 have not been fully characterized. Possible mechanisms include vasculopathy due to endothelial cell infection,[11] a hypercoagulable state,[12] or conventional stroke risk exacerbated by critical illness. A large proportion of patients had altered mental status, seven of whom had encephalitis, defined as encephalopathy plus evidence of CNS inflammation. Altered mental status is not uncommon in patients admitted to hospital for severe infection, especially if they require intensive care. Excluding the patients with encephalitis, it is not clear whether patients developed altered mental status as a direct effect of SARS-CoV-2 or as an indirect effect of infection, hospitalization, treatment or other factors.

The current study lists numerous neurologic and psychiatric disorders diagnosed in a cohort of patients with COVID-19 infection. Unfortunately, the reported data have limited clinical value given several study pitfalls. Pitfalls include reporting bias, absence of a comparison group without COVID-19, and lack of reporting about clinical context and specific clinical characteristics. For example, what were the non-COVID-19 stroke risk factors? What was the clinical context for unspecified encephalopathy? Was mania drug related? Further research is needed to fully define the spectrum of neurological and psychiatric illness associated with COVID-19 infection.

Endotheliopathy in COVID-19 infection — new data on hypercoagulability

As noted in the above article, microvascular thrombosis, particularly in the pulmonary vascular bed, is a hallmark of COVID-19 infection. The endothelial cell is pivotal in the mediation of this process. SARS-CoV-2 enters the pulmonary endothelial cell via the ACE2 receptor, causing viral pneumonia, followed by a systemic inflammatory phase characterized by respiratory failure and multiorgan dysfunction. A key feature of COVID-19 infection is micro- and macrovascular thrombosis. This is characterized by high D-dimer and fibrinogen concentrations which define a prothrombotic state, with a venous thromboembolism prevalence of up to 69% in critically ill patients, even with the use of pharmacological thromboprophylaxis.

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Researchers at Yale have described the laboratory parameters that may suggest the etiology of this hypercoagulability.[13] They looked at markers of endothelial cell and platelet activation in 20 non-critically ill patients and compared the results with 48 critically ill patients with COVID-19. Both Von Willebrand Factor (VWF) antigen and soluble thrombomodulin were significantly correlated with mortality among all patients. VWF is stored only in endothelial cells and megakaryocytes therefore this elevation is likely due to endothelial damage. VWF activates platelets causing adhesion and aggregation and large VWF multimers can cause microvascular obstruction. The elevated VWF levels in these patients correlated with increasing disease severity (mean VWF antigen of 565% above normal in 48 patients admitted to the intensive care unit vs. 278% above normal in 20 non-ICU patients ($p < 0.0001$). Thrombomodulin elevation was also associated with increased mortality. Thrombomodulin normally lines endothelial cells and serves an anticoagulant function. Damage to endothelial cells releases thrombomodulin into the circulation. The authors proposed that COVID-19-associated coagulopathy is an endotheliopathy that results in augmented VWF release, platelet activation and hypercoagulability, leading to the clinical prothrombotic manifestations of COVID-19-associated coagulopathy, which can include venous, arterial and microvascular thrombosis. The factors responsible for this endotheliopathy and platelet activation are uncertain but could include direct viral infection of endothelial cells. This may underscore the need for early anti-viral and anti-inflammatory therapy in patients with COVID-19 pneumonia.

Sustained home SpO2 <92% — a reliable indicator of need for emergency care[14]

In this study, researchers followed 77 COVID-19 positive patients discharged from the emergency department (ED) with orders to self-check SpO2 every 8 hours via pulse oximetery and return to the ED if they experienced sustained SpO2 of <92% or otherwise felt they needed urgent medical care. During the next seven days, 25% of the patients experienced sustained SpO2 <92%. Of the 25% of patients with sustained hypoxia, 84% were subsequently hospitalized, with 30% also experiencing an ICU admission. Of the 75% of patients without sustained SpO2 depression, 10% were hospitalized and only 3% experienced an ICU admission.

Sustained SpO2 <92% was far more predictive of the need for hospitalization than any other demographic or laboratory marker studied by the authors. It was also predictive of ICU admission and septic shock, but not of mortality. The 92% cutoff is clinically useful because it corresponds to a PaO2 value of <60 mmHg, the threshold value for hypoxemic respiratory failure. Below 60 mmHg, blood oxygen delivery drops precipitously. Importantly, half of the patients hospitalized with SpO2 <92% had no other worsening symptoms — in other words, they would not have presented to the ED when they did if they were not checking SpO2 levels. Patients managing moderate to severe COVID-19 at home should regularly monitor SpO2 levels and present for emergency evaluation when SpO2 drops below 92% over two measurements 10 minutes apart, even if they feel stable symptomatically. Recall from the last edition of the COVID Forum (June 26), that prone ventilation in nonventilated patients corrected hypoxia in 76% of patients within 1–2 hours and therefore a trial of prone ventilation is reasonable prior to ER evaluation, assuming patients are otherwise stable.

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Kenneth Roy Cohen, MD, FACP | *Chief Medical Officer*

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA | *Senior Medical Director*

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD | *Senior Clinical Practice Performance Consultant*

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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