

Update: October 30, 2020

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, Andrew Kerkhoff, MD, PhD, Annelys Roque, MD, Rand Dadasovich, MD, MS

EPIDEMIOLOGY

LOCAL

[San Francisco](#) averaged **34 new reported cases per day** over the last week and as of October 30, **12,320 cases** and **147 deaths** have been reported since the start of the pandemic. Less than 1% of [COVID-19 tests](#) in San Francisco have returned positive each day since the beginning of October. Statewide, **924,259 confirmed COVID-19 cases** and **17,575 deaths have been reported in California**. There are some concerning signs that the state and the Bay Area may be in the early stages of another surge, with upticks in case counts and hospitalizations. The [positive test rate statewide](#) over the last week was 3.3%, up from 2.7% two weeks ago. Imperial County, along the border of Mexico, and Tehama County, in northern California, saw the [highest rates of new infections](#) over the last 2 weeks. The director of Tehama County health services has attributed the rise in cases to [social gatherings](#) and issued an announcement asking the county to hold off on gatherings. [Outbreaks](#) have also occurred in a long-term care facility, a local business, and churches. Several [schools](#) were forced to close due to cases within the schools, however these cases were all linked back to infected household members and no transmission has been observed in the schools. The [Imperial County Health Officer](#) also links the rising COVID-19 case count in the county to social gatherings.

NATIONAL

The [United States](#), which has remained the global epicenter of the pandemic since March, is well into the 3rd surge. Daily reported cases are increasing with over 74,000 cases reported/day over the last week, the highest 7-day average since the start of the pandemic. More concerning, [hospitalizations](#) are up over 46% over the last month and [deaths](#) have started to rise again. Over **8.9 million cases** of COVID-19 have been reported and more than **229,000 people have died** due to COVID-19, although the true toll is certainly higher. The CDC estimated that [299,028 excess deaths](#) occurred in the United States between January 26 and October 3, with the highest burden of excess deaths among adults age 25-44 years and the Hispanic/Latinx population. Two-thirds of these excess deaths were attributed to COVID-19, however the additional excess deaths were likely indirectly related to COVID-19 through lack of access to medical care for other health problems; for example, 40 states have reported an increase in [opioid-related mortality](#) since the start of the pandemic. The current surge is widespread; 45 states report increasing case counts with the highest rates in the upper mid-West, including South Dakota, North Dakota, Montana, and Wisconsin. South Dakota leads the nation with a staggering [test positivity](#) of 41%. Wisconsin recently opened a [field hospital](#) at the State Fairgrounds.

GLOBAL

There are currently over **45 million** reported cases of COVID-19 and **1.1 million deaths globally**. The current surge is being experienced throughout the world. In Latin America, cases are rising steadily in [Argentina](#), which largely escaped the first wave, and is currently experiencing the 5th highest death rate in the world (behind the United States, India, Brazil, and Mexico). In [Europe](#) health officials in Belgium and Switzerland warn they could run out of beds in 2 weeks. Poland, which had very few cases during the spring has one of the most rapidly increasing epidemics in Europe. The [Warsaw stadium](#) was converted into a field hospital and 4 days ago Polish [President](#) Duda announced that he was infected with COVID-19 (just days after meeting with the presidents of Bulgaria and Estonia). In contrast, in China, a single asymptomatic case was reported last Saturday in Xinjiang prompting the government to conduct a mass testing campaign of over 5 million people, which identified an additional 137 asymptomatic infections.

UP TO THE MINUTE DISPATCHES

Should the SOLIDARITY Trial change how we use remdesivir for the treatment of COVID-19?

Remdesivir (RDV) is the only antiviral [FDA approved](#) for the treatment of COVID-19. [SOLIDARITY](#) is a 30-country WHO-sponsored open label trial that evaluates mortality among hospitalized patients at all stages of disease severity. 11,266 hospitalized COVID-19 patients were randomized to local standard of care vs. one of four study drugs: RDV, hydroxychloroquine (HCQ), lopinavir/ritonavir with interferon beta, and interferon beta alone. Data collection was limited, and some sites did not have all interventional arms available. The trial permitted steroids, other antivirals, and anti-inflammatories. In a pre-print, they reported no significant impact on the primary endpoint of in-hospital mortality in any of the arms; RDV (RR 0.95, 0.81-1.11), HCQ (RR 1.19 (0.89-1.59)), lopinavir/ritonavir (RR 1.10 (0.79-1.25)), interferon (RR 1.16 (0.96-1.39)) nor impact on initiation of ventilation or duration of hospital stay. Focusing on RDV (n=2742 vs. control n=2708), there was no significant difference in mortality by baseline oxygen requirement (none vs. any O₂ vs. intubated). Of note, 47% on RDV received steroids; an analysis of steroid association with outcomes was not presented.

How does this impact our understanding of remdesivir use? The NIH sponsored double blinded RCT of RDV vs. placebo ([ACTT-1](#)) in hospitalized patients found mortality varied according to baseline disease severity, with a significant reduction in those on low-flow oxygen (HR 0.30 [0.14-0.64]) in a secondary analysis. In analyses of patients with all stages of disease severity, like SOLIDARITY, they also did not find a statistically significant impact of RDV use on overall mortality at day 29 (HR 0.73, (0.52-1.03)). **Conclusion:** The short answer to the question is “No”, the SOLIDARITY trial should not be interpreted to mean there is no clinical benefit to RDV use. Indeed, in ACTT-1, RDV was associated with a 50% faster clinical status improvement (primary endpoint), 8 days less oxygen support, lower progression to invasive and non-invasive ventilation, and lower mortality among those on low flow oxygen. We continue to recommend remdesivir for the treatment of patients with COVID-19. We are continuing to study optimal combinations of anti-inflammatories and anti-virals to improve outcomes and reduce mortality in severe COVID-19. Stay tuned.

Tocilizumab, an IL-6 Receptor Blocker, for the treatment of COVID-19

Reports of elevated proinflammatory cytokines in severe COVID-19 led to interest in studying tocilizumab, an IL-6 receptor monoclonal antibody, and results from three peer-reviewed randomized trials have now been published. In a double-blind, randomized, placebo-controlled [trial](#) at 7 U.S. hospitals of 243 patients with severe COVID-19 and elevated inflammatory markers, tocilizumab did not reduce risk of progression to intubation or death (HR 0.83, 95% CI 0.38 to 1.81). The second [trial](#), an unblinded, randomized, open-label study of 130 patients at French hospitals with moderate or severe COVID-19, demonstrated lower rates of disease progression or death at day 14 in the tocilizumab group (24% vs. 36% with 95% posterior probability of HR <1), however there was no difference in day-28 mortality (adjusted HR, 0.92; 95% CI 0.33-2.53). The third [study](#) reported results from a prospective open-label RCT of tocilizumab vs. standard care in 124 patients in Italy with confirmed COVID-19 pneumonia and PaO₂:FiO₂ ratios of 200-300. The study was halted early in the setting of decreasing infections and resulting interim analysis, which showed comparable 14-day clinical worsening or death (rate ratio, 1.05, 95% CI, 0.59-1.86) and comparable mortality rates. These trials have many limitations, including small sample sizes, unclear timing of tocilizumab administration in disease course, lack of blinding and placebo controls, crossover, and potential confounding by other therapies received by the participants. It's also difficult to compare the studies since the study populations, primary endpoints, and methodologies were different. **Conclusion:** Current data does not support the routine use of tocilizumab in hospitalized COVID-19 patients. Additional randomized trial results are expected and may provide additional information on the role, if any, for this medication.

Case report of repeated short exposures to someone with COVID-19 resulting in infection

A “close contact” was previously defined by the CDC as someone who spent at least 15 minutes consecutively within 6 feet of a confirmed case. A recent [report](#) describes a Vermont correctional officer who had numerous, brief encounters during an 8-hour shift with 6 incarcerated or detained persons (IDPs) with RT-PCR positive, asymptomatic COVID-19. The officer developed mild symptoms one week after the shift and a positive RT-PCR. During contact tracing, it was

discovered that, while the officer's encounters (roughly 1 minute each) did not meet the above definition of "close contact," they added up to a cumulative 17 minutes of exposure within 6 feet. During all interactions, the officer wore microfiber cloth mask, gown, and goggles. IDPs were masked most (but not all) the time. The officer denied any non-occupational exposures. As a result of the study, the CDC has expanded their definition of "close contact" to someone who spends a cumulative 15 minutes over a 24-hour period within 6 feet of a confirmed COVID-19 case. **Conclusion:** This study may redefine contact tracing for congregate living situations where frequent, close interactions are necessary. However, the CDC has been criticized for a) changing close contact definitions based on one case since contact tracing may become more complicated and b) not including facial mask wearing by the exposed and infected individual in contact definitions.

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). 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.

FAQ

1. Do antibodies against seasonal coronaviruses that protect against "colds" help protect against SARS-CoV-2?

Seasonal coronaviruses are a common cause of upper respiratory tract infections ("colds"). Researchers have wondered whether cross-reactive immune responses elicited by seasonal coronaviruses could protect against SARS-CoV-2? Previous non-peer reviewed studies have detected the presence of SARS-CoV-2 reactive antibodies in pre-pandemic serum, but whether these patients had recent seasonal coronavirus infection was not addressed. In this new [study](#), the authors examined sera of 37 individuals with RT-PCR-proven seasonal coronavirus infection prior to 2020. They were able to detect neutralizing antibodies against the infecting strain of seasonal coronavirus in each sample. Some of the neutralizing antibodies against the infecting strain was cross-reactive to another seasonal coronavirus strain but none were found to be neutralizing to SARS-CoV-2. **Conclusion:** No, antibodies produced following seasonal coronavirus infections are not cross protective in laboratory studies against SARS-CoV-2.

2. What is the latest information on COVID-19 infection in cats and dogs?

A number of cases of COVID-19 have been reported in cats and dogs. A recent [study](#) sought to characterize the susceptibility of cats and dogs to SARS-CoV-2 infection. Five cats and three dogs were experimentally infected with SARS-CoV-2 into their nares. Two additional cats were exposed to two of the directly inoculated cats. Both the directly inoculated and the contact cats developed evidence of viral shedding as well as positive antibody titers. None of the cats developed symptomatic disease. None of the dogs developed evidence of viral shedding or clinical disease but all seroconverted. Three of the cats were re-challenged with direct nasal inoculation with SARS-CoV-2; none developed subsequent viral shedding. **Conclusion:** Based on this small study, cats can develop asymptomatic infection with SARS-CoV-2, transmit to other cats, and acquire immunity that protects against repeat exposure to the virus whereas dogs show serological evidence of infection but do not appear to shed virus.

The FDA Approval of Remdesivir

An interview with Katherine Yang, PharmD and Camille Beauduy, PharmD



Katherine Yang, PharmD, MPH
Clinical Pharmacist, Infectious Diseases
Clinical Professor, School of Pharmacy
University of California, San Francisco



Camille Beauduy, PharmD, BCIDP
Clinical Pharmacist, Infectious Diseases
Assistant Clinical Professor, School of Pharmacy
University of California, San Francisco

Remdesivir (Veklury®) was FDA approved last week. There are several changes in the FDA package insert when compared to the EUA, can you describe some of those changes that are important to providers?

The package insert recommends baseline serum creatinine and liver function tests prior to starting therapy, as well as a new recommendation to check the prothrombin time. Daily lab assessments are no longer required but should be checked as clinically appropriate. Lastly, while the EUA required discontinuation of remdesivir with ALT elevations ≥ 5 x upper limit of normal (ULN), the commercial labeling states to consider discontinuation if ALT ≥ 10 x ULN. Similar to the EUA, remdesivir is not recommended in patients with CLcr ≤ 30 mL/min, but as we saw in the last COVID Infectious Diseases Digest, the likelihood of renal toxicity is minimal and no dose adjustment is recommended.

Based on the package insert, can we use remdesivir for children?

Remdesivir is FDA approved for children aged 12 years and older who weigh at least 40 kg based on extrapolated data in adults who weighed 40 to 50 kg and limited data from the compassionate use program (N=39 pediatric patients). Given the lack of data, remdesivir approval has not been extended to those who do not meet the age and weight criteria; however, patients under 12 years old who weigh at least 3.5 kg can still receive remdesivir under the EUA. In these cases, remdesivir is given as a weight-based, rather than a fixed dose. A single-arm, open-label Phase 2/3 study of remdesivir in pediatric patients of all ages is in the recruitment phase.

Can we use remdesivir outside of the hospital?

The FDA approval states that remdesivir should be given in a hospital or other healthcare setting capable of providing similar acute care services as an inpatient hospital. This language allows for flexibility in interpretation, so there may be some outpatient facilities able to administer remdesivir based on their ability to provide higher acuity services. A Phase 3 randomized double-blind placebo-controlled trial of remdesivir in the outpatient setting is also currently underway. The primary objective of this study is to evaluate the safety and efficacy of 3 doses of remdesivir in reducing hospitalization and death.

Are there any drug interactions with remdesivir?

Clinical studies evaluating drug-drug interactions are lacking. While remdesivir is a substrate for many drug metabolizing enzymes such as cytochrome P450 (CYP) 3A4, Organic Anion Transporting Polypeptides (OATP) 1B1 and

P-glycoprotein (Pgp) transporters, remdesivir is predominantly metabolized by carboxylesterases and exhibits a high hepatic extraction ratio. Strong inducers of CYP3A4 (e.g., rifampin, phenobarbital, phenytoin) may reduce remdesivir concentration by up to 30%. The clinical relevance of these interactions is unknown. The Liverpool Drug Interaction Group provides up-to-date information on drug-drug interactions with all COVID therapies and can be accessed at <https://www.covid19-druginteractions.org>

Why is remdesivir not available as an oral formulation? Could other formulations be possible?

Remdesivir is a phosphoramidate and exhibits a high first pass hepatic extraction ratio which reduces its oral bioavailability. While it is currently limited to intravenous delivery, two Phase 1, randomized, placebo-controlled studies are underway to evaluate the pharmacokinetics and safety of inhaled remdesivir in patients with less severe disease; one via a [nanoparticle formulation](#) and the other as an [aerosolized solution](#). The hope is that these may show favorable effects and could be used earlier in infection before disease progresses to require hospitalization.

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.sfcddcp.org/infectious-diseases-a-to-z/coronavirus-2019-novel-coronavirus>

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