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COVID-19 DIGEST

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

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EPIDEMIOLOGY

LOCAL

California now reports **772,236 confirmed COVID-19 cases** and **14,735 deaths**. The positive test rate statewide continues to decrease and was 3.3% over the last week. As of September 16, **10,569 positive cases** and **91 deaths** have been reported in San Francisco. Both new cases and test positivity have been steadily declining since mid-August: over the last 7 days an average of 58 new cases were diagnosed per day and the positive test rate was 2.1%.

NATIONAL

Over **6.6 million reported cases** of COVID-19 and more than **197,000 deaths** have been reported in the United States, the undisputed global epicenter. While new diagnoses, hospitalizations, and deaths are improving across most of the country, the Midwest is currently experiencing the highest rate of new infections. Disparities in COVID-19 infections, hospitalizations, and deaths have been well-documented among Black, Latinx, and Native American populations in the U.S. The Pacific Islander community has also been devastated by the COVID-19 pandemic, particularly immigrants from the Marshall Islands. At the peak of the COVID-19 outbreak in Arkansas the Marshallese, which made up 3% of the State's population, accounted for half of the deaths from COVID-19. In Oregon, the rate of COVID-19 infections among Pacific Islanders is 12x higher than the rate among the White population. In Hawaii, non-Hawaiian Pacific Islanders make up just 4% of the State's population but 30% of COVID-19 cases. This population is especially vulnerable to COVID-19; they predominantly immigrated under the Compact of Free Association (COFA), which allows residents from Micronesia, the Marshall Islands, and Palau to establish residence in the United States, but are not entitled to citizenship or legal permanent residency, which makes it more challenging for them to access social safety net services. In addition, multigenerational living is common, they are disproportionately employed in low-wage frontline occupations at high risk for outbreaks, such as meat or poultry plants, and have the highest rates of diabetes in the world, a risk factor for poor outcomes from coronavirus infection. Quantifying the impact on this community is further challenged by data that does not report Pacific Islanders as a separate category (instead including in the "Asian" or "Other" categories).

GLOBAL

Worldwide there are currently over **29.9 million** reported cases of COVID-19 and **almost 1 million deaths (942,896 as of Thursday afternoon).** Israel, experiencing a surge in new cases, became the first country to impose a second national lockdown. In Southern Africa the effects of the pandemic continue to be far reaching despite infection rates that appear to be declining, as a recent analysis from the Southern African Development Community projects a surge in food insecurity and an increase in acute malnutrition of at least 25%.

UP TO THE MINUTE DISPATCHES

Is eating at a restaurant a higher risk activity for contracting symptomatic COVID-19 than other community-based activities?

To better understand drivers of community transmission of SARS-CoV-2, a case-control study conducted at 11 U.S. healthcare facilities compared community and close contact exposures in symptomatic, PCR-confirmed COVID-19 cases and unmatched, symptomatic, PCR-negative controls. A total of 154 cases and 160 controls were interviewed about contact with known COVID-19 cases, workplace exposures, mask-wearing behaviors, and other activities. The researchers found that controls were significantly more likely than cases to be non-Hispanic, White and college educated. Forty-two percent of cases reported close contact with a person with known COVID-19 infection (51% of whom were family members), compared to 14% of controls. Cases were twice as likely as controls to report dining at a restaurant in the two weeks preceding symptom onset (aOR = 2.4, 95% CI 1.5-3.8) although the survey did not distinguish between indoor versus outdoor dining. When participants with known exposure were excluded, the cases were significantly more likely to report going to a bar/coffee shop (aOR 3.9, 95% CI 1.5-10.1). Other community exposures, including shopping, social or religious gatherings, visiting a salon or gym, and use of public transportation, were not shown to be associated with COVID-19 although sample sizes were small. **Conclusion:** Community-based activities where mask wearing cannot be maintained, such as when eating and drinking, may be higher risk for contracting symptomatic COVID-19 than activities where mask wearing can be maintained.

Promising preliminary results for two COVID-19 therapeutics: Baricitinib & monoclonal antibodies

Eli Lilly and Company announced preliminary results from two clinical trials this week. The NIH-sponsored ACTT-2 platform trial evaluated the anti-inflammatory baricitinib, a Janus tyrosine kinase (JAK)-1/JAK-2 inhibitor approved to treat rheumatoid arthritis. This double-blinded placebo controlled trial randomized over 1000 hospitalized patients to receive 4 mg of oral baricitinib daily versus placebo for up to 14 days while hospitalized, and all patients received open label remdesivir for up to 10 days. Those receiving baricitinib recovered 1 day faster than the placebo group, a statistically significant difference. Overall patient outcomes on an 8-point ordinal scale favored baricitinib. **Conclusion**: Baricitinib appears to provide modest benefit for treatment of COVID-19. Additional details from this trial will be needed to understand the balance of benefits and harms across the spectrum of COVID-19 disease severity. In addition, we now need to understand if baricitinib has an advantage over corticosteroids, when given in conjunction with standard of care remdesivir, and if baricitinib has any role in combination with steroids. Of note, baricitinib is substantially more expensive that steroids, which will need to be weighed along with the clinical benefits.

The second press release reported results from the ongoing BLAZE-1 phase II study of the LY-CoV555 neutralizing monoclonal antibody, which targets the spike protein of SARS-CoV-2. This trial randomized 452 outpatients with mild to moderate COVID-19 to receive placebo or one of three antibody doses (700 mg, 2800 mg, 7000 mg) within 3 days of an initial positive COVID test. For the primary endpoint, only middle dose of 2800 mg resulted in significant decline in viral load by day 11 compared to placebo, though most patients in all arms including placebo had viral clearance by that time. Hospital admission occurred for 5/302 (1.7%) of those receiving active antibody and 9/150 (6%) in the placebo group. Those who received the antibody demonstrated faster viral clearance at the earlier day 3 endpoint and demonstrated less frequent prolonged shedding. The treatment was generally well-tolerated. This antibody is under active study in several additional trials, including the NIH- sponsored COVID therapeutic platform trials ACTIV-2 (outpatients) and ACTIV-3 (inpatients). Zuckerberg San Francisco General Hospital is enrolling into ACTIV-2 (Annie.Luetkemeyer@ucsf.edu or call/text: (415) 806-8554) while UCSF Health is a site for ACTIV-3 (PI: Michael Matthay). **Conclusion**: Monoclonal antibody treatment carries significant promise for treatment and prevention of COVID-19. We need outpatient treatments to prevent progression to severe disease and that can help prevent forward transmission by reducing viral loads. Monoclonal antibodies are given intravenously and will likely need to be administered as early as possible to be effective, highlighting the need for early diagnosis and linkage to care.

Clinical outcomes among survivors of severe COVID-19

A recent study describes clinical outcomes among survivors of COVID-19 who had required ICU admission at a single institution in the US. As of July 30th, 102 patients were admitted to the ICU, 58% were discharged, 22% died, and 21%

remained hospitalized. Among the 59 discharged, 47% attended a post-COVID clinic ~6 weeks following discharge. The median age was 56 years. 25% were African American and 36% were Hispanic. 86% had required mechanical ventilation, for a median of 11 (0-27) days, and 75% had experienced ICU delirium. At clinic follow up, ~40% had abnormal pulmonary function tests (15% had obstructive lung disease, 19% had restrictive lung disease, 4% had both), and exercise tolerance was impaired. 25% had depression and 57% showed mild cognitive impairment. Only one patient had difficulties with their activities of daily living and no one required supplemental oxygen. **Conclusion**: Survivors of ARDS often have significant pulmonary disease, weakness, cognitive, and psychiatric problems even years out from their illness. Larger case series will be helpful to better understand long-term outcomes of patients with severe COVID. This study suggests that pulmonary, cognitive, and psychiatric issues are common in patients with severe COVID-19 post discharge but may be at a lower rate than with other types of ARDS.

FAQ

1. **Update on Astra-Zeneca vaccine trial hold due to possible transverse myelitis cases**
   The multi-national phase III AstraZeneca COVID vaccine study has been put on hold to investigate an adverse event occurring in a study participant in an ongoing Phase 1/2 UK study, evaluating the non-replicative adenovirus vector vaccine (ChAdOx1). In the limited information available to date, the participant developed symptoms after vaccination that may be due to transverse myelitis. Transverse myelitis is a rare inflammatory disorder which affects the spinal cord and can be caused by infection, immune-mediated neurologic diseases like multiple sclerosis, and autoimmune diseases like lupus. Case reports have suggested a rare association of transverse myelitis and other neurologic inflammatory syndromes with vaccination, but a series of over 64 million vaccinations and multiple additional analyses have failed to showed a conclusive association with currently available vaccines. The cause of transverse myelitis is unknown in up to 15-30% of cases even after a comprehensive evaluation. The current case is being evaluated by the FDA, the study DSMB and the NIH to make a determination if and when it is safe to proceed with the 30,000 person Phase III study. After review by British medical regulatory authorities, the Phase I/II study has resumed enrollment. **Conclusions:** Possible vaccine-associated serious side effects will inevitably occur during the numerous large COVID vaccine trials underway; it is reassuring that this case was reported and led to an appropriate temporary hold to allow for a thorough evaluation. In an unprecedented event, nine CEOS issued a joint safety pledge statement on Tuesday. We need an effective vaccine that the public has confidence of its safety for it to have maximal effectiveness.

2. **What testing is available to determine if a patient is still infectious with SARS-CoV-2?**
   Culture is the gold standard test for assessing SARS-CoV-2 infectiousness, however it is not clinically available nor easily performed in most research laboratories due to the requirement for biosafety level III containment as well as technical challenges. Several studies have now demonstrated that viral load correlates with infectiousness and that the cycle threshold of a PCR assay can serve as a proxy for infectiousness, with a cycle threshold (Ct) > 35 on most PCR assays equating to lack of infectiousness. Because peak viral load and infectiousness occurs before symptom onset and then markedly declines, time from symptom onset is often an accurate metric for infectiousness and is now recommended by the CDC to guide hospital transmission-based precautions. Most COVID-positive individuals are non-infectious after 10 days due to the production of neutralizing antibodies, although severely ill or immunocompromised individuals may remain infectious for up to three weeks, with few exceptions thus far identified. **Conclusion**: As of today, we continue to use symptom-based strategy to define the end of the period of infectivity for most patients but PCR Ct values > 35 and other testing methods may become more widely used in the future.

3. **What are the clinical outcomes of young adults admitted to the hospital with COVID-19?**
   While the burden of disease was highest in older adults at the beginning of the COVID-19 pandemic, hospitalizations for COVID-19 among younger adults have increased in the later stages of the pandemic. A recent study analyzed the clinical characteristics and outcomes of young adults (aged 18-34 years) in the US who were hospitalized with COVID-19. Of the 3222 adults included in the study, 10% required mechanical ventilation and 2.7% died. Factors

associated with a greater risk of mechanical ventilation or death included morbid obesity, hypertension, and male sex. Young adults with more than one of these risk factors had a risk of mechanical ventilation or death similar to that of middle-aged adults (aged 35-64 years) with COVID-19 and no comorbidities. **Conclusion:** Although the mortality rate among hospitalized patients with COVID-19 remains higher in older age groups, young adults, particularly those with morbid obesity and hypertension are at risk for severe COVID-19. The public should be made aware of this data to reinforce the importance of prevention strategies such as masking and social distancing for all age groups.

Q&A on the SARS-CoV-2 Immune Response with Dr. Tim Henrich and Dr. Rachel Rutishauser

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What are they ways we develop immunity to viruses? What determines whether short vs. long term immunity is induced?
The immune response to viral infection involves (1) activation of the innate immune system (cells that recognize broad pathogen classes and produce inflammatory cytokines, such as type I interferons) followed by (2) activation of the adaptive immune system. The cells of the adaptive immune system recognize specific pathogens and include B cells, which make antibodies, and T cells, including CD4+ T cells that help B cells to produce antibodies and CD8+ T cells which can directly kill infected cells. Pathogen-specific adaptive immune responses can persist long-term, and individuals who have persistent immune responses may be protected against developing high viral loads and/or symptoms upon re-infection. Many factors including host genetics, antigen load, and inflammatory milieu during acute infection determine how long adaptive immune responses persist.

What do we know about human immunity to coronaviruses?
Four other coronaviruses (CoV) circulate widely in the human population and cause symptoms of the common cold, and two (MERS-CoV and SARS-CoV), like SARS-CoV-2, have caused outbreaks of severe lower respiratory tract infection with the potential for multiple organ inflammation and dysfunction. Coronaviruses have developed many mechanisms to evade and dysregulate the type I interferon response. Infection with CoV results in development of virus-specific B and T cell responses and antibody production. Previous studies have shown substantial waning of neutralizing antibody titers after infection with common cold CoVs as well as SARS-CoV and MERS-CoV (particularly after mild disease), while long-lived virus-specific T cell responses have been found in individuals who have undetectable levels of neutralizing antibodies.

What have we learned about the types of immune responses generated following SARS CoV-2 infection?
SARS-CoV-2 can also suppress activation of the innate immune system. SARS-CoV-2-specific antibodies are detectable within 1-2 weeks, and neutralizing antibodies as well as SARS-CoV-2-specific CD4+ and CD8+ T cells have been observed in patients following infection. Neutralizing antibody titers wane early after infection (as expected) and individuals with mild/asymptomatic disease have lower antibody titers. However, memory B cell responses are

capable of rapidly producing neutralizing antibodies and functional virus-specific memory T cell responses have been detected in individuals with low or undetectable neutralizing antibody levels (reviewed here). Finally, antibody and T cell cross-reactivity with other coronaviruses has been described. The contributions of these immune responses to protection from SARS-CoV-2 is unclear.

Based on what we have learned to date, what types of immunity are most important following SARS-CoV-infection?
As discussed above, antibody and T cell responses likely play a critical role in the immune response to active disease and prevention of re-infection. Higher titers of antibodies, especially those that exhibit potent viral neutralizing activity, may be particularly important. Mucosal immune responses (e.g., IgA antibodies and tissue resident memory T cells) may also play a crucial role in the immune response as this is the initial and major site of SARS-CoV-2 infection and replication. Although there are currently no established immune correlates of protection for SARS-CoV-2 (i.e., a known level or type of immune response required to confer protection), memory and B and T cell responses generated in response to natural infection and/or vaccination are an essential component of the coordinated immune response to SARS-CoV-2.

Based on our understanding of immunity, do we expect certain types of vaccines to be more effective and longer lasting?
Several vaccine approaches are currently in later-state human trials, including those that incorporate SARS-CoV-2 protein subunits, recombinant viral vectors (*e.g.* adenovirus-based), inactivated virus, virus-like particles, and direct delivery of viral protein coding nucleic acids (RNA and DNA). Many of these approaches have been developed for preventative and/or therapeutic vaccination for HIV and have been rapidly redeployed for COVID-19. However, very few of these formulations have FDA approval even in other settings and there is a paucity of data suggesting how protective or durable the elicited immune responses may be. A number of these vaccine strategies may elicit high neutralizing antibody responses and virus-specific T cell responses, but larger Phase 3 placebo-controlled clinical trials will be crucial in understanding vaccine safety and efficacy.

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UCSF Hospital Epidemiology and Infection Prevention COVID-19 webpage:
https://infectioncontrol.ucsfmedicalcenter.org/ucsf-health-covid-19-resources
San Francisco DPH link: https://www.sfcdcp.org/infectious-diseases-a-to-z/coronavirus-2019-novel-coronavirus/

Previous digests can be found: hividgm.ucsf.edu/covid-19
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