Update: December 11, 2020

COVID-19 DIGEST

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

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VACCINE UPDATES

In record speed, the global scientific community has developed first-generation vaccines, several with proven efficacy for prevention of symptomatic COVID disease. The news is exhilarating, and it could not have come at a better time. Every day, there are many unanswered questions and new information. We will do our best to keep you updated.

Updates on the Pfizer BioNTech mRNA vaccine: The New England Journal of Medicine published results from the pivotal efficacy trial of vaccine candidate BNT162b2. Additional information is in their FDA briefing document. Primary efficacy among 36,621 persons were included in the per-protocol efficacy analysis in preventing COVID-19 at least 7 days after the second dose of vaccine was 95%. There were 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses showed similar efficacy point estimates across age groups, genders, racial and ethnic groups. The vaccine appeared to show protection beginning at 14 days after Dose 1. Adverse reactions included injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%) and fever (14.2%). Severe adverse reactions were more frequent after Dose 2 and less frequent in participants ≥55 years (≤2.8%) vs. younger participants (≤4.6%). Four cases of Bell's palsy were seen in the vaccine group with no cases in the placebo group. The FDA advisory group voted to recommend approval on December 10th; final FDA approval is pending review. Doses of the vaccine are already positioned across the US for immediate use as soon as FDA-approval is in place. Roll out has begun in the UK where the vaccine is already approved. Two recipients with a history of severe allergies experienced an allergic reaction, prompting the UK health service to advise against vaccination of those with significant allergies for now.

Updates on the Moderna mRNA vaccine: Over 30,000 people enrolled into the US Phase 3 study. An updated press release described their primary analysis based on 196 cases of COVID-19, of which 185 cases were observed in the placebo group vs. 11 cases in the vaccine group, resulting in a point estimate of vaccine efficacy of 94.1%. All 30 cases of severe COVID-19 occurred in the placebo group. Efficacy was consistent across age, race and ethnicity, and gender demographics. No new serious safety concerns were reported. A report on immunogenicity data of 34 participants of the Phase 1 trial at 119 post-vaccination (90 days after second vaccination) reported high levels of binding and neutralizing antibody that declined slightly overtime. When compared to 41 controls who were convalescing from COVID-19 (mean 34 days post diagnosis), titers in the vaccine recipients were higher. Moderna will be presenting to the FDA on December 17th to request approval of EUA.

Updates on the AstraZeneca adenoviral vector vaccine: Unlike the other 2 vaccines, this is a replication-deficient chimpanzee adenoviral vector vaccine. Results of a pooled analysis of phase 2/3 trials in the UK and Brazil were reported. The Brazilian study used two full-dose vaccinations where efficacy among 8,895 participants was 62.1%. In the UK study, 2,741 participants were randomized to a half-dose followed by a full-dose (due to an initial testing error) and 4,807 to full-dose for 1st and 2nd vaccine, compared to a meningococcal vaccine active control. The half/full dose efficacy was 90%, whereas the full/full dose efficacy was 60.3%; whether these strategies truly differ in efficacy and if so, why, is an area of active debate. Notably, the majority received the 2nd vaccination more than 6 weeks after the first dose and some more than 12 weeks later, due to evolving trial design. A pooled analysis of all 11,636 participants reported efficacy of 70.4%, and all severe cases occurred in the placebo arm of the trial. In the UK study, swabs were self-

collected weekly for SARS-CoV-2 PCR in all participants regardless of symptoms. Efficacy of the vaccine to prevent asymptomatic infection was only 27.3% overall, 58.9% with half/full dose and 3.8% with full/full dose strategies. Adverse events were similar in both treatment and control arms. The trial was halted at one point for safety concern due to several cases of transverse myelitis, one that was possibly related to vaccine, and two cases deemed unrelated—one in the control arm and one attributed to pre-existing multiple sclerosis. AstraZeneca is planning to use these data to prepare submission to regulatory agencies worldwide.

Summary of vaccine study results, characteristics, and approval status

Vaccine	Type; dosing	Study results	Storage; production	Status
Pfizer BioNTech	mRNA; 2 doses	**Enrollment:** 43,661 **Efficacy**: COVID cases—162 in placebo and 8 in vaccine group. Efficacy 94%. **Tolerability:** Injection site and systemic reactions common, particularly with second dose. More common in <55 years. No significant safety concerns. **Long-term immunogenicity**: Unknown	-70°C; 50 million doses in 2020 and up to 1.3 billion doses in 2021	Presented to FDA on 12/10/20 for EUA
Moderna	mRNA; 2 doses	**Enrollment**: >30,000 **Efficacy**: COVID cases -- 196 cases in placebo group and 11 cases in the vaccine group. Efficacy 94.1%. **Tolerability**: mild/moderate injection site reactions, with systemic reactions more common after the 2nd dose. No significant safety concerns. **Long-term immunogenicity:** Report of 34 Phase 1 trial participants at 119 post first vaccine dose had high levels of binding and neutralizing antibody.	-20°C but can store at 2-8°C for 30 days; 20 million doses in 2020; 0.5-1 billion doses globally in 2021	Present to FDA on 12/17/20 for EUA
Astra Zeneca	Replication-deficient chimpanzee adenoviral vector; 2 doses	**Enrollment**: 11,636 (pooled data from 2 trials using different dosing regimens) **Efficacy**: COVID cases 131—101 cases in control and 30 cases in vaccine arm. Efficacy 70%. Efficacy for preventing asymptomatic infection 27.3%. **Tolerability**: Non-severe local and systemic reactions common, less frequent in older participants. No significant safety concerns. **Long-term immunogenicity:** Unknown	2-8°C; 3 billion doses globally in 2021	Preparing submission to regulatory agencies worldwide

Vaccine implementation across the UCSF campuses: UCSF Health and ZSFG are awaiting receipt of a limited supply of the Pfizer BioNtech vaccine for distribution to healthcare workers caring for patients in areas highest-risk for exposure to SARS-CoV-2. Implementation strategies including staggering vaccination among units—taking into account that the side effects of the vaccine and how it may result in healthcare workers screening positive for COVID-19 symptoms. Additional

supplies of the Pfizer BioNtech and Moderna vaccines will hopefully be coming shortly to allow for complete vaccination of all healthcare workers across campuses.

THERAPEUTICS UPDATES

Clarity on the benefit of convalescent plasma in the treatment of COVID-19?

A double-blind, placebo-controlled clinical trial conducted in Argentina (PlasmAr), randomized 333 hypoxemic—but not intubated—patients with COVID-19 in a 2:1 ratio to receive a single unit of convalescent plasma (CP) vs placebo. CP was administered a median of 8 days (IQR 5-10) after symptom onset and was required to have an antibody titer of at least 1:400. More than 90% of participants in each arm received glucocorticoids; remdesivir was not available during the trial. There was no significant difference in the primary outcome of clinical status 30 days after plasma administration (OR 0.83, CI 0.52 – 1.35), nor secondary outcomes of 30-day mortality (11.0% vs 11.4%), time to hospital discharge, or SARS-CoV-2 total antibody titers at day 7 and 14 between the two groups. **Conclusion** Convalescent plasma did not improve outcomes in this cohort of hospitalized, hypoxic patients who were generally a week or more from symptom onset and is consistent with an increasing number of studies that have failed to establish benefit later in disease. Several studies have demonstrated a benefit within the first three days of symptoms, suggesting CP should be reserved for higher risk patients who can be treated very early in disease. The benefit of CP in immunocompromised patients, even later in disease, needs further exploration.

Baricitinib plus Remdesivir receives EUA for treatment of COVID-19

Baricitinib is a Janus kinase inhibitor FDA-approved for the treatment of rheumatoid arthritis. The FDA issued an Emergency Use Authorization for baricitinib in combination with remdesivir to treat hospitalized patients with COVID-19 requiring supplemental O_2. In the ACTT-2 randomized controlled trial of baricitinib plus remdesivir, 1,033 patients with moderate, severe, and critical COVID-19 illness were enrolled. Compared to placebo + remdesivir, the baricitinib + remdesivir group had a shorter time to recovery [7 vs. 8 days; HR 1.15 (95% CI 1.00-1.31), p=0.047] for all patients and was more pronounced among patients on high-flow nasal cannula or non-invasive ventilation [10 vs. 18 days; HR 1.51 (95% CI 1.10-2.08). There was no significant difference in rates of infection or thromboembolic events between the two groups. **Conclusion:** Baricitinib in combination with remdesivir reduces time to recovery, particularly in patients on high-flow nasal cannula or non-invasive ventilation. It can be considered in patients who have severe COVID-19 with a contraindication to steroids. The ACTT-4 trial has begun and will compare dexamethasone to baricitinib (both in combination with remdesivir) for the treatment of hypoxic, hospitalized patients with COVID-19. This study is enrolling patients on the UCSF Health and ZSFG campuses.

Regeneron's monoclonal antibody cocktail receives EUA for treatment of high-risk ambulatory patients

Following recent Emergency Use Authorization (EUA) approval of the monoclonal antibody, Bamlanivimab, the FDA issued an EUA for Regeneron's monoclonal antibody combination (casirivimab and imdevimab) for treatment of mild to moderate (e.g. non-hypoxic) COVID-19 in patients at high risk for progression. These two antibodies bind different parts of the spike protein, providing theoretical protection from mutational escape of the virus. The non-peer reviewed study was a double-blind, placebo-controlled, multicenter trial that randomized ambulatory participants with mild to moderate COVID-19 diagnosed within 3 days to receive placebo (n = 266) or two different antibody doses (n = 266 and 267 for the 2400 mg and 8000 mg doses, respectively). The antibody group demonstrated significantly larger drop in viral load at 7 days, the primary endpoint. Fewer patients in the antibody groups had medically attended visits for COVID-19 at 28 days (2.8% versus 6.5%) or hospitalization/ED visit (2% versus 4%), especially in those at high risk (3% versus 9%). A major adverse effect of the cocktail is infusion reaction. **Conclusion**: Casirivimab plus imdevimab carries promise for early treatment of COVID-19 disease to prevent progression in high-risk outpatients, but ongoing trials for both prevention and treatment must continue. Until additional results are available, these medications are not yet considered standard of care but may provide benefit for certain high-risk outpatients.

Remdesivir use in mechanically ventilated patients is associated with hospital discharge and extubation

The ACTT-1 study demonstrated shorter time to recovery in patients with COVID-19 treated with remdesivir, though subgroup analysis did not show clear benefit in patients requiring mechanical ventilation. In light of this finding and the results from the large, pragmatic WHO Solidarity Trial showing no mortality difference with remdesivir treatment, including those mechanically ventilated at baseline, many guidelines now advocate against use of remdesivir for mechanically ventilated patients. A recent observational study conducted in Italy assessed whether remdesivir use was beneficial in COVID-19 patients requiring mechanical ventilation. In the study, 113 patients requiring mechanical ventilation were observed over a period of 31 days. Remdesivir was used in 33 (29%) patients. After multivariate analysis, remdesivir use was significantly associated with hospital discharge (HR 2.25, 95% CI 1.27-3.97, p=0.005) and was independently associated with extubation (HR 2.10, 95% CI 1.19-3.73, p=0.011.) Although fewer deaths (15.2% vs 38.8%) were observed in those treated with remdesivir, this association was not statistically significant. The median time to receiving remdesivir was 7 days since intubation and further analysis showed that earlier use of remdesivir had a stronger association with hospital discharge. **Conclusion:** Remdesivir use in mechanically ventilated patients was associated with faster hospital discharge and higher extubation rates. The ACTT-1 study may not have followed these patients long enough to evaluate this outcome. Given this limitation of the ACTT-1 results and US hospital bed crises in the COVID surge, remdesivir should still be considered in mechanically ventilated patients, in conjunction with steroids. Getting persons extubated faster, discharged and opening up beds for both ill COVID and non-COVID patients will be lifesaving.

FAQs

1. **Is testing to shorten quarantine a safe strategy to prevent spread of SARS-CoV-2?**
   Quarantine is a cornerstone public health strategy for preventing transmission of SARS-CoV-2. Previously, a 14-day quarantine period from the time of last exposure had been recommended for persons exposed to others with COVID-19. Based on updated analyses and modelling data, the CDC recently provided additional options to reduce the duration of quarantine in asymptomatic individuals—7 days with PCR testing (performed on days 5-7)—or 10 days without testing. These durations should be effective for preventing most transmission events (96% and 99%, respectively, Table from CDC). **Conclusion**: Yes, these evidence-based reductions in quarantine duration safely allow for a faster return to work and a reduced burden of quarantine precautions for most persons exposed to individuals with COVID-19. In certain settings such as in hospitals or nursing homes, however, a longer duration of quarantine may still be warranted to maximally prevent transmission of SARS-CoV-2 to high-risk populations.

Quarantine duration	Residual post-quarantine transmission risk (%)					
	No testing		RT-PCR testing		Antigen testing	
	Median	Range	Median	Range	Median	Range
7	10.7	10.3-22.1	4	2.3-8.6	5.5	3.1-11.9
10	1.4	0.1-10.6	0.3	0.0-2.4	1.1	0.1-9.5
14	0.1	0.0-3.0	0	0.0-1.2	0.1	0.0-2

2. **What is our updated understanding of the association of Chilblain-like lesions and COVID-19 infection?**
   An increased frequency of chilblain-like lesions (colloquially known as "COVID toes") has been described since the beginning of the COVID-19 pandemic. Although postulated to be related to SARS-CoV-2 infection, a definitive link has not been found. In fact, two prior reports found no association and suggested that shelter-in-place lifestyle factors (more time barefoot, sedentary) might be a possible explanation. A recent study reported on 40 patients with chilblain-like lesions (all outpatients, median age 22 years, 53% female). SARS-CoV-2 PCR was negative in all patients, and 14 (30%) had a positive serology (note, 8 were positive for IgA, which has lower specificity than IgG or IgM). Patients with chilblains had higher IFN-alpha production (via whole blood stimulation) than a control group of

COVID-19 patients without chilblains. The authors suggest these results indicate a virus-induced interferonopathy, and they note that chilblains are described in genetic type I interferonopathies (reviewed here). **Conclusion:** This study reports an intriguing finding that chilblain-like lesions may be related to interferon-alpha dysregulation. However, definitive proof of a causal link with SARS-CoV-2 was not found.

3. **Did the D614G mutation contribute to the pandemic potential of SARS-CoV-2?**
While SARS-CoV-2 mutates at a slower rate than many other RNA viruses, one mutation has been under close scrutiny, the replacement of aspartate with glycine at amino acid 614, located in the spike protein. Viruses harboring this mutation quickly became the predominant strain world-wide, now accounting for >96% of isolates. This observation raises the question as to whether this viral variant is more virulent—i.e., does it enter cells and grow better and/or is it more transmissible? This amino acid change may allow the spike protein to bind more efficiently to its cellular receptor, the ACE2 protein. It has also been observed that patients infected with D614G have higher upper respiratory tract viral loads, but not altered disease severity. Several new studies provide additional evidence that the D614G change enhances virulence. Analysis of the spread and frequency of the D614G variant in Great Britain suggests that this strain has a higher R_0, is associated with higher viral loads in younger patients, but does not correlate with higher COVID-19 clinical severity or mortality. In another study, the virus engineered to encode the D614G mutation exhibited more efficient infection, replication and fitness upon infection of primary human airway cells. The D614G mutant virus also transmitted faster between Syrian hamsters and showed enhanced competitive fitness. In a third study, a virus engineered with the mutation showed enhanced replication in human lung epithelial cells and in primary human airway tissues, as well as improved viral fitness in the upper airway of infected hamsters. **Conclusion**: These studies provide additional support for the idea that this single amino acid change in the spike protein leading to D614G strain has likely contributed to the extensive spread of the SARS-CoV-2 pandemic.

4. **How long do neutralizing antibodies persist after SARS-CoV-2 infection?**
Most individuals develop neutralizing antibodies to SARS-CoV-2 after infection, but the duration of their detection may depend on initial disease severity. This study evaluated changes in antibodies over 60 days among frontline healthcare workers in 13 hospitals across the U.S. Participants with positive SARS-CoV-2 spike protein antibodies at baseline in spring 2020 (n=156) underwent a second blood draw 60 days later. The antibody level (signal-to-threshold value) declined over time among 146/156 (94%) and 44 (28%) participants experienced seroreversion (antibodies below signal-to-threshold value). A higher proportion of participants who were asymptomatic seroreverted within 60 days: 23/48 (48%) of participants *without* symptoms compared to 21/108 (19%) with symptoms. In a multivariable model, lower baseline antibody levels and older age were associated with losing detectable antibodies at follow-up. **Conclusion**: Antibodies to SARS-CoV-2 decline over time and are more likely to become undetectable among those who were initially asymptomatic. However, memory T and B cell responses were not measured in this study and may both track past infection more reliably and protect against re-infection. Relying on just antibodies to detect past COVID-19 infection may underestimate prevalence.

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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

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