

COVID-19 DIGEST

From the Cross-Campus Infectious Diseases COVID-19 Task Force

Members: Joanne Engel, MD, PhD, Harry Lampiris, MD, Lisa Winston, MD, Annie Luetkemeyer, MD, Chaz Langelier, MD, PhD, Vivek Jain, MD, MAS, Deborah Yokoe, MD, MPH, Sarah Doernberg, MD, MAS, Jennifer Babik, MD, PhD, Monica Gandhi, MD, MPH, Rachel Bystritsky, MD, Ted Ruel, MD, Lynn Ramirez, MD, Charles Chiu, MD, PhD, Bryn Boslett, MD & Chesa Cox, MPH; **Co-Chairs & Digest Editors:** Brian Schwartz, MD & Diane Havlir, MD; **Guest Contributors:** Lillian Brown, MD, PhD, Monica Fung, MD, Andrew Kerkhoff, MD, PhD, Sarah Puryear, MD, Emma Bainbridge, MD, MPH

EPIDEMIOLOGY

LOCAL

The Bay Area and California are clearly and unfortunately on the upslope of a 3rd surge. Reported cases per day have tripled and the positive test rate has doubled over the last 3 weeks in [San Francisco](#), where an average of **105 cases per day** have been reported over the last 7 days and the [positive test rate](#) is currently 2.01%. While the Mission, Bayview-Hunters Point, and Excelsior continue to be the hardest hit neighborhoods, [new cases are distributed much more widely](#) across the city with the Marina and Presidio Heights among neighborhoods with some of the highest rates of new cases over the last month. As of the morning of November 20, **14,251 cases** and **156 deaths** have been reported since the start of the pandemic. More than **1 million cases of COVID-19** and **18,560 deaths** have now been reported in [California](#). [Hospitalizations](#) across the state have increased ~40% over the last 2 weeks with 4,755 people currently hospitalized with COVID-19—although numbers remain below the summer peak of 7,170 persons hospitalized on July 21. The [positive test rate statewide](#) over the last week is now up to 5.6%. On Monday, the governor's office announced 28 counties would be moved back to the most restrictive re-opening tier (the purple tier under the state's color-coded system), and 9, including San Francisco, would be moved to the second-most restrictive tier (red). The State announced a [curfew order](#) between 10 p.m. and 5 a.m. for residents of all counties in the most restrictive tier. Both the [California Department of Public Health](#) and the [San Francisco Department of Public Health](#) have issued travel advisories ahead of the Thanksgiving Holiday, advising residents to avoid all non-essential travel and to self-quarantine for 14 days following travel or after the departure of guests who have traveled from outside of the state.

NATIONAL

There are now more than **11.7 million cases** reported in [United States](#), and on November 18, **deaths due to COVID-19 exceeded 253,000**. More than 1 million cases and an average of an astounding 155,000 cases/day have been reported [over the last 7 days](#). Over **80,000 people** nationwide are currently [hospitalized](#) with COVID-19, the highest burden of hospitalizations to date since the pandemic began. [Deaths](#), which started increasing in late October, continue to rise and over the last 7 days an average of 1,975 people have died every day from COVID-19. While every region of the country is experiencing surging cases and hospitalizations, the upper mid-west, continues to experience the highest rates of new infections, hospitalizations, and deaths severely stressing the [health care system](#) as rural access hospitals and regional referral hospitals are reaching, or exceeding, capacity to care for patients. Unlike previous surges that hit the Northeast in the spring and the South/Southwest in the summer, the exponentially growing hospitalization burden nationwide means healthcare workers from other regions are less able to provide assistance. [Counties](#) designated as "Medically Underserved" by the Health Resources and Services Administration (HRSA), indicating areas with insufficient primary care providers, high infant mortality, concentrated elderly population, and/or high poverty have experienced death rates from COVID-19 1.5x higher than the general population. However, one bright spot is the surging interest in public health, with [applications](#) to Masters in Public Health programs up 20% this year.

GLOBAL

There are currently over **57 million** reported cases of COVID-19 and **1.3 million deaths globally**. As cases rise rapidly throughout Europe countries have re-imposed various levels of [restrictions](#): France and the [UK](#) are in a second national lockdown, Germany is in partial lockdown, Spain has declared a state of emergency, residents of Greece must send an SMS message to get permission to leave their home, nationwide tiered restrictions are in place in Italy, Ireland has

banned home gatherings. Notably, [schools have remained open](#) and an analysis of infections among children in [Germany](#) suggested that children were four times more likely to get infected at social gatherings than at school. [Sweden](#), which is currently experiencing a steep spike in infections, banned gatherings of more than 8 people. However, Sweden's Nordic neighbors, [Finland and Norway](#), are not currently experiencing similar surges despite less stringent restrictions. Both countries have implemented strict border controls, mandatory quarantines, and detailed contact-tracing focused on preventing superspreading events. Health officials also cite the overall trust in the government and adherence to health recommendations (in addition to low population density) as key to their epidemic response to date

VACCINES: SOME VERY GOOD NEWS

Two SARS-CoV-2 mRNA vaccines show high efficacy in first interim analysis of Phase 3 randomized control trials

[Pfizer BioNTech](#) and [Moderna](#) reported > 94% efficacy of their 2-dose vaccines to prevent symptomatic COVID infection during interim analyses of phase 3 trials. These vaccines use injected mRNA to stimulate hosts cell to produce coronavirus spike protein and thereby stimulate an immune response. mRNA is unstable and therefore nanotechnology and cold storage are required. It is a huge accomplishment to get these results within this timeframe, and a tribute to an unprecedented global effort. A summary of available data from recent press releases are below.

	Study participants	Interim results	Storage Parameters	Production expectation
Pfizer BioNTech	<ul style="list-style-type: none"> • 43,661 enrolled globally <ul style="list-style-type: none"> ○ 42% of global and 30% of US participants have racially and ethnically diverse backgrounds ○ 41% global and 45% US were 56-85 years of age 	<ul style="list-style-type: none"> • 170 COVID cases - 162 in placebo and 8 in vaccine group. Efficacy 95% • Efficacy consistent across age, gender, race, and ethnicity demographics • Efficacy in adults > 65 years was > 94% • No significant safety concerns 	-70° C	50 million doses in 2020 and up to 1.3 billion doses in 2021
Moderna	<ul style="list-style-type: none"> • > 30,000 enrolled in US <ul style="list-style-type: none"> ○ ~23% > 65 years ○ 42% < 65 years with high-risk chronic diseases ○ 37% from communities of color 	<ul style="list-style-type: none"> • 95 COVID cases - 90 placebo vs. 5 vaccine group. Efficacy 94.5% • All 11 cases of severe COVID in placebo group • No significant safety concerns 	-20° C but can be stored at 2-8° C for 30 days	20 million doses in 2020 and 500 million to 1 billion doses globally in 2021

Pfizer BioNTech [reported conclusion](#) of their phase 3 study, meeting all primary efficacy endpoints and having followed at least half of their participants for 2 months after vaccination. Participants will be followed for 2 year for long term safety. They plan to request for Emergency Use Authorization (EUA) from FDA in the coming days. Moderna has not reported final primary efficacy results.

Conclusion: These results are a bright spot in 2020. These vaccines work and may receive EUA from FDA in the near future. We expect distribution to health care workers and higher-risk populations shortly following approval.

Long-term safety follow-up and continuation of other vaccine studies is critical. Vaccines will not be effective at stopping the pandemic without broad uptake. Therefore, effective communication strategies to combat vaccine hesitancy is needed. We need to use these promising results now to motivate persons to follow effective public health measures to reduce transmission in the meantime.

LATE-BREAKING THERAPEUTICS UPDATES

Bamlanivimab, a viral-neutralizing monoclonal antibody, gains emergency use authorization COVID-19 treatment for high-risk outpatients

BLAZE-1 is a US-based phase 2 double-blind, randomized placebo-controlled [trial](#) of a monoclonal antibody targeted to the viral spike protein. 452 outpatients with mild to moderate COVID-19 were randomized to an IV infusion of one of three dosages of bamlanivimab (700, 2800, or 7000 mg) or placebo. In a pre-planned interim analysis, they found that (1) viral load decreased in all groups by day 11 (primary endpoint)—this reduction was significantly different with only a 2800mg dose, 0.53-fold lower than placebo; (2) symptoms from days 2-6 were less severe in the treatment group than placebo; and (3) 28-day incidence of emergency room visits or hospitalizations were significantly lower in the pooled treatment arm (1.6%) compared to placebo (6.3%), and 4.2% vs 14.6% in higher risk patients (age ≥ 65 or BMI ≥ 35) in a post hoc analysis. Infusion reactions were rare, but more common in the Bamlanivimab group. **Conclusion:** This study provides a proof of concept that bamlanivimab hastens viral clearance and mitigates disease severity. More data will be forthcoming on populations most likely to benefit and approaches to safely implement this intervention and reach affected communities.

Nebulized interferon beta-1a for COVID-19: early results from a Phase 2 trial

Interferon-beta-1a (IFN-B-1a) is a key antiviral cytokine of the innate immune response and levels have been shown to be decreased in patients with severe COVID-19. In a double-blind phase 2 trial, adults hospitalized, but not in the ICU, with COVID-19 were randomized to 14 days of daily nebulized IFN-B-1a vs. placebo. 101 adults were randomized; 48 received IFN-B-1a and 50 received placebo. Participants had a median duration of symptoms of 10 days. Odds of achieving the primary outcome (change in WHO 9-point Ordinal Scale for Clinical Improvement [OSCI]: 0, no infection; 8, death) was 2.32-fold higher among IFN-B-1a recipients. Severe disease or death (OSCI ≥ 5) occurred in 11/50 (22%) of placebo and 6/48 (13%) of IFN-B-1a recipients ($p=0.046$). Recovery (OSCI ≤ 1) at day 14 was seen in 21/48 (44%) of IFN-B-1a and 11/49 (22%) placebo recipients. IFN-B-1a treated patients showed improvements in self-reported breathlessness, but not in cough or sputum production. **Conclusion:** Nebulized IFN-B-1a in non-ICU, hospitalized patients with COVID-19 looks promising, but this trial was done prior to adoption of remdesivir and dexamethasone, so its impact in combination with these therapies is unknown and awaits further study. The nebulized delivery of IFN-B-1a excluded intubated patients and may also create infection control challenges for infectious patients.

Results of a phase 2 study of Fluvoxamine for the treatment of early COVID-19

Fluvoxamine, an SSRI that is FDA approved for the treatment of obsessive-compulsive disorder, has also been shown to dampen the inflammatory cascade through binding the σ -1 receptor (SIR) and appears to [protect mice](#) from septic shock. A small placebo-controlled, double-blind [RCT](#) fluvoxamine versus placebo x 15 days for prevention of deterioration in symptomatic outpatients without baseline hypoxia. The primary endpoint was clinical deterioration measured by meeting both 1) self-reported dyspnea or hospitalization for lower respiratory tract infection and 2) documented oxygen saturation $< 92\%$. Of 1337 adults assessed for eligibility, 181 (14%) ultimately were randomized with 152 (11%) receiving at least one dose of study drug. Six patients in the placebo group (8%) versus none in the fluvoxamine group met the primary endpoint (95% CI for absolute difference, 1.8-16.4%, $p = 0.009$). Major limitations include large numbers (18%) lost to follow-up, imbalance in distribution of those with low baseline oxygen saturations between groups (though median saturations did not differ), only 6 endpoints so a small number of events could affect

the statistical significance, and failure to analyze beyond the modified intention to treat population. **Conclusion:** This study raises the possibility that fluvoxamine may prevent progression of disease in non-hypoxic outpatients with COVID-19. However, it has significant limitations and patients with COVID-19 should not be prescribed fluvoxamine until a larger study can better assess its effectiveness.

Press release reports that canakinumab did not improve survival in patients with COVID-19 pneumonia

Canakinumab is a monoclonal antibody against IL-1 β and is FDA-approved for the treatment of several diseases including adult-onset Still's disease and familial Mediterranean fever. In a recent [press release](#), Novartis announced the interim Day 29 results of their CAN-COVID study, a phase 3 multicenter randomized control trial of canakinumab versus placebo for hospitalized patients with COVID-19-induced pneumonia and cytokine release syndrome. 454 patients were enrolled (including 25 at ZSFG and 10 at UCSF Health). Patients were all hypoxic but not requiring mechanical ventilation and had elevated C-reactive protein (≥ 20 mg/L) or ferritin (≥ 600 μ g/L). Patients who received canakinumab and standard of care (SOC) vs. SOC alone, had no significant difference in the primary endpoint of survival without needing mechanical ventilation (88.8% canakinumab + SOC vs 85.7% SOC, $p=0.29$) or the secondary endpoint of 4-week COVID-19-related mortality (4.9% canakinumab + SOC vs 7.2% SOC, $p=0.33$). There were no differences in safety measures between the groups. **Conclusion:** Canakinumab did not significantly improve outcomes in hospitalized patients with COVID-19 pneumonia. Analysis is ongoing to assess confounding due to concurrent therapies. Canakinumab should not be used routinely in the care of patients with COVID-19.

UP TO THE MINUTE DISPATCHES

What is the potential impact of college re-openings on vulnerable community members in surrounding communities?

Universities have been forced to weigh potential health risks versus educational and social benefits associated with reopening campuses. In September 2020, La Crosse County, Wisconsin experienced a large outbreak of COVID-19 coinciding with resumption of in-person education at three local colleges. In this [pre-print study](#), researchers used surveillance data and genomic sequencing to understand transmission events in La Crosse County. They found that the largest increase in new COVID-19 cases between March and September 2020 was during the second week of September directly following the return of students to campus, and that cases were concentrated in the immediate vicinity of the three colleges. Sequencing of a subset ($n=111$) of the county's September cases revealed that incident cases were largely explained by two COVID-19 sub-strains (clusters). The majority of cases (57%) were among those 17-29 years old and there was evidence of rapid spread among college-age individuals. However, 17% of cases were in those >60 years of age and genomic analysis revealed two independent transmission events into two community nursing facilities resulting in eight COVID-19 cases among residents of whom two died. **Conclusion:** This study supports a sobering reality—uncontrolled COVID-19 outbreaks at universities can spill into older populations in the community, including nursing homes, leading to tragic outcomes.

Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19

Patients with COVID-19 may be at high risk for venous and arterial thrombotic events, however the pathogenesis of hypercoagulability is not well understood. Some patients with COVID-19 have a prolonged aPTT, therefore a relationship with anti-phospholipid antibodies (aPLs) has been proposed. The detection of aPLs in patients with COVID-19 infection has been previously reported. A recent study, which measured eight types of aPLs in a cohort of 172 patients hospitalized with COVID-19 found aPLs in 52% of patients. The study also found that the presence of aPLs was associated with hypoxia, neutrophil activation and impaired renal function. IgG fractions isolated from patients with COVID-19 was found to accelerate venous thrombosis in a mouse model. **Conclusion:** This study presents an intriguing hypothesis on

the pathogenesis of hypercoagulability in patients with COVID-19. At present, the [American Society of Hematology](#) does not recommend screening for aPLs in patients with COVID-19 or empiric anticoagulation when aPLs are identified without another indication. Their guidance does not take into account this recent study.

FAQ

1. Can SARS-CoV-2 replicate and cause infection via the eye?

A recent [meta-analysis](#) showed that ~12% of COVID-19 patients have ocular symptoms, including conjunctivitis, discharge, redness, foreign body sensation, and pain; SARS-CoV-2 was detected by PCR from conjunctival swabs or tears in 3.5%. Ocular infection (and transmission) is thought to be theoretically possible since the ACE2 receptor is [highly expressed](#) in corneal epithelium and conjunctiva. However, a [recent study](#) called this into question by showing that SARS-CoV-2 could not replicate in human corneal tissue (using 7 donor corneal explants), in contrast to HSV-1 and Zika virus. The authors commented that corneal explants also contain some conjunctiva, so it is possible that neither corneal nor conjunctival tissue can support infection with SARS-CoV-2. **Conclusion:** This small study showed that SARS-CoV-2 was not able to replicate in corneal tissue. Further research is needed to confirm these results and to determine if SARS-CoV-2 can infect other structures of the eye (e.g., conjunctiva) and/or be transmitted via contact with the ocular surface.

2. Are immunocompromised patients capable of shedding virus longer than immunocompetent hosts?

Previous studies have shown that culturable virus (marker of infectivity) can be found for ~8-10 days after infection in most hosts. The duration of infectivity in immunocompromised patients is not known. Several recent case reports suggest that in select immunocompromised patients, shedding of infectious virus can be prolonged. Summary of 3 cases reports is below:

	Immunocompromising condition	Clinical disease	Duration of infectivity
Case 1	71 y/o with CLL and acquired hypogammaglobulinemia	Asymptomatic	70 days (culture positive)
Case 2	45 y/o with antiphospholipid syndrome treated with steroids, cyclophosphamide, rituximab, eculizumab	Pneumonia with 3 relapses over 152 days	152 days (culture not done but high virus levels by PCR)
Case 3	60 y/o with lymphoma treated with 2 anti-B-cell antibodies, cyclophosphamide, doxorubicin, and prednisone	Pneumonia with 3 admission over 4 months	119 days (culture positive)

Conclusion: Patients with profound immune suppression (particularly B-cell defects) may be infective for longer than immunocompetent hosts and may have relapsed disease in the setting of intensified immune suppression. It is unlikely that patients with more mild immune suppression are infective for such prolonged periods, but this does warrant continued study. Given that culture is not practical in clinical laboratories to guide discontinuation of patient isolation in severely immunocompromised patients, surrogates for the presence of infectious virus include measures of virus levels using standard RT-PCR, RT-PCR for replicative subgenomic RNA, and/or seroconversion titers.

3. Is mask wearing and social distancing reducing other viral infections in the United States?

Non-pharmaceutical interventions (NPIs), such as masking and social distancing, for COVID-19 will likely decrease the incidence of other respiratory viruses such as influenza A/B and RSV. Researchers at two academic medical centers in Boston and Atlanta therefore [compared](#) absolute case counts and pathogen-specific reproductive numbers of RSV/fluA/B, from the 2019-2020 season to the prior four seasons. Using respiratory viral panel data from outpatient and inpatients from January-May 2020, RSV/fluA/B transmission consistently decreased at an earlier timepoint in the season when compared prior seasons. Cases of influenza A in Atlanta, for example, decreased at week 12 of the viral season this year, coinciding with the first COVID-19 case and implementation of NPIs there, compared to week 15 in prior years. **Conclusion:** NPIs for COVID-19 likely reduce transmission of other respiratory viruses, resulting in abbreviated respiratory viral seasons. A similar phenomenon occurred in the [Southern Hemisphere](#)'s winter season, where little influenza activity was seen during their typical peak season. One challenge of this advantageous event is that less influenza data will be available to predict which strains to put in the yearly influenza vaccine for next year.

INSTITUTIONAL CONTACTS FOR CLINICAL OPERATIONS

ZSFG Hospital - Infection Control Team: Lisa Winston, MD (lisa.winston@ucsf.edu) and Vivek Jain, MD, MAS (vivek.jain@ucsf.edu) *Program Manager:* Elaine Dekker (elaine.dekker@ucsf.edu)

UCSF Health - COVID-19 Preparedness Leadership Team - Infection Prevention Team: Deborah Yokoe, MD, MPH (deborah.yokoe@ucsf.edu), Lynn Ramirez, MD, MPH (lynn.ramirez@ucsf.edu), Chaz Langelier, MD, PhD (chaz.langelier@ucsf.edu), and Amy Nichols (amy.nichols@ucsf.edu)

UCSF Benioff Childrens Hospital Oakland – Infection Prevention & Control Team: Ann Petru, MD (Ann.Petru@ucsf.edu), Charlotte Hsieh, MD (Charlotte.Hsieh@ucsf.edu), *Program Manager:* Amanda Lucas, MS RN CIC (Amanda.Lucas@ucsf.edu)

SFVAHCS - Infection Control Team: Harry Lampiris, MD (harry.lampiris@va.gov), Shelley Dwyer, RN (shelley.dwyer@va.gov), Alma Pipkin, RN (alma.pipkin@va.gov), and Scott Miller, RN (dean.miller2@va.gov)

UCSF Hospital Epidemiology and Infection Prevention COVID-19 webpage:

<https://infectioncontrol.ucsfmedicalcenter.org/ucsf-health-covid-19-resources>

San Francisco DPH link: <https://www.sfdcp.org/infectious-diseases-a-to-z/coronavirus-2019-novel-coronavirus>

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