May 1, 2020
Keck School of Medicine of USC
COVID-19 Evidence-Based Summary
Section 1: What’s new this week
Section 2: Epidemiology, Seroprevalence, Incubation and Transmission
Section 3: Clinical Care
  a. Presentation, Diagnosis, Treatment, ICU Care, Outcomes and Immunity
  b. Pediatrics, Pregnancy, Breastfeeding, and the Elderly
  c. Palliative Care and Ethical Considerations
Section 4: Preventing Spread in Healthcare Settings
  a. Personal Protective Equipment and Hospital Precautions
  b. Airway Management and Intubation and Managing Exposures in Healthcare Settings
Section 5: Health System Best Practices
  a. The Four S’s of Disaster Relief Planning
  b. Primary/Outpatient Care (Telemedicine) and Surgery
  c. Supplemental Resources
Section 6: Virology, Drug and Vaccine Development
  a. Virology and Drug Targets
  b. Vaccine Development
Section 7: Public Health Considerations
  a. Modeling and Predictions, Simulations using “suppression” and “mitigation approaches”, ICU Needs Estimation
  b. Approaches to Easing Social Distancing Restrictions/Reopening the Economy
Acknowledgments
Section 1: What’s new this week?

- **Remdesivir:** The big news this week was the announcement of preliminary results of a randomized trial funded by the National Institute of Allergy and Infectious Diseases involving 1063 patients with COVID-19. The initial findings showed a median time to recovery of 11 days with remdesivir vs. 15 days with placebo (P<0.001). There was also a nonsignificant trend towards lower mortality with the drug (8.0% with remdesivir vs. 11.6% with placebo, P=0.059). Gilead also announced results from their own Phase 3 trial evaluating 5-day vs 10-day dosing duration, finding similar effects with both treatment durations and suggesting that 5 days of treatment may be sufficient. Based on these findings, the FDA plans to announce an emergency use authorization, which does not constitute a formal approval, but allows the Gilead to sell the drug during this public health crisis. Gilead reports that it currently has sufficient remdesivir to treat 140,000 patients, and intends to have sufficient supply for 1 million treatments by the end of the year. Despite the encouraging news, these two promising studies are preliminary and have not yet been peer-reviewed. Additionally, not all the news for remdesivir has been favorable. Another placebo controlled trial in the Lancet failed to demonstrate benefit.

- **Clarification Regarding the WHO's Statement on Immunity:** In response to critiques, the WHO clarified the conclusion of a recent scientific brief that indicated “there is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection … there is not enough evidence … to guarantee the accuracy of an ‘immunity passport’ or ‘risk-free certificate.’” In a clarifying tweet, the WHO explained: “We expect that most people who are infected … will develop an antibody response that will provide some level of protection.”

- **CDC List 6 New COVID-19 Symptoms:** The CDC has added six new symptoms to its list to watch for: chills, repeated shaking with chills, muscle pain, headache, sore throat and new loss of taste or smell.

- **New California Testing Guidelines:** California has released new recommendations, which suggest the need for testing among all those who are symptomatic as well as asymptomatic healthcare workers/essential employees, residents of congregate living facilities, the elderly and those with high risk comorbidities.

- **Link with out-of-hospital cardiac arrest:** A new report in the NEJM suggests a potential link between COVID-19 and a rise in out-of-hospital cardiac arrest in Italy.

- **Cerebrovascular complications:** There are increasing reports of cerebrovascular complications of COVID-19, including among younger individuals.

- **Pregnancy:** A new study concludes that “pregnant women have comparable clinical course and outcomes compared with reproductive-aged non-pregnant women when infected with SARS-CoV-2. No evidence supported vertical transmission of COVID-19 in the late stage of pregnancy including vaginal delivery.”

- **Diabetes is a risk factor for severe disease/death.** In a meta-analysis of 30 studies, there was a 4.64-fold increased risk of ARDS and a 2.12-fold increased risk of death.

- **Disparities:** A case series of hospitalized patients with COVID-19 in Georgia reports that “black patients were overrepresented, and their clinical outcomes were similar to those of nonblack patients.”
Factors Associated with Spread: A new CDC report offers insights on factors associated with the rapid spread of COVID-19 during February and March, including “travel-associated importations, large gatherings, introductions into high-risk workplaces and densely populated areas, and cryptic transmission resulting from limited testing and asymptomatic and presymptomatic spread.”

New Model Predicts Pandemic May Last up to Two More Years: A University of Minnesota report suggests that, absent a vaccine, this pandemic “will likely last 18 to 24 months [and] likely won’t be halted until 60% to 70% of the population is immune.”

Vaccine updates: An adenovirus vector vaccine developed at the University of Oxford, began a Phase I trial (1,100 people) last week and will start a combined Phase II/III trial (5,000 people) in May. Injection with an “old-fashioned” killed virus vaccine (PiCoVacc) protected macaques from challenge. Human trials began April 16. Numerous other vaccines are in development.

Potential new drug target: A trial is underway in NY to test if the heartburn drug famotidine could inhibit the main viral protease Mpro. Computational modeling and other observations support a drug-Mpro interaction.

Criteria for Lifting ‘Stay at Home’ Orders in LA County: Los Angeles County has announced four criteria it will use to determine when to lift ‘stay at home’ orders: a) Ensuring hospitals have capacity to care for both COVID-19 and non-COVID-19 patients; b) Ensuring adequate protections are in place for the most vulnerable (e.g. homeless, elderly); c) Ensuring capacity to “test, isolate and quarantine” all who are ill and conduct surveillance; and d) Be prepared to provide clear guidance to businesses to ensure appropriate social distancing is maintained when the economy reopens.

California Releases Four-Phased Reopening Plan: In the plan, phase 1 involves ‘stay-at-home’ orders (current phase); phase 2 will involve lifting restrictions on low-risk workplaces; phase 3 will involve reopening higher risks businesses (e.g. gyms, in-person religious services); and phase 4 will involve higher risk activities (e.g. large in-person audiences) once a vaccine and/or an effective therapeutic is available.
Section 2: Epidemiology, Incubation and Transmission

Infection Burden
- L.A. County: Current LA County Numbers, interactive city and community level map and projections to when to ease social distancing. There is a new LA County DPH interactive portal.
  - As of April 26: L.A. County has 23,182 cases and 1,111 deaths, with 4,623 (22.6%) ever hospitalized and 14% of hospitalized cases ever intubated. The number of cases is fluctuating and is likely to due to new outbreaks in many of the 217 institutional settings with at least one case.
  - There is at least one COVID-19 at 200 institutional settings in Los Angeles County. Cases among staff and residents account for 7% and 12% of all cases in Los Angeles County, respectively, and 45% of all deaths.
  - There have been 1,968 confirmed cases in health care workers and first responders in Los Angeles County, and 11 deaths, mostly among nurses in skilled nursing facilities. Of the 9 with information, all had underlying conditions.
  - Characteristics of cases with known age: 2.2% ages 0-17 yrs, 31% ages 18-40 yrs, 43.6% in ages 41-65 yrs, 23.2% in ages >65 yrs, median age is 50. 49.6% of cases but 59.4% of the deaths are males.
  - Characteristics of cases with known race/ethnicity: 11.7% Asian, 8.6% Black, 46% Hispanic/Latino, 23.9% White, 1.6% American Indian, Alaskan Native, Native Hawaiian, Other Pacific Islander, and 8% Other.
  - Of the 901 deaths with known age, 0%< in ages 0-17 yrs, 3% in ages 18-40 yrs, 21% in ages 41-65 yrs, 76% in ages >65 yrs, median age is 50.
  - Case-fatality rates in L.A. County increases with age, at 0% in 0-17 yrs, 0.5% in 18-40 yrs, 2.2% in 41-65 yrs, and 14.8% in those 65 yrs and older, and are 5.5% in males and 3.7% in females overall.
  - Of the 894 deaths with known race, 18.3% were Asian, 13.5% were Black, 37% were Latino, 1.3% were Native American/Pacific Islander, 1% were Other and 28.6% were non-Latino white.
  - Case-fatality rates in L.A.County by race/ethnicity are 6.3% in Latinos, 9.3% in non-Latino whites, 6.1% in Native Hawaiian/Pacific Islander/Alaska Native/American Indian, 12.2% each in Blacks and Asians (not age-adjusted) and 1.1% in Other.
  - Underlying comorbidities were present in 92.7% of deaths in L.A. County. The case-fatality rate in those with comorbidities of all ages was 4%, in those without comorbidities <1%.
  - Although older age is a stronger risk factor for severity and death, poor outcomes are also seen in younger patients, especially those with underlying conditions.
  - New data from the New York City Health Department indicates that the most important comorbidities predicting disease severity, in order, are hypertension, diabetes, high cholesterol, coronary artery disease, dementia, and atrial fibrillation. A recent paper noted that asthma and COPD are underrepresented among conditions predicting risk and severe disease.
○ A new NEJM study reports that 0.6% of 2,283 randomly selected individuals in Iceland tested positive for COVID-19. No child <10 years tested positive.

○ A new Lancet analysis concluded: “the first wave of COVID-19 outside of Hubei has abated … however given the substantial risk of viral reintroduction … close monitoring of the reproduction number (Rt) … is needed to inform strategies against a potential second wave to balance health and economic protection.”

○ Geographic variation: CDC report highlights variation across the U.S. in COVID-19 incidence from 20.6/100,000 in Minnesota to 915.3/100,00 in NYC.

○ Smoking increases risk of severe disease. A preprint of a meta-analysis of 12 papers on smoking showed a 2.25-fold (p=0.001) risk of severe COVID-19 disease and progression associated with current smoking.

○ Cats test positive: Two pet cats living in separate locations in NYC with mild respiratory illnesses have tested positive for COVID-19. There is no evidence of transmission to humans.

- California as of 04/29/20: 48,917 cases and 1,982 deaths: CDPH
- U.S. as of 05/1/20: 1,062,446 cases & 62,406 deaths: CDC
- Worldwide: As of 05/1/20: 3,329,740 cases & 237,647 deaths: JHU Map

Note: Peak in number of new cases on 4/19/2020 was due to inclusion of backlogged tests. The actual new daily count was 293 new cases diagnosed on 4/19/2020.
Note: COVID19 seems to have been introduced to LA County by the affluent, most likely by travel. After about 10 days, others, notably the least affluent, began to be diagnosed, and within a few days rates in the least affluent, probably service workers, exceeded all others. (graph and comment courtesy of Tom Mack)
Seroprevalence

- **Preliminary Results of Seroprevalence Antibody Testing:** A USC/LA County seroprevalence analysis found that: “Approximately 4.1% (range 2.8%-5.6%) of the county’s adult population has antibodies to the virus ... which translates to approximately 221,000 to 442,000 adults in the county who have had the infection.” A similar study in Santa Clara County among more than 3,000 residents (not randomly selected) suggests that the prevalence likely ranges from 2.5%-4.2% -- about 85-fold higher than the number of confirmed cases. And another study suggests a rate of 21% in New York City. Based on these estimates, the COVID-19 case fatality rate may be lower than previously believed (as low as 0.1%-0.6%). Nevertheless, these studies have not yet been peer-reviewed and some experts worry the antibody testing results may not be accurate.

Disparities, Homelessness and Jails

- A case series of hospitalized patients with COVID-19 in Georgia reports that “black patients were overrepresented, and their clinical outcomes were similar to those of nonblack patients.”
- A health disparity is emerging, with African Americans experiencing a higher burden of severe disease compared to other racial/ethnic groups. In Los Angeles County, the unadjusted case-fatality rates were similar in Blacks and Asians (12.2%). Lower socioeconomic status communities in Los Angeles County are now experiencing the highest increases in cases and deaths. In addition, males comprised 49.6% of cases in Los Angeles County but 59.6% of deaths.
- **Homeless Populations:** A new CDC analysis reports on clusters of infections in homeless shelters, finding rates of positive residents and staff, respectively, of 17% and 17% in Seattle, 36% and 30% in Boston and 66% and 16% in San Francisco. More details about the Seattle cluster are reported here.
- **Jails:** A perspective piece covers the unique challenges of COVID-19 within jails.

Incubation

- Most cases occur 4-5 days after exposure, but there’s an estimated range of 2-14 days.
- Median of 4 days (IQR= 2-7 days), 1099 Chinese cases through 1/29/20.
- Median ~5.1-5.2 days, 97.5% will develop symptoms within 11.5 days.

Transmission

- **Person-to-person transmission** occurs mainly via respiratory droplets, similar to influenza, and thus droplet precautions are recommended.
- Studies report secondary spread rates of 1-5% and 0.45%.
- **Airborne spread:** Though some experts have suggested that there may be airborne transmission of COVID-19 via aerosolized particles, guidelines from the CDC and WHO suggest that the disease predominantly spreads via respiratory droplets within 6 feet, except during certain high risk aerosolizing procedures such as intubation. Emerging data also seems to support droplet spread.
- **Environmental Contamination:** New CDC paper reports that COVID travels up to 13 feet and frequently contaminates floors in healthcare facilities.

- **Transmission Indoors vs. Outdoors:** As is the case for many other respiratory viruses, transmission appears to occur more readily indoors vs. outdoors.

- **Particulate Matter:** A small Italian study, not yet peer-reviewed, found SARS-CoV-2 in tiny particle of air pollution, leading some to believe that the virus can travel longer distances and perhaps explains its devastating impact on more polluted city centers.

- COVID-19 can live on surfaces for up to 72 hours (plastics, stainless steel). NEJM paper suggests the virus can remain viable and infectious in aerosols for hours.

- **Fecal-oral transmission.** Some studies suggest that fecal-oral transmission isn’t significant, however others suggest it may occur, particularly in pediatric populations. Patients with diarrhea in particular seem to be more likely to carry the virus in their stool.

- **Asymptomatic and Presymptomatic Spread:** There is growing evidence of asymptomatic spread. A study in Iceland has screened 9,000 citizens with and without symptoms; 1% were positive for SARS-CoV-2 but only half were symptomatic. In Singapore, investigation of all 243 cases revealed 7 clusters in which presymptomatic spread was thought to be the most likely means of transmission. Data from Japan reports the proportion of asymptomatic COVID-19 patients ranged from 17.9% (95% CI=15.5-20.2) and 30.8% (95% CI: 7.7-53.8). There also appears to have been asymptomatic transmission in a Seattle nursing home.

- A new case study found: “Rapid and widespread transmission of SARS-CoV-2 was [in a] skilled nursing facility. More than half of residents with positive test results were asymptomatic at the time of testing and most likely contributed to transmission. Infection-control strategies focused solely on symptomatic residents were not sufficient to prevent transmission after SARS-CoV-2 introduction into this facility.”

- **Asymptomatic/Pre-Symptomatic Spread and the Challenges of Contact Tracing:** Evidence for substantial asymptomatic/presymptomatic spread continues to grow, highlighting the challenges of contact tracing for COVID-19.

- **Close contact is probably necessary for transmission,** according to a study of a call center in South Korea, where 97 people out of 1,143 tested positive and 94 of these were working in a small area on the same floor. The secondary attack rate (to their families) was 16.2%. Four out of 97 positives remained asymptomatic and none of their family members were infected.

- **COVID-19 Infectiousness May Peak at Time of Symptom Onset:** A study of viral shedding found “the highest viral load in throat swabs at the time of symptom onset” suggesting that “infectiousness peaks on or before symptom onset.” The study also suggested that 44% of 77 secondary viral transmissions occurred during the presymptomatic period.

- **Seasonal Variation:** A National Academy of Sciences report finds that data are insufficient to indicate whether COVID-19 will dampen in hot/humid summer months. A case study suggests that COVID-19 is transmitted even in hot and humid conditions.

- **Evidence for community spread in the U.S. in February:** A Northeastern University model indicates there may have been tens of thousands of cases of COVID-19 in the U.S. by February 2020, long before community spread had been recognized; these findings have not yet been published in a peer-reviewed journal.
● **Facemask use by the general public:** After considerable debate, the [CDC has begun recommending](https://www.cdc.gov) voluntary use of cloth face coverings by the public, particularly in areas where there is substantial community spread. There is mechanistic evidence to support this recommendation, as well as some [experimental evidence from the SARS epidemic](https://www.cdc.gov).

● **New CDC Guidance for Essential Workers Who Have Been Exposed:** New [CDC guidelines](https://www.cdc.gov) indicate that “to ensure continuity of operations of essential functions, CDC advises that critical infrastructure workers may be permitted to continue work following potential exposure to COVID-19, provided they remain asymptomatic and additional precautions are implemented to protect them and the community.”

● **SARS-CoV-2 detected in blood donations in China:** A new [research letter](https://www.cdc.gov) found that blood donations from asymptomatic donors was positive for the SARS-CoV-2 virus, suggesting the potential need for screening of the blood supply.
Section 3: Clinical Care

Clinical Presentation

- COVID-19 presents similarly to many other viral respiratory infections.
- In a study of 138 hospitalized patients in Wuhan, initial symptoms were as follows:
  - Fever in 99% (In another study, however, fever was present in only 44% of patients on admission, though 89% experienced fever during the hospitalization).
  - Fatigue in 70%
  - Dry cough in 59%
  - Anorexia in 40%
  - Myalgias in 35%
  - Dyspnea in 31%
  - Sputum production in 27%
- GI symptoms: Contrary to earlier reports, digestive symptoms including diarrhoea may be a symptom in up to 50% of cases; patients presenting with GI symptoms may have worse outcomes. Recent evidence suggests that digestive symptoms -- including anorexia -- may be a common presenting symptom of COVID-19. There is also growing concern that fecal-oral transmission may occur, though this remains uncertain. LFT abnormalities were present in a third of hospitalized patients in one analysis.
- Anosmia: A study from Italy reports at least one taste or olfactory disorder in 33% of patients with SARS-CoV-2 infection. Olfactory and taste disorders (OTDs) are more frequent in patients and these symptoms may precede the onset of clinical disease. Patients may also experience runny nose and sore throat as well as a loss of smell. The American Academy of Otolaryngology Head and Neck Surgery has suggested that anosmia be included in testing and self-isolation criteria.
- Ocular Symptoms: Ocular symptoms may be “relatively common in COVID-19 disease and may appear just before the onset of respiratory symptoms.”
- Ambulatory care: A case series describes the clinical presentation of patients with COVID-19 in an ambulatory setting; anxiety-related dyspnea is more common soon after infection while COVID-related dyspnea occurs more often several days later.
- Tool to Predict Disease Severity: A tool has been developed to predict disease severity among hospitalized patients with COVID-19.

Diagnostic Testing

- Testing for COVID-19 involves the reverse transcriptase-PCR, typically utilizing a nasopharyngeal sample.
- Testing with saliva samples: A new study has found that “saliva is a viable and more sensitive alternative to nasopharyngeal swabs and could enable at-home self-administered sample collection for accurate large-scale SARS-CoV-2 testing.”
- FDA approved an Abbott Labs point-of-care COVID-19 test, offering results within several minutes.
- FDA has also authorized a home sample collection kit to facilitate testing within the home environment.
Antibody Test Approved. The FDA authorized the first COVID-19 antibody test on April 1, and there are now 7 serology tests approved. Quest and Labcorp are providing their own serology testing.

There is growing interest in antibody screening tests to identify immune individuals who can drive the return to work. However, important questions remain -- which are just beginning to be addressed -- regarding the sensitivity, specificity, and positive/negative predictive value of antibody testing, as well as whether positive antibodies actually indicate immunity.

According to one analysis from China, the median duration of IgM detection is 5 days, while IgG is detected at a median of 14 days after symptom onset.

Criteria for who should be tested remains controversial:

- Prioritize patients with serious, unexplained respiratory illness as well as those who are symptomatic with contacts of known cases.
- Because of the incubation period, experts also highlight that “a negative result does not rule out infection, particularly for people with a known exposure [and a] positive result in an otherwise well or mildly ill patient does not require urgent medical attention but does require isolation …”

California has released recommendations about COVID-19 testing, which suggest the need for testing not just among those who are symptomatic but also asymptomatic individuals who are in high risk groups, such as healthcare workers and other essential employees and residents of congregate living facilities, the elderly and those with high risk comorbidities.

Actual sensitivities and specificities are not yet available.

Nasopharyngeal testing for COVID-19 may have limited sensitivity. In 1,050 samples from 205 patients with confirmed COVID-19, samples were positive in only 72% sputum specimens and 32% pharyngeal swabs while 29% had positive feces. New analyses continue to raise concerns about whether negative NP swabs are sufficient to clear patients. However, these analyses were conducted in China during an earlier phase of the epidemic and testing methods may now be better. According to one paper, “It is likely that lower respiratory samples (eg, minibronchial alveolar lavage) are more sensitive than a nasopharyngeal swab … it is important to emphasize that, depending on the clinical presentation, a negative RT-PCR result does not exclude COVID-19.”

False negative test results may lead to a false sense of security, leading to risk of further viral spread.

Treatment and Management

Treatment Guidelines

- For the vast majority of COVID-19 cases, treatment includes supportive care.
- Hydroxychloroquine/Chloroquine: Early in the pandemic, Hydroxychloroquine was suggested as a potential antiviral medication based on the medications’ cellular interaction with the virus and in vitro data.
  - Initial anecdotal evidence suggested the medication helps with pneumonia in regards to shortening of disease course and improvement of lung imaging. This led to the CDC suggesting the use of Hydroxychloroquine and the FDA enacting
its emergency use without rigorous clinical trials. This has led to much controversy given potential for cardiac complications, prompting medical experts to advocate for caution.

- Two small non-peer reviewed randomized studies have shown seemingly contradictory results. In one study, hydroxychloroquine made no difference in regards to fever improvement and negative PCR. In another study, hydroxychloroquine showed significant improvement in symptoms and pneumonia (by CT scan).
- One new non-randomized study failed to demonstrate a benefit among patients hospitalized with an oxygen requirement while an open-label RCT involving 150 patients demonstrated modest alleviation of symptoms.
- A retrospective VA analysis concluded that no clear evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19. An association of increased overall mortality was identified in patients treated with hydroxychloroquine alone.”
- Another study showed drug-related Qtc prolongation, leading to early study termination.
- A phase IIb randomized trial of hydroxychloroquine involving 81 patients showed that a higher dosage of chloroquine for 10 days was associated with more toxic effects and lethality, particularly affecting QTC interval prolongation.
- The FDA issued a safety communication cautioning “against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.”
- Because the data is still unclear, there are several ongoing trials of hydroxychloroquine.
- Hydroxychloroquine and Azithromycin: A small non-randomized study -- which subsequent to publication received an expression of concern from the sponsoring society -- has suggested a benefit of combining hydroxychloroquine with azithromycin for treating COVID-19. Larger studies are needed to further evaluate the safety of combining these meds, as the combination of the two can potentiate cardiac complications.

- **HIV protease inhibitors:** Lopinavir-Ritonavir (Keletra) is being investigated, but studies to date have failed to show improvement over standard of care.

- **Other antiviral drugs:** Randomized study of two influenza drugs, Favipiravir versus Arbidol, in moderate severity patients showed better outcomes with Favipiravir.

- **Remdesivir:** Early in the pandemic, anecdotal evidence suggested remdesivir as a therapeutic option. This led to clinical trials and compassionate use programs, the latter which showed promise.

  - The first randomized double-blind, placebo-controlled trial recently was published with seemingly disappointing results. Investigators, in this peer-reviewed study, evaluated 237 patients with severe COVID-19 across 10 hospitals in China showing no difference in clinical improvement. Authors did note, however, a trend toward faster recovery time compared to placebo; this was not statistically significant. The study was under-powered which poses a
challenge for interpretation and makes some question if the findings are inconclusive.

- Preliminary results from a NIH randomized trial is encouraging. The study involved 1063 patients with COVID-19 and showed a median time to recovery of 11 days with remdesivir vs. 15 days with placebo (P<0.001). There was also a nonsignificant trend towards lower mortality with the drug (8.0% with remdesivir vs. 11.6% with placebo, P=0.059).
- Gilead announced results from their own Phase 3 trial evaluating 5-day vs 10-day dosing duration, finding similar improvement in clinical course which suggests patients don’t require a long treatment period.
- In light of encouraging news, FDA plans to announce an emergency use authorization, which does not constitute a formal approval, but allows the maker Gilead to sell the drug during this public health crisis. Gilead reports that it currently has sufficient remdesivir to treat 140,000 patients, and intends to have sufficient supply for 1 million treatments by the end of the year.
- As much of the data is new and preliminary, some caution has been advocated.
- Clinical trials are ongoing and remdesivir is no longer available via compassionate use but may be obtained via an expanded access program.

- **Immunomodulators:** Because a cytokine storm may be the catalyst for severe disease, clinicians are investigating immunosuppressants which target IL-6. Early indication shows Tocilizumab (Actemra) to be effective in severe cases and its use has been advocated. Two major studies are now underway. Recently, preliminary results from a randomized control trial showed Tocilizumab led to significantly reduced number of deaths.
- **Convalescent serum:** In response to new encouraging but small and uncontrolled studies, the FDA has approved convalescent serum for COVID-19 treatment under an emergency Investigational New Drug (IND) application. Not all studies of convalescent plasma have been favorable, however.
- **Blood purification device:** Despite limited data, the FDA issued an emergency use authorization for a blood purification device that filters inflammatory mediators.

**Expert Recommendations on Treatment**

- In light of no FDA approved treatment for COVID-19, multiple expert groups have issued guidance for treatment.
- **ATS Guidelines:** ATS recognizes the lack of empirical evidence to guide COVID-19 management. In light of ongoing daily new cases, ATS offers guidance based on scarce direct evidence, indirect evidence, and clinical observations. Their main points are:
  - Hydroxychloroquine: Reserved for hospitalized patients with evidence of pneumonia, on a case-by-case basis, with shared decision making with the patient.
  - Lopinavir/ritonavir- For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.
  - Remdesivir- For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.
  - Tocilizumab- For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.
○ Systemic corticosteroids: For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.

- **IDSA Guidelines:** The IDSA issued evidence-based treatment guidelines for COVID-19. In general, the guidelines emphasized the importance of recruiting patients into clinical trials to better determine safety and efficacy of available treatments. Specific recommendations include:
  - HQ/chloroquine +/- azithromycin may be considered in context of a clinical trial
  - Lopinavir/ritonavir may be considered in context of a clinical trial
  - Recommends AGAINST steroids for patients admitted with pneumonia
  - Recommends steroids for patients admitted with ARDS in context of clinical trial
  - Recommends tocilizumab for admitted patients only in context of a trial
  - Recommends convalescent plasma in context of clinical trial

- **New NIH Treatment Guidelines:** The NIH has released COVID-19 treatment guidelines. The guidelines do not recommend any specific antiviral or immunomodulatory drug treatment for COVID-19 disease outside of a research setting, nor for pre- or post-exposure prophylaxis; the group recommends against systemic steroids for patients who are mechanically ventilated who don’t have ARDS; the guidelines do recommend low-dose steroids for patients with refractory shock.

**Management Guidelines**

- **Chest Imaging for COVID:** An international consensus statement concludes that routine chest imaging is not indicated for those with mild symptoms and should be reserved for those with worsening respiratory status, regardless of their COVID-19 test results.

- **Management recommendations for MI amidst COVID:** Recommendations highlight special considerations to ensure infection control for patients and staff.

- **Venous Thromboembolism Prevention:** Literature continues to emerge highlighting the VTE risk in COVID-19 patients. In one Chinese study, the incidence of VTE was high in ICU patients and potentially related to poor prognosis. In a retrospective French study, a high incidence of VTE in ICU led to suggestions of systematic screening of VTE and therapeutic anticoagulation in severe cases. Studies like these have led many to advocate for close attention to VTE risk in COVID-19 patients. This has led some centers to create management algorithms for VTE prevention and treatment.

- **SARS-CoV-2 utilizes ACE2 for binding,** which raises a potential role for ACEIs/ARBs/NSAIDs, all of which impact ACE2.
  - **NSAIDS:** Because NSAIDs may upregulate ACE2, some have questioned their safety in patients with COVID-19. While some organizations are calling for further evaluation, the WHO doesn’t recommend avoiding NSAIDs.
  - **ACEIs/ARBs:** Early in the pandemic, concerns were raised about ACEIs/ARBs, which prompted the ACC/AHA and other medical experts to advocate for continuation of these agents and to caution against discontinuation of proven therapies. A retrospective, single-center case series evaluated 1178 COVID-19 hospitalized patients, focusing on the 362 patients with hypertension and found no difference between those taking ACEIs/ARBs and those who did not in regards to severity of disease and risk of death. In fact, a retrospective, multi-center study looked at 1128 patients with hypertension and COVID-19, finding those on
ACEIs/ARBs actually had a lower mortality rate than those not on the medications. Studies like these have led to proposed clinical trials for further investigation.

- **Adjunct Care:** In the absence of FDA approved treatment for COVID-19, a number of existing medications have been suggested to be repurposed for the management of COVID-19.
  - **Statins:** Due to its anti-inflammatory properties, statins have been suggested for respiratory illness. Early observational data suggested a trend toward better outcomes for those with Pneumonia and Influenza. As such, statins were suggested for MERs. Because statins increase ACE2 receptors, its therapeutic potential in COVID-19 has been proposed. Despite no clinical evidence to suggest its use, many institutions are utilizing statins. Cardiologists have weighed in, suggesting the continuation of statins for those with atherosclerotic cardiac disease or diabetes and consideration of initiating if COVID-19 patients have cardiac injury. If patients are not on a statin as an outpatient, then it is unclear if there is a role in initiating the medication, but some have suggested to initiate if at increased risk for clinical atherosclerotic cardiovascular disease.
  - **Zinc:** Over the years Zinc has been reported to have antiviral effects. Animal studies with the Avian Influenza showed promise and in vitro studies showed an ability to reduce viral replication in SARS. Refined research has been mixed on the use of Zinc in treating patients with respiratory illnesses. To date there is no research on the use of Zinc with COVID-19. Despite weak clinical evidence, Zinc has been suggested as an adjunct in the management of COVID-19. A clinical trial combining Zinc with Hydroxychloroquine is currently being investigated.

**Intensive Care Unit (ICU)**

- The ICU lies on a continuum of care (community, outpatient, inpatient ward/telemetry/ICU, discharge or death). Prevention and treatment in one part of the continuum have effects throughout the continuum with implications for resource availability.
- Useful overviews in: JAMA; Internet Book of Critical Care; Cochrane review.
- **Risks factors for hospitalization and critical illness:** An analysis from New York reports that “age and comorbidities are powerful predictors of hospitalization; however, admission of oxygen impairment and markers of inflammation are most strongly associated with critical illness.”
- **Obesity a risk factor for severe disease:** Studies from NYU and France show higher rates of ICU admittance of obese patients. CDC now lists severe obesity as a risk factor.
- **Common complications include:**
  - Acute Respiratory Distress Syndrome (ARDS) diffuse alveolar damage, pneumocytes with viral cytopathic effect implying direct viral damage.
  - New study shows incidence of venous thromboembolism (VTE) amongst COVID-19 patients with severe pneumonia is 25%; another study highlights the need for early surveillance and screening for VTE in hospitalized patients.
  - Cytokine storm syndrome which is a dysregulated hyperinflammatory response to the viral pathogen.
Cardiomyopathy and arrhythmias which can occur late, may be multifactorial in etiology.

Neurologic complications may include encephalopathy, agitation/confusion and corticospinal tract signs.

- **Clinical markers** include: elevated C-reactive protein and ferritin

- **Current management** largely involves supportive care:
  - Invasive Ventilation/Personal Protective Equipment
  - ARDSnet lung protective ventilation protocol
  - Conservative fluid resuscitation, Early vasoactive support.
  - Prone Positioning - A recent small study has shown the potential benefit of prone positioning for ventilated COVID-19 patients with ARDS.
  - Prone positioning in non-ventilated patients with moderate ARDS (non COVID in a recent paper) supported by high flow O2 or NIV reduced need for intubation
  - Increasing use of prone positioning in the non-ventilated patient - management guidelines including useful flow chart

- **Considerations** for extracorporeal membrane oxygenation (ECMO)

- **Resources from European ICU** including papers and blogs from Italian ICUs

- **Published resources**:
  - JAMA paper (4/6/2020) from Italy: baseline characteristics and outcomes
  - JAMA paper (3/19/2020) from 21 ICU patients in Washington State
  - NEJM case series (3/30/2020) from Seattle of ICU patients

- **Guidelines include**:
  - “Surviving Sepsis campaign” guidelines for management of the adult ICU patient with COVID (3/27/2020)
  - JAMA Clinical Guidelines Synopsis (3/26/2020)

- **Interviews with**:
  - Maurizio Cecconi (EICSM) from Italian centers: practice PPE before you need to do it in real life and ICU management - JAMA interview (3/16/2020)
  - Derek Angus - Update on Critical Care management: JAMA interview (4/1/2020)

**Prognosis and Outcomes**

- **Prognostic indicators**: Models are being developed to assist in predicting disease severity and mortality.

  - Elderly Age and Comorbidities: A review article of 53,000 patients found that the strongest predictors of disease severity were age ≥50, smoking, and co-morbidities, particularly CKD, COPD, and cerebrovascular disease. Age >60, CVA, HTN, and DM were found to be independent prognostic factors for death. Another review article, found elderly male patients were more likely to develop into critically ill patients. In a single-center, cross-sectional analysis, elderly age (age >65) and heart failure were strong risk factors for hospitalization.

  - Obesity a risk factor for severe disease: Studies from NYU and France show higher rates of ICU admittance of obese patients. CDC now lists severe obesity as a risk factor.
○ **Lab Data:** Elevated D-dimer on admission has been found to be both a predictor of severity and mortality. Elevated CRP has been found to be associated with severe COVID-19. Lymphopenia may also indicate disease severity.

- **Morbidity Data for U.S. Patients:** CDC data continue to suggest that older patients with comorbidities are more likely to develop COVID-19 complications, though younger, healthy patients can experience serious illness: “The percentage of COVID-19 patients with at least one underlying health condition or risk factor was higher among those requiring intensive care unit (ICU) admission (78%) and those requiring hospitalization without ICU admission (71%) than that among those who were not hospitalized (27%).” A CDC report also found that case-fatality percentages increased with increasing age with the highest percentages (6%–27%) among adults aged ≥85 years.

- Illness severity varies considerably. In China, mortality rates have been reported ranging from 0.7% (other areas in China) vs 5.8% (Wuhan).

- **COVID in the Kaiser Population:** In a cohort analysis of more than 9.5 million Kaiser members, the cumulative incidence of a COVID-related hospitalization ranged from 10.6-12.4 per 100,000 (depending on the region); among hospitalized patients, 41.9% required ICU care the mortality rate was 17.8%; the effective reproductive number dropped substantially from March 1-20 in conjunction with social distancing.

- **Distribution of China’s Cases** (n=72,134):
  - Mild (no or mild pneumonia): 81%
  - Severe disease (dyspnea, hypoxia, or >50% lung involvement on imaging): 14%
  - Critical disease (respiratory failure, shock, or multiorgan dysfunction): 5%.

- **Hospitalized Patients**:
  - 10-20% admitted to ICU
  - 3-10% require intubation

- **Case Fatality Rate**
  - Overall: 2.2%; median age of deaths: 75 years (as of Jan 25, 2020)
  - Time from onset of symptoms to death: 6-41 days, Median: 14 days, shorter for those greater than 70

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**Immunity**

- It is not clear whether those who have previously been infected can be reinfected. “Other coronaviruses demonstrate evidence of reinfection [but] this usually does not happen for many months or years.”

- A WHO scientific brief has concluded that “there is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection … there is not enough evidence … to guarantee the accuracy of an ‘immunity passport’ or ‘risk-free certificate.’”

- There does seem to be immunity in other primates.
Pediatric Populations

- Prevalence and Clinical Course
  - **CDC data from Feb 12–April 2, 2020** reported 2,572 (1.7%) of 149,760 lab confirmed COVID-19 cases in the U.S. were aged <18 years (median 11 years) but had limited data on clinical course; confirmed it was generally mild.
  - Among 2,143 Chinese children with likely COVID-19, few developed severe infection:
    - 55% asymptomatic-mild (4% asymptomatic), 39% moderate (pneumonia, dry cough, fever, lung lesions), 5% severe (fever, cough, GI symptoms, shortness of breath, decreased oxygen saturation), and 0.6% critical (respiratory failure, heart failure, multi-organ dysfunction)
  - Infants (<1 year) are more likely to have severe infection (10.6%).

- Transmission
  - In a study of 391 SARS-CoV-2 cases and 1,286 close contacts, children were as likely to be infected as adults <50-60 infected (attack rate 7.4% for 0-9 yo vs 9.4 for 50-59).
  - Children mostly infected by household and child-to-child transmission.
  - Fecal-oral transmission may be possible based on studies in children and fecal shedding may persist weeks after respiratory infection has resolved - concern for school-based transmission.

- Overview and Recommendations
  - A systematic review of SARS CoV2 in 1,065 children from 18 studies in China and Singapore. Main symptoms: fever, dry cough years. Mild respiratory symptoms except one 13 month-old, Vomiting reported in 2 studies.
  - CDC resources regarding children and COVID-19.

Pregnant Women and Breastfeeding

- Clinical course and management of pregnant women
  - Among 118 pregnant women with Covid-19 in Wuhan, 92% had mild disease and 21% of deliveries were premature. The authors conclude that COVID-19 may be less severe than flu for pregnant women.
  - Comparison of 28 pregnant and 54 reproductive age women, shows similar clinical course: severity of disease (OR=0.73, 95% CI=0.08-5.15; p = 0.76), virus clearance time (HR=1.16, 95% CI=0.65-2.01; p = 0.62). None of 23 neonates infected.
  - Recommendations for the care of pregnant women: flowchart of steps in care.
  - In areas of high COVID-19 prevalence such as New York City, universal screening of women admitted for delivery is recommended due to frequent asymptomatic infection.

- Birth outcomes
  - Preterm delivery in ~50% of pregnant women (n=32) hospitalized with COVID-19.
Similar coronavirus infections (MERS, SARS) found increased fetal loss for first term infection and also observed increased preterm birth for later infection.

Maternal-child transmission
- Among 6 babies delivered by C-section to women with COVID-19, all had anti-COVID antibodies (IgG) and two had IgM (which does not usually cross the placenta), raising concern about transplacental infection.
- However small studies (N=19) report no maternal-child COVID-19 transmission to newborns.

Management
- American Academy of Pediatrics has issued recommendations for the care of infants delivered by COVID-19 positive or suspect mothers including bath after birth, protective clothing for health care workers

Breastfeeding
- CDC recommendations: Breastfeeding women with or suspected to have COVID-19 are recommended to express milk and feed the infant by someone who is healthy.
- WHO recommendations: Breastfeeding with precautions (hand washing, masking) but not to breastfeed if severely ill.

The Elderly
- Experience worldwide shows increasing case fatality rates with increasing age, especially over 60 years. Comorbidities further increase the risk of death.

General resources
- CDC resources for and about elderly
- CDC guidance for retirement communities.

Mortality rate by age
- Mortality for persons >59 yrs in Wuhan was 5.1 times that of persons 30-59 years
- Among 191 hospitalized adults, 54 decedents were older with mean age 69 vs 52 years for discharged survivors. Adjusted odds of death rose by 10% per year of age (p=0.004).
- Among 1,625 deaths in Italy: mean age 81+ years and 2/3 had diabetes, cardiovascular disease, cancer, or smokers. The case fatality rate among persons <60 was 1% or less versus 8% for 70-79 and 20% for 80+ years.
- Among 5,700 patients hospitalized with COVID-19 in New York, 553 (9.7%) died (of these 75.8% ≥65); 2,081 (36.5%) discharged alive (32.5% were ≥65); 3,066 (53.8%) still hospitalized (48.5% were ≥65).

Comorbidities
- CDC study of 7,162 COVID-19 cases found that 71% of 1,037 hospitalized and 78% of 378 in ICU had 1+ comorbidity vs 27% of 5,143 not hospitalized (commonly diabetes, cardiovascular, and chronic lung disease).
- A CDC report found that “among COVID-19–associated hospitalizations in older adults, nearly 90% had one or more underlying medical conditions.”
- Comorbid cardiovascular disease increases risk of death (acute coronary syndrome due to inflammation, depressed myocardial function, arrhythmias)
Out of hospital cardiac death increased in Lombardy, Italy by 58% in 2/21/2020-3/21/20 compared to the same month in 2019; 103 likely had COVID, contributing to increase; mean age 77 years at death.

In >400 hospitalized patients in Wuhan, 20% had cardiac injury with elevated cardiac biomarkers (e.g., HSTroponin), older in age (mean 74 years vs 60 years), and amongst those with cardiac injury, 50% died.

Among 5 patients with COVID-19 complicated by Guillain-Barre syndrome, 3 patients were 60+ years of age.

Predictors of mortality

A nomogram to predict inpatient mortality based on 1,590 patients with COVID-19: age 75 or older (hazard ratio [HR]: 7.86, 95% CI: 2.44 to 25.35), age 65 - 74 (HR: 3.43, 95% CI: 1.24 to 9.5), coronary heart disease (HR: 4.28, 95% CI: 1.14 to 16.13), cerebrovascular disease (HR: 3.1, 95% CI: 1.07 to 8.94) dyspnea (HR: 3.96, 95% CI: 1.42-11), and laboratory measures.

Challenges in specific settings

Long-term care facilities have been an epicenter of COVID-19 infection, morbidity, and mortality.

Poor outcomes from ICU care: Among 1,689 patients (median age 64 years) admitted to the ICU with an outcome reported, 51% died after an average of 6 days (ICNARC report, 10 April 2020).

Limited ventilator supply may restrict use to younger patients.

Acute kidney disease with COVID-19 is placing demands on limited dialysis units and dialysis units are at risk for spread of infection.

Social issues

Recommendations to assist older, isolated persons living at home.

Despite the increased risks among the elderly, another study found that “many adults with comorbid conditions lacked critical knowledge about COVID-19 and, despite concern, were not changing routines or plans.”

Palliative Care and Ethical Considerations

Ethical Concerns:

Learning from the past

WHO and CDC developed ethical guidance for Pandemic Influenza

Society of Critical Care Medicine’s Ethics of Outbreaks Position Statements on Therapies, Treatment Limitations, Duty to Treat, and Family-Centered Care

AMA’s Code of Medical Ethics: Guidance in a Pandemic

Decision-making for limited resources

With limited ventilator resources, a volunteer committee of respected clinicians and leaders can assist in decision-making for withdrawing ventilator support, communicating with families, and empowering palliative care to intervene to buffer clinicians from disabling distress, providing symptom management and family support.
○ 6 recommendations regarding allocation of resources during pandemic to include maximizing benefits of resources; prioritizing care for front-line healthcare workers; not to allocate based on a first-come, first-serve basis; respond quickly to evidence; recognize research participation; and applying same principles to COVID and non-COVID patients.
○ Italy’s SIAARTI’s Ethics Section: Recommendations for intensive care treatments to aid in provider moral distress, transparency, and allocation of scarce resources.
○ In 2019, a framework was developed to guide statewide allocation of scare ventilators during disaster.
○ In the setting of mask shortages, experts have highlighted the role of government officials in discouraging hoarding in order to protect the safety of frontline healthcare workers.
○ AMA’s recommendations for fair access to resources
○ ACS’s ethical framework recommended use of mortality prediction tools

- Balancing disease control, economic damage, and civil liberties
- Proposed ethical framework for healthcare institutions during COVID-19 pandemic manages uncertainty with planning, safeguarding communities, and guiding practice.
- Health Equity: A report highlights that providing high quality care for vulnerable patients globally is both ethical and necessary to ensure Americans’ health. Ensuring access to technology for marginalized populations during social isolation.
- Alleviation of suffering: Pandemics amplify suffering with physical, existential, financial and social instability. In Italy, ethical concerns have arisen regarding patients dying alone in hospitals without family or palliative care. Symptom management including sedation to unconsciousness.
- Research considerations: Pressures of a crisis, may lead to reliance on anecdotes over evidence-based approaches. Ethical commencement and completion of a controlled trial also requires “no treatment preference.” Recommendations that studies on COVID be considered highly sensitive and protect the wellbeing of participants.
- Managing radical redesign: “One size fits all” management approach to patient care may not be in the best interest of non-COVID patients
- Students graduating early to enhance workforce requires safe, ethically sound practice
- Responsible prescribing recommendations
- Providing remote care responsibilities
- Further AMA guidance on obligations to protect healthcare professionals, use of public registries during a public health emergency, and responsibility of physicians in the media

Palliative Preparedness:
- Triage Planning: During pandemics, a triage plan should include palliative care.
- Crisis Standards of Care: A discussion paper from the National Academy of Medicine aims to assist in healthcare planning and application of Crisis Standards of Care for COVID-19. CAPC’s Specialty Palliative Care Crisis Service Design.
- Immediate and Long-Term preparedness for palliative care from COVID-19
- Need for surgeons to embrace palliative care

Advance Care Planning:
● **Mechanical Ventilation and Prognosis:** An analysis of 5700 patients reported an 88.1% mortality rate for mechanically ventilated patients. This provides prognostic information and highlights the need for research on harms of mechanical ventilation.

● A JAMA paper reviews the importance of advance care planning during COVID-19 and offers a framework for informed assent.

● **ACC’s recommendation** for pre-hospital ACP and symptom management in patients with cardiovascular disease during COVID-19

● **GEDC recommends** for ED physicians to understand a patient's goals and preferences as well as the capabilities of the nursing home to inform transitions of care.

● In primary care, **group visits** improve ACP documentation among older adults.

● In nursing homes, medical directors should collaborate with social work and nursing to ensure **updated and appropriate** ACP and Advance Directives.

● **Communications Tools:**
  ○ VitalTalk: COVID-Ready Communication Skills
  ○ Respecting Choices [Guide for proactive care planning for COVID-19](#)
  ○ Serious-Illness [Conversation Guide](#) for Inpatient and Outpatient Care
  ○ [Best case/Worst Case](#): ICU conversations with COVID-19

● **POLST form:**
  ○ Recommend to [complete or review POLST](#) for COVID in appropriate patients
  ○ Completing POLST forms in [Crisis Standards or Care](#)

**Symptom Management:**

● **Nursing Home:** Palliating symptoms of COVID-19

● Nonpharmacologic **dyspnea** management in COVID-19

● **Pharmacologic** management of COVID-19 symptoms including psychological distress

● Dementia-related behaviors may be caused by pain, hunger, fear, frustration, boredom, hallucinations, overstimulation, environment/routine changes, unfamiliarity with PPE
  ○ [Alzheimers Associations](#) recommends a HIPPA-compliant [personal information form and strategies to respond](#) to the behaviors
  ○ Recommendations for [communication with masks](#)

**Hospice:**

● CMS relaxes requirements for in-person evaluation, allowing [telehealth](#) services, among other changes.
Section 4: Preventing Spread in Healthcare Settings

Personal Protective Equipment

- [New short paper in Nature](https://www.nature.com/articles/s41591-020-0937-6) on aerosolization of COVID, cleaning of staff rooms and decontamination of PPE before doffing suggested, plus more evidence for mask wearing
- [Paper published in CDC journal](https://www.cdc.gov/mmwr/mmwrhtml/mm6912a2.htm) COVID travels up to 13ft and is on the floor particularly in ICUs - health care workers should clean their shoes, half of the samples from the soles of ICU staff shoes tested positive
- [Nature paper on aerosolization](https://www.nature.com/articles/s41591-020-0937-6) suggests face masks may be useful in preventing spread from asymptomatic individuals and [BMJ analysis favoring masks for general public](https://www.bmj.com/content/370/bmj.n88)
- General [infection precaution advice](https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/clean-your-space.html) from the CDC for healthcare providers Personal protective equipment recommendations for close patient interaction include:
  - N95 respirator mask if available, medical facemask if not.
  - N95 is strongly preferred when performing aerosol-generating procedures.
  - Eye protection: goggles or disposable face shield that covers front/sides of face.
  - Gloves
  - Gown use is preferable but can be prioritized for aerosol-generating procedures, anticipated splashes and sprays, high-contact activities.
- **Before/After Work:** [coming home from work guide on how to stay safe](https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/everyday-prevent-measures.html) from American College of Emergency Physicians
- [CDC infographic](https://www.cdc.gov/coronavirus/2019-ncov/hcp/prevent-infection.html) on donning and doffing PPEs.
- HCW need to be prioritized for testing and care else healthcare systems risk [absenteeism](https://www.cdc.gov/coronavirus/2019-ncov/healthcare-settings/absenteeism.html)
- **Equipment Supplies:** CDC suggested [strategies](https://www.cdc.gov/coronavirus/2019-ncov/healthcare-settings/equipment-supplies.html) to optimize facemasks supply, including use of homemade masks; FDA issued guidance on preserving gloves and ventilators.
- **Reuse of N95 Masks** Duke has begun a [novel initiative](https://www.dukehealth.org/news/novel-initiative-decontaminates-n95-masks) to decontaminate N95 masks and allow for their reuse, which they are [currently evaluating](https://www.dukehealth.org/news/novel-initiative-decontaminates-n95-masks) as well. A [website](https://www.decontaminationprotocols.com) is collating data about different decontamination practises for N95 masks.

Hospital Precautions

- Nevertheless, there are reports out of Italy, [Spain](https://www.cdc.gov/coronavirus/2019-ncov/healthcare-settings/outbreak.html) and China strongly suggesting in-hospital transmission, perhaps due in part to suboptimal adherence to infection control practices.
- Limit visitors and traffic.
- Patients with known or suspected COVID-19 should be placed in a single room with a door closed and a dedicated bathroom, and should wear a facemask.
● Airborne infection isolation rooms should be reserved for patients who will be undergoing aerosol-generating procedures.

● **Caution when considering high-flow nasal oxygen or noninvasive ventilation** as increased risk of dispersion of aerosolized virus.

● Facilities could consider designating entire units within the facility, with dedicated HCP, to care for known or suspected COVID-19 patients.

● Some Asian countries cohorted healthcare workers and patients, though rigorous evidence that these measures were effective are lacking:
  ○ Singapore’s Ministry of Health **limited doctors to a single facility**. Singapore also limited movement of patients and healthcare staff between facilities.
  ○ Many Asia countries developed dedicated hospitals and units exclusively for treating patients with COVID-19.
  ○ There are not rigorous studies evaluating the extent to which cohorting – rather than other measures – explains the success of other Asian countries in containing COVID-19.

● Universal masking of healthcare workers and patients is one emerging best practice for limiting nosocomial spread, though the data to support this practice are nascent:
  ○ Strong evidence suggests that **asymptomatic/presymptomatic transmission** may be a key driver of spread within healthcare facilities.
  ○ Because of the apparent high rate of asymptomatic/presymptomatic transmission, many experts are now recommending **universal masking** of patients and healthcare workers – in addition to other evidence-based preventive measures – even among those without documented COVID-19 infections.
  ○ Though the benefit of patient masking has not been rigorously demonstrated, **mechanistic evidence** and **some experimental evidence** suggests the potential value.

**Airway Management and Intubation**

● Practical guidance for precautions and preventive measures to be taken in very high-risk exposure situations such as patient intubation are linked below:
  ○ **American Society of Anesthesiologists**
  ○ **UK Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists**
  ○ Papers in a **special edition** of Anesthesiology
  ○ Very practical blog with images from an ED intensivist

● **ASA guidelines on purchase and wearing of PPE** for anesthesiologists and other anaesthesia professionals.

**Managing Exposures in Healthcare Settings**

● **Guidance** on what to do if potential exposure occurs to a healthcare professional:
  ○ Covers potential risk of different types of exposures, what action should be taken, and what monitoring of the health care provider should occur.
Section 5: Health System Best Practices

- **Central challenge**: Optimize use of resources for complex decision making in real time with large amounts of uncertainty and incomplete data
- **Goals**: Reduce morbidity and mortality; Minimize disease transmission; Protect healthcare personnel; Preserve healthcare system functioning
- A Checklist from HHS was developed for hospital systems planning pandemic response.

The Four S’s of Disaster Relief Planning

**Staff**
- Interim CDC guideline for healthcare facilities emphasizes preparation for potential personal protective equipment supply and staff shortages.
- **Surge planning** includes anticipating absenteeism in response to contagion and planning for staff shortages, while supporting staff to prevent this
  - Create registries of volunteers, plans for emergency or rapid credentialing.
  - Coordination with military medical corps is an option to expand staffing
- Clinician and staff psychosocial needs/distress must be addressed
  - Increased need for emotional/psychological support for staff and patients.
- Consider alternate housing and childcare for workers with families at risk
- Malpractice/liability for good samaritans as enacted in the State of New York
- UCSF Healthforce recommendations describe staff scale up during surges
- George Washington University has a model to predict staff attrition
- A recent NEJM article cited advocacy in key workforce areas: “top of license” and expanded practice for allied health professionals, malpractice and indemnity reform to protect providers working outside their typical scope of practice, COVID work credit to senior medical and nursing students, focus on comprehensive social needs for patients/providers, streamlined hospital accreditation practices, recruitment of non-practicing providers (eg dentists, retirees),

**Stuff**
- 3 C’s, conventional, contingency, crisis with protocols for blood, IV medications (antibiotics, antipyretics, O2, NS/crystalloids)
- Systems to track depleted resources and share between hospitals may be helpful.
- With increasing evidence of asymptomatic spread and increasing testing capabilities, some are advocating for routine universal screening of HCW to prevent nosocomial spread.
- Experience from an academic specialty team in NYC emphasizes changes in staffing of teams, flexibility in workflows, and staff wellness by allowing for staff to physically distance and address mental health concerns.

**Space/Structure**
- Increasing hospital capacity is the most commonly cited factor. This will be limited as social distancing will require re-engineering of spaces, especially as they re-open.
- To increase “surge capacity” using “alternate sites” in the hospital, resurrect decommissioned buildings, or create temporary, mobile, modular hospitals.
Regional coalition with local, county, state health systems to coordinate bed capacity

Environmental management is also key (hand sanitizers freely available throughout the facilities, along with trash receptacles, tissues, etc).

EMTALA changes: CMS has relaxed EMTALA requirements regarding medical screening exams allowing redirection to alternative screening locations

Will need to build capacity for mortuary services as patient volume increases

University Hospital Cleveland created a negative pressure infusion center.

Federal alternative care sites (ACS) toolkit describes models for acute, hospital and non-acute care

Systems

“Micro-surges” will be the foreseeable future of COVID systems planning until effective therapeutics and vaccines are available.

○ Table-top tested operational plans should be in place for 100%, 200%, 300% capacity with plans to re-deploy staff, beds, ventilators and PPE.

○ Ramping up and down capacity will depend on local infection rates as well as the intensity of NPI (non-pharmacological interventions; see public health section)

○ Northeastern has a model to predict staffing, LOS, ICU, bed, vent needs

Protocol: Identify, Isolate, Inform (PUI/COVID+ patients) based on CDC’s Ebola plan

Research has consistently demonstrated systems inefficiencies - namely not matching resources with needs - is a key limiting factor in the healthcare facilities’ responsiveness.

C’s: command, control, communications, coordination, continuity of operations, and community. This is similar to the U.S. National Incident Management System

Determine capacity (what exists in present condition) and capability (increase in capacity under appropriate mobilization of resources).

Systems organization - Organizations that have dispersed, decentralized decision making are more agile because they rapidly share information internally(Organization 2).

Communication: Regular updates to patients and staff needed through multiple channels (web, email, text, social media). Designated internal and external spokespeople should serve as points of contact during changing situations.

Implementation of universal COVID screening for patients admitted for non-COVID illnesses-- in NYC, 14% of asymptomatic labor and delivery patients tested positive for COVID.

CDC and CMS released guidance specific to long term care facilities to mitigate spread.

Primary/Outpatient Care

Alternatives to face-to-face visits: Many leading professional societies and other groups have called for a shift towards telemedicine. Medicare has broadened telehealth reimbursement opportunities in response to the pandemic and waived HIPAA penalties.

California requires reimbursement for telephone visits.

○ Many systems have telemedicine screening as the first contact for PUI/Covid-19

○ Apple, in conjunction with the CDC, has created a COVID-19 screening app

○ 3/30 CMS Announced “Hospitals Without Walls” Initiative to expedite telehealth, increase use of MD extenders, and reimburse for care at non-hospital sites
Knowledge sharing networks. Penn State has launched Project Echo to share expertise, best practices between specialists and smaller healthcare facilities.

BMJ article offers practical advice for assessing COVID-19 remotely.

“From one to many” group telemedicine concept in the COVID era.

American College of Physicians (ACP) released a telehealth toolkit to help with implementation and billing.

- One degree has developed an online toolkit for LA County connecting COVID patients to social and financial resources that can be applied for online.
- Practices can consider proactively identifying patients with long term health conditions and elderly to avoid interruptions in care.
- Virtual chatbots, direct to patient channels, and remote patient monitoring are other tools.
- Scheduling redesign: The AAP has suggested separating well vs. sick patients to separate times and spaces (ie., well visits in AM, sick visits after).
- There are calls for urgent changes to quality monitoring in the COVID era.

Surgery and Procedures

- The American College of Surgeons and AAP has called for surgeons to cancel elective cases, with guidelines for triage of various procedures. CMS has called for delaying all elective surgeries, non-essential medical, surgical, and dental procedures.
  - Specific guidance from other specialty societies below:
    - American College of Obstetricians and Gynecologists
    - American Society for Reproductive Medicine
    - Children’s Hospital Association and American Academy of Pediatrics

Reopening Health Systems

- As of April 22, Governor Newsom (CA) allowed partial re-opening of hospitals for procedures “foundational to people’s health” including cancer surgeries, colonoscopies, heart valve surgeries, and surgeries related to diabetes. Purely cosmetic procedures are prohibited.
- The White House with the CDC has issued a gated strategy for re-opening healthcare systems
  - Symptoms - downward trajectory of reported ILI (influenza like illness) within a 14 day period AND downward trajectory of covid-like syndromic cases reported in a 14 day period
  - Cases - downward trajectory of confirmed COVID cases in a 14 day period OR downward trajectory as a function of total tests in a 14 day period (flat or increasing volume of tests).
  - Hospitals - treat all patients without crisis care AND robust testing in place for at-risk healthcare workers, including emerging antibody testing
  - Critics have noted these criteria lack metrics or specificity. It is unclear how much of a downward trajectory is required for reopening.
- CMS suggests a phased re-entry of procedures will start in low COVID areas in conjunction with state DOH depending on projected COVID rates in the near future.
including likelihood of surges; availability of testing (including swabs/reagents); workforce capacity; and PPE inventory.

- Medical and surgical societies are anticipated to issue guidelines in the coming weeks. Rigorous testing to monitor for potential outbreaks during this time is key. Non-covid care zones (NCCs) in hospitals can facilitate this.
- Guidelines will need to be discussed now about when to ease limitations on semi-urgent and elective procedures. Best practice suggests doing this in 2 week blocks in conjunction with rigorous testing, digital and in-person contact tracing, and tracking of PPE to identify any potential outbreaks and shortage of protective equipment. Limiting low value care is essential.

**Supplemental Resources**

- HHS COVID healthcare emergency preparedness information gateway (Tracie)
- WHO: Phases of influenza pandemics
- WHO: Pandemic influenza risk management
- BMJ: COVID-19 Remote Assessment in Primary Care
- JHU Center for Security: Top Priorities for Pandemic Preparation
- CDC: Hospital Preparedness Checklist for COVID-19
- FEMA: Incident Command System
- ASPR: Hospital Pandemic and Emergency Planning Checklist
Section 6: Virology, Drug and Vaccine Development

Virology and Drug Targets

- **Coronaviruses:** COVID-19 is caused by the coronavirus SARS-CoV-2. Seven coronaviruses infect humans: 4 cause common colds, while SARS, MERS and COVID-19 are more serious diseases caused by the other 3 human pathogens.
- **Origin:** Many (100s) strains of coronaviruses circulate in animals, with the closest relatives so far to SARS-CoV-2 found in bats. Although possible that bat to human transmission occurred via an intermediate animal host, as happened in SARS (palm civets) and MERS (camels), bat virus sequence analysis instead suggests direct transmission from horseshoe bats to humans. Moreover, other bat coronaviruses have the presumed necessary characteristics to suggest additional future transmissions from bats to humans is likely. Possibility that SARS-CoV-2 was a lab accidental release has not been ruled out.
- **RNA replication and mutation rates:** SARS-CoV-2 is a large RNA virus of 30,000 nucleotides. Although some RNA viruses mutate rapidly, SARS-CoV-2 shows limited mutation. Early reports of strains evolving to have greater virulence have been disputed.
- Differences in circulating virus strains can identify origins of outbreaks. For example New York was seeded mostly through European introductions.
- RNA replication is a drug target, inhibited by e.g. the nucleoside analog remdesivir.
- Other candidate drugs such as EID-2801 act by increasing the mutation rate of the virus to a point of ‘lethal mutagenesis’
- **Spike (S) protein and entry:** S protein on the outside of the virus binds ACE2 which helps determine tropism (alveolar epithelial type II cells, upper respiratory tract). Soluble recombinant ACE2 inhibits the virus in vitro and is a potential therapy.
- Spike protein is activated by cleavage by TMPRSS2, which is also a drug target.
- Entry also requires low pH (endosome) which chloroquine blocks, hence possible drug.
- **Main viral protease:** The main protease (Mpro), also called 3C-like or papain-like protease (PLP), is important in the early stages of an infection, cleaving the viral polyprotein, deubiquitinating viral and cellular proteins, and antagonizing the interferon (IFN) response (data from SARS).
- The structure of Mpro is being used to suggest drugs that could inhibit it.
- A trial is underway to test if a common heartburn drug, famotidine, could also inhibit Mpro due to observations in Chinese coronavirus patients taking the drug, and computational modeling.
- **Other drug targets:** Antiviral drugs used against other viruses are being evaluated for cross-reactivity against SARS-CoV-2 including HIV drugs and influenza drugs.
- Study identified human cell partners of 26 of the 29 unique coronavirus proteins, and lists 69 potential drugs that could target those interactions.

Vaccine Development

- **Types of vaccines:** Both traditional and newer technologies are being deployed in race to make a vaccine. mRNA and DNA based vaccines that encode one or more viral proteins (typically the Spike protein) are expected to be faster to produce than more traditional
vaccines based on: killed virus particles, attenuated virus strains, recombinant viral proteins (Spike protein) or viral vector vaccines such as adenovirus expressing one or more viral proteins. A summary of vaccine types being developed here.

- **Vaccine development challenges:**
  - Efficacy - will it make the right type of immunity, with an effective combination of either neutralizing antibodies or T cell responses?
  - Safety - some vaccines can make coronavirus infections worse through antibody-dependent enhancement of entry into cells.
  - Time and scalability - ease of manufacture varies for different vaccine technologies.

- A list of vaccines under development is here.
- First clinical trial was Moderna’s mRNA vaccine (mRNA-1273), started 3/16/20 in Seattle. Injected mRNA makes the spike protein inside the body.
- J&J announced intent to partner with US DHHS to start clinical trials by September 2020, to deliver first vaccine for emergency use in early 2021, and supply one billion vaccines worldwide for emergency pandemic use.
- Tobacco plants are being evaluated to make a vaccine, using a rapid and large-scale technology that was previously effective for an Ebola vaccine.
- Gates Foundation and others are planning how to scale vaccine production capacity.
- Pilot studies of killed virus vaccine (PiCoVacc) protected macaques from challenge.
- Macaque studies also showed protection for an adenovirus vector vaccine developed at the University of Oxford, which began a Phase I trial (1,100 people) in late April and will start a combined Phase II/III trial (5,000 people) in May.
- Pfizer and BioNTech started a Phase 1/2 clinical trial in Germany of a mRNA vaccine (BNT162) and expect to start in the U.S. soon. If successful, they estimate potential to supply millions of vaccine doses by end of 2020, and hundreds of millions in 2021.
- Other vaccine approaches: The anti-TB vaccine, BCG, non-specifically boosts immunity and is hypothesized to confer some protection. BCG vaccination is being tested in Australia and the Netherlands.
- Passive immunization: Screens are being carried out to identify neutralizing antibodies in patients that could then be synthesized and used as a therapy.
Section 7: Public Health Considerations

Simulations
- Without interventions, mortality in the U.S. would peak in mid-June with ~55,000 deaths per day and culminate with 2.2 million fatalities.
- A model developed at USC accounting for underlying conditions and age projects 5,500 hospitalizations in the Service Planning Area covering Metropolitan Los Angeles, our main catchment area, by 100 days with a reproductive number of 2.2 and by 250 days with a reproductive number of 1.5.
- Two scenarios reflecting various combinations of interventions:
  - Mitigation strategy: Goal is to reduce the health impact and not to interrupt transmission completely. Strategy includes closure of schools and universities, case isolation and household quarantine, social distancing of those aged over 70. Duration: 3 months.
  - Contact tracing: Testing, contact tracing and isolation of contacts strategies have the best chance of breaking the chain of transmission, as was accomplished in China and is being accomplished in South Korea.
  - Suppression strategy: Goal is to reduce the average number of secondary cases each case generates. Strategy includes closure of schools and universities, case isolation, population-wide social distancing, and household quarantine. Duration: 5 months.
    - With close monitoring of disease trends, possibly relax measures temporarily as things progress but will need to be maintained until a vaccine becomes available (18 months).
    - A suppression strategy could reduce deaths by about 49% and peak ICU beds needed by about 67%.
- The U.S. needs approximately 295,000 ICU beds under the worst case scenario.
  - Currently, there are 96,596 critical care beds where two-thirds are likely occupied by other non COVID-19 patients.
  - Tsai et al. estimated (assuming a 40% population infection rate), if transmission occurs over six months, the need for hospital beds will be at 274% of capacity, and the ICU need will be 508% of capacity.
- Healthcare system capacity: A tool has been published to help determine a healthcare system’s capacity for managing cases of COVID-19.
- Local Modelling Tool: A new local modelling tool may help local communities with capacity planning and evaluating the impact of public health interventions.
- Another simulation model from the Institute of Health Metrics and Evaluation projects that with current social distancing policies in place, peak resource need occurred around April 15, and they project decreasing need going forward.
  - In California, the peak is expected to be much lower than other parts of the country, and is not expected to cause shortages of ICU beds, hospital beds, or ventilators.
  - U.S. deaths attributable to COVID-19 is expected to be 60,000 (~18 deaths per 100,000), with approximately 1,600 in California (~4 deaths per 100,000).
• **Projections on duration of social distancing:** Absent a vaccine, a [new projection](#) suggests that social distancing may be required until 2022 or beyond.

## Evidence Regarding Social Distancing

• **Social distancing policies and community mobility:** A [CDC analysis](#) documents the impact of community-level policy changes in 4 large metropolitan areas with community mobility (as measured based on publicly available data on personal electronic devices); more data are needed to assess the impact of these changes on COVID-19 transmission.

• **Effects of extreme social distancing, testing and quarantine in Wuhan, China:** Before the mitigation, the reproductive number was 3.0 before January 26; after these measures were implemented these decreased to below less than 0.3 after March 1.

• **Effect of Travel Restrictions:** An [analysis](#) of travel restrictions in China found that: “travel quarantine of Wuhan delayed the overall epidemic progression by only 3 to 5 days in mainland China but had a more marked effect on the international scale, where case importants were reduced by nearly 80% until mid-February.”

• **Suppression in Vo, Italy:** A [case study](#) of a 14-day lockdown in Vo, Italy found that the prevalence of COVID-19 in the community decreased from 2.6% before the lockdown to 1.2% afterwards.

• **Crowding and Risk:** [Modelling studies](#), which have not yet been published in peer-reviewed journals, strongly highlight the role of crowding/population density in viral spread both at the community level and within institutions.

• **Mental Health Consequences of Social Distancing:** This [perspective piece](#) highlights some of the potential mental health consequences of social distancing.

## Approaches to Easing Social Distancing Restrictions/Reopening the Economy

• **Plans to Reopen the Economy:** Comprehensive plans to reopen the economy from the [Center for American Progress](#) and [American Enterprise Institute](#) focus on criteria needed to reopen and state responsibilities including increasing testing, case isolation, contact tracing, travel restrictions, disease surveillance, increasing availability of PPE in healthcare settings, and use of nonmedical cloth face coverings in the general public. The [Harvard Center for Ethics](#) and [Paul Romer](#) have additional plans that focus only on testing capacity. The [White House](#) has also released a plan.

• **Easing of Social Distancing Measures:** As COVID-19 rates peak in the U.S., experts have begun suggesting validated approaches -- such as “suppress and lift” policies, “targeted approaches” and [immunity testing](#) -- as well as [criteria](#) and [monitoring tools](#) for cautiously easing social and economic restrictions without triggering sudden and dramatic recurrences of disease spread that could overwhelm the healthcare system.

• **Testing Capabilities for Reopening the Economy:** A [Harvard white paper](#) estimates that it will require millions of daily COVID-19 tests to safely reopen the economy; Economist [Paul Romer](#) similarly estimates that testing of the entire US population weekly or biweekly may be necessary, and is still effective to inform case isolation even with a high false negative rate.
  • **Testing could be ramped up** by significantly increasing federal reimbursement, and reinforcing the supply chain for intermediate supplies (swabs, reagents, etc.).
○ **Pooled sample testing** could also be used whereby several samples are run on the same test, and if the pool is positive, individual tests are used to determine which individuals are positive.

- **Contact Tracing:** The United States may need as many as **100,000** paid or volunteer contact tracers.

- **Challenges of Contact Tracing with Asymptomatic Spread:** Contact tracing is **substantially more challenging** for conditions with asymptomatic/presymptomatic spread.

- **Digital Contact Tracing:** Researchers -- including some from USC -- are investigating the potential for **digital tools** to support contact tracing as social distancing measures are relaxed. Contact tracing is **one key approach** for preventing subsequent waves of disease.

- **Preventing a Second Wave:** In China, non-pharmacologic, public policy measures, including social distancing were able to reduce the reproduction number, R, below 1, which caused the number of cases to fall towards zero. However, new cases imported from other countries may require close monitoring to prevent a second transmission wave as these public policy interventions are relaxed.
Acknowledgements

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