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## Acknowledgments
Section 1: What’s new this week?

- **American Academy of Pediatrics Advocates for School Reopening in the Fall:** The guidance highlights the value of in-person education for the health of children and the well-being of society, and recommends measures to minimize risk. New data from Europe also suggests that schools can be safely reopened as long as rates of community spread are modest and appropriate safety-measures are in place.

- **Mass Testing:** CDC report has demonstrated the value of repeated facility-wide surveillance testing in skilled nursing facilities and jails, however the CDC has advised against repeated mass testing in most other settings including Universities. When conducting mass testing, it appears that testing frequency and speed of results may be more important than test sensitivity.

- **More Data on the Effectiveness of Masks:** From Italy, as well as from a laboratory study that found “that most home fabrics substantially block droplets, even as a single layer. With two layers, blocking performance can reach that of surgical mask without significantly compromising breathability.”

- **Temperature and Humidity:** New models do not suggest a link between temperature, humidity and disease rates.

- **Seroprevalence Estimates in the U.S.:** A new study reports that “the proportion of persons seroreactive to the SARS-CoV-2 spike protein ranged from 1.13% in WA to 6.93% in NYC (collected March 23-April 1) [to] 1.85% (collected April 6-10) for FL to 4.94% for CT (April 26-May 3). The estimated number of infections ranged from 6 to 24 times the number of reported cases in each site.

- **Outcomes in Children:** New data suggest that overall outcomes in children are excellent, however” a small proportion develop severe disease requiring ICU admission and prolonged ventilation, although fatal outcome is overall rare.”

- **Immune Response:** A new study has found that “forty percent of asymptomatic individuals became seronegative and 12.9% of the symptomatic group became negative for IgG in the early convalescent phase.” It is not known how well IgG levels correlated with immunity.

- **Drug Targets:** Proteomics studies revealed that SARS-cCo-2 alters phosphorylation of host proteins, resulting in production of cytokines, cell cycle arrest and induction of cell protrusions containing viral particles. Eighty-seven FDA-approved drugs were identified that could block these events including Silmitasertib, which is being evaluated as an anti-COVID-19 therapy.

- **Pollution Levels May Accelerate Spread:** Based on data from subway systems.

- **Microwaving N95s** using household props - glass container, elastic band, mesh produce bag and appears to be effective in decontamination appears to be effective for decontamination.
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 LA County DPH interactive portal.
  - As of June 29: LA County has 103,529 COVID-19 positive people. The cumulative crude incidence rate (CCIR) is 764/100,000 and the two-week crude incidence rate (CIR) is 281/100,000, up from 188/100,000 on June 16.
  - As of June 29, there have been 9,057 persons hospitalized at some point with COVID-19 (8.6%, down from 9.5%), with 17.7% intubated (stable for at least a month).
  - As of June 29, there have been 3,369 deaths, with a two-week cumulative mortality rate of 4.06%, down from 4.26% June 24 and 5.72% on May 22.
  - Percent positivity of tests and people is slightly increasing (8.76% on June 29, up from 8.35% on May 27).
  - **Age:** Characteristics of cases with known age: 7% ages 0-17 yrs, 40% ages 18-40 yrs, 37% in ages 41-65 yrs, 15% in ages >65 yrs, with higher %’s in cases 18-40 younger cases compared to 2 weeks ago (see Figure 4. below). 3,227 deaths had 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.
  - **Sex:** 50.5% of cases but 55.6% of the deaths are in males (holding steady since the beginning of the outbreak).
  - **Race/Ethnicity:** Characteristics of the cases with known race/ethnicity: 7% Asian, 5% Black, 51% Hispanic/Latino, 14% Non-LatinoWhite, 1% American Indian, Alaskan Native, Native Hawaiian, Other Pacific Islander, and 23% Other (increased from 6% on May 24).
  - Of the 3,233 deaths with known race, <1% were Native American/Pacific Islander, 1% were Other, 12% were Black, 16% were Asian, 42% were Hispanic, and 29% were non-Hispanic white. Blacks and Asians overrepresented in deaths relative to population and the distribution of cases.
  - **Underlying comorbidities were present in 94% of deaths in L.A. County.** 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.
  - 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.
  - **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.
  - **New CDC High Risk Categories:** CDC expanded and modified the high risk categories. Age alone is no longer a high risk category if there are no underlying
conditions. CDC added several high risk categories including pregnant women, as 9%, and expanded the list of underlying health conditions to include chronic kidney disease, BMI of 30+, sickle cell disease, immunocompromised state and type 2 diabetes.

- **Pregnant women** were significantly more likely to be hospitalized, admitted to the ICU and receive ventilation than non-pregnant women; however they were not at greater risk of death from COVID-19.
- **Asymptomatic health care workers** screened: In the UK, 1,032 asymptomatic health care workers at a hospital were tested. 30 (3%) were positive and were more likely to have worked in specific wards, suggesting cluster transmission.
- **Superspreader events:** High Attack Rates Among Churchgoers in Arkansas: Among 92 attendees at a rural Arkansas church during March 6–11, 35 (38%) developed laboratory-confirmed COVID-19, and three persons died. Attack rates were significantly lower among persons aged ≤18 years (6.3%–25.0%) than among adults aged 19–64 years (59.4%–82.6%) (p<0.01). Risk ratios for persons aged ≤18 years compared with those for persons aged 19–64 years were 0.1–0.3. No severe illnesses occurred in children. Transmission during high-intensity fitness classes: During 24 days in Cheonan, South Korea, 112 persons were infected with severe acute respiratory syndrome coronavirus 2 associated with fitness dance classes at 12 sports facilities. Intense physical exercise in densely populated facilities could increase risk for infection. Vigorous exercise in confined spaces should be minimized during outbreaks.

- • California as of 06/29/20: 222,917 cases and 5,980 deaths: [CDPH](#)
- • U.S. as of 06/30/20: 2,581,229 cases & 126,739 deaths: [CDC](#)
- • Worldwide: As of 07/1/20: 10,512,383 cases & 512,331 deaths: [JHU Map](#)

**Fig1. Number of new cases and deaths from COVID-19**

![Number of New Daily Cases and Deaths from COVID-19, Los Angeles County](#)
Fig 2. New cases and deaths from COVID-19, Log Scale

Fig 3. Three-day rolling average of new hospitalizations and deaths

Fig 4. Proportion of new daily cases by age group
Seroprevalence

- **LA County:** A USC/LA County seroprevalence study found that the “prevalence of antibodies to SARS-CoV-2 was 4.65%.” However, a follow-up analysis from this same group, perplexingly, now suggests that just 2.1% of LA County residents have previously been infected.
- 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.
- **Seroprevalence in Geneva:** Repeated seroprevalence estimates were 4.8% (first week), 8.5% (second week), 10.9% (third week), 6.6% (fourth week), and 10.8% (fifth week), according to a Lancet study. In addition, “a significantly lower seroprevalence was observed for children aged 5–9 years and adults older than 65 years, compared with those aged 10–64 years.
- **COVID-19 Surveillance:** A report found that respiratory illness was “above the seasonal average in March 2020” and “this surge correlated with COVID-19 case counts across states … [these findings indicate that] over 80% infected patients [are] undetected.”
Disparities, Homelessness and Jails

- **Blacks are experiencing a higher burden of severe disease** compared to other racial/ethnic groups.
- **Nationally**, recent estimates suggest that **Blacks and Hispanics are approximately three times as likely to contract the virus and Blacks are nearly twice as likely to die from the disease.**
- There are significant disparities in **Los Angeles County:**
  - **Hispanics have the highest rate of cases in LA.** Per 100,000 people there are 102.3 cases among Blacks, 113.6 among Hispanics, 73.2 among Asians and 78.2 among Whites, after adjusting for age.
  - In Los Angeles County, Blacks are more than twice as likely as Whites to die from COVID. Hispanics and Asians also have a higher risk of dying from COVID.
  - Lower socioeconomic status communities in Los Angeles County are now experiencing the highest increases in cases and deaths.
- **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.” Another **new study** found that the number of hospitalizations and deaths in NYC was highest in the Bronx, the area with the lowest SES and highest percent of Blacks, and lowest in Manhattan, in spite of the Bronx having the lowest proportion of adults > 65 (12.8%) compared to Manhattan (16.5%).
- An **analysis** suggests Latinos are at increased risk for COVID-19 while another **study** suggests African Americans are at elevated risk. An **analysis** also suggests that “African Americans, men, and people younger than 55 years were less likely to know how the disease is spread, were less likely to know the symptoms of coronavirus disease 2019, washed their hands less frequently, and left the home more often.”
- **Homeless Populations:**
  - The **homeless in New York face disproportionately high mortality rates**
  - 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.
  - COVID-19 cases and deaths in prisons can be tracked [here](#).

**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.**
- A systematic review concluded SARS-CoV-2 is mainly transmitted via inhalation of respiratory droplets containing the virus and has an incubation period of four to six days;
- **Speech droplets:** Not just coughing but also speech may disperse these droplets.
- 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.
- **Preventing Airborne Spread:** While CDC guidance indicates that SARS-CoV-2 primarily spreads via respiratory droplets that typically don’t travel more than 6 feet, a new article contends that “SARS-CoV-2 is silently spreading in aerosols exhaled by highly contagious infected individuals with no symptoms.” The authors suggest that future research should focus on identifying masks that effectively control release of airborne particles at the source, as well as strategies to improve ventilation.
- **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 particles 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. A new report shows that live virus can be cultured from stool samples, though more evidence is needed to determine if the virus can be spread via stool.
- **Ocular Spread:** Lab studies suggest SARS-CoV-2 may be able to transmit via the eyes.
- **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.”
A new analysis in the Annals of Internal Medicine concludes that “asymptomatic persons seem to account for approximately 40% to 45% of SARS-CoV-2 infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days.” Nevertheless, the WHO reported that the extent of asymptomatic spread remains uncertain.

Italian case study also highlights role of asymptomatic spread.

**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.

Infection Clusters: A new article explains that a disproportionate amount of spread occurs in clusters, highlighting the need to better understand factors associated with “superspreading”. Disease clusters seem to occur when an individual interacts closely in an indoor environment during a period of high infectivity early in the disease course.

**Health care workers were infected early in the outbreak:** HCW in the Netherlands had relatively high infection rates early in the pandemic, with 47% reporting no fever. The index of suspicion for COVID-19 was low early on so protective gear was not employed. Later in the pandemic, HCW were regularly using PPE so the infection rate is now lower in HCW than in the general community.

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 JAMA analysis concludes that “the distribution of … community outbreaks of COVID-19 along restricted latitude, temperature, and humidity measurements was consistent with the behavior of a seasonal respiratory virus. Using weather modeling, it may be possible to estimate the regions most likely to be at a higher risk of substantial community spread of COVID-19 in the upcoming weeks …” Previously, a National Academy of Sciences report found that data are insufficient to indicate whether COVID-19 will dampen in hot/humid summer months. A case study suggested, however, 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 voluntary use of cloth face coverings by the public. There is mechanistic evidence as well as some experimental evidence from the SARS epidemic.

**Face covering options:** There is some evidence that medical masks provide better protection vs. cloth face masks. Face shields are another potential option.
New Evidence for Face Coverings: A new modeling study -- not yet officially published nor peer-reviewed -- indicates that consistent use of face coverings might dramatically reduce COVID-19 spread. An analysis among healthcare workers also suggests that face coverings are highly effective in preventing spread.

- A new analysis has found that “wearing of face masks in public corresponds to the most effective means to prevent interhuman transmission, and this inexpensive practice, in conjunction with simultaneous social distancing, quarantine, and contact tracing, represents the most likely fighting opportunity to stop the COVID-19 pandemic.” Another analysis from Germany suggests that “face masks reduce the daily growth rate of reported infections by around 40%.” Furthermore, testing results of 45 direct contacts of two infected hair stylists who worked while symptomatic has thus far found that none acquired the infection; since the stylists and their clients wore masks, it supports the effectiveness of masks for preventing spread.

WHO Now Recommending Multi-Layered Cloth Masks for the General Public: New guidance from the WHO recommends three-layered cloth masks with a water-resistant external layer; a cotton absorbent inner layer; and a middle filtering layer.

California Mask Order: Gov. Newsom issued an order that all Californians must wear masks in public and high risk settings.

Transmission Via Toilets? A fluid dynamics simulation suggests that toilet flushing may lead to “massive upward transport of virus particles”. The authors recommend consideration of measures such as toilet lids to protect against spread via toilets.

Factors Associated with Infection Clusters in Japan: Japanese researchers report that “many COVID-19 clusters were associated with heavy breathing in close proximity, such as singing at karaoke parties, cheering at clubs, having conversations in bars, and exercising in gymnasiums.” Japanese policymakers advise avoiding “the “Three Cs”: closed spaces with poor ventilation, crowded places, and close-contact settings.”

Effectiveness of Simple Measures to Prevent Spread: A study of 124 families in China found that masks, disinfection and physical distancing substantially reduces transmission of SARS-CoV-2 within households. Another case study at a Wuhan Medical Center found that “standard preventive measures against infectious diseases can prevent SARS-CoV-2 exposure in medical staff.”

Meta-Analysis of Preventive Measures: A meta-analysis of observational studies found the following odds ratios for various preventive measures: OR 0.18 for physical distancing of at least 1 meter; OR 0.15 for face mask use; and OR 0.22 for eye protection.

New CDC Guidance for Essential Workers Who Have Been Exposed: New CDC guidelines 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.”

Factors Associated with Spread: A new CDC report offers insights on factors associated with the early 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.”
- **Ultraviolet Light to Disinfect:** Though some have suggested the role of UV light to kill the virus on surfaces, evidence to support this practice is limited.
- **CDC Guidance on Discontinuation of Transmission Precautions:** The latest [CDC guidance](https://www.cdc.gov/coronavirus/2019-ncov/dlib/when-ending-guidance.html) indicates that transmission precautions (i.e. quarantine) can be lifted after “at least 3 days (72 hours) have passed since recovery defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath); and, at least 10 days have passed since symptoms first appeared.” Alternatively, precautions can be lifted after two consecutive negative RNA tests from a respiratory specimen at least 24 hours apart.
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 (though lower rates have been reported from other studies, particularly those from China); 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. LFT abnormalities were present in a third of hospitalized patients in one analysis. A new meta-analysis has found that “12% of patients with COVID-19 will manifest GI symptoms” and 40.5% will shed virus in their stool. The extent to which the virus spreads via stool is uncertain, however.
- 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.”
- CDC Updates: The CDC has updated its list of conditions associated with increased COVID-19 complication risk; the list now includes sickle cell disease, and those with chronic kidney disease (not just those on dialysis) and those with a BMI 30 or greater (rather than 40 or greater). The CDC has also added three new symptoms to its list of common COVID-19 symptoms: congestion/runny nose, nausea and diarrhea.
- Effects of Age on Prognosis: An analysis has found that “susceptibility to infection in individuals under 20 years of age is approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% of infections in 10- to 19-year-olds, rising to 69% of infections in people aged over 70 years.”
- Genome Associations with Severe Respiratory Failure: An analysis has found associations between ABO blood group loci and COVID-related respiratory failure. Group O is associated with decreased risk while A with increased risk
- A systematic review concluded that commonly reported symptoms were fever (80%) and cough (60%), however using these symptoms in isolation will miss a proportion of cases.
● **Characteristics of Hospitalized Patients**: A cohort analysis of more than 20,000 hospitalized patients found that the median age of hospitalized patients was 73; median duration of symptoms prior to hospitalization was 4 days; most common comorbidities were cardiac disease, diabetes, pulmonary disease and kidney disease, while 23% had no major comorbidity. Of those hospitalized, 41% were discharged alive, 26% died and the remainder were still receiving care in the hospital at the time of study reporting.

● **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.

● **Ambulatory care**: An analysis of ambulatory patients has found that “the most commonly reported symptoms ... were cough (83%), headache (73%) loss of smell or taste (71%), sinus congestion (71%), and body ache (67%). Symptoms remained common at 3 weeks, including cough (41%), shortness of breath on exertion (24%), loss of smell or taste (23%), sinus congestion (23%), and headache (20%).” 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.

● **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.

● **Artificial Intelligence to Aid in Diagnosis**: A new study reports on a digital App that may help predict the probability of COVID-19 based on symptoms patients enter.

● **COVID Triage Tool**: A 9-question triage tool, developed based on a national symptom survey in Israel, may help identify those likely to test positive for COVID-19.

● **Tools to Predict Disease Severity**: A tool has been developed to predict disease severity among hospitalized patients with COVID-19; another was recently released as well.

● **Clinical and Immunological Features of Asymptomatic Infection**: A study has found that asymptomatic individuals may have a longer duration of viral shedding (median duration 19 days) vs. those with symptoms; may be more likely to become seronegative during the early convalescent phase (40% in asymptomatic vs. 12.9% in symptomatic); and that asymptomatic individuals have a weaker immune response.

### Diagnostic Testing

- **Summary** of diagnostic testing.

- Testing for active COVID-19 generally involves the reverse transcriptase-PCR, typically utilizing a nasopharyngeal sample.

- **New COVID-19 Antigen Test Approved**: The FDA has approved the first antigen test for COVID-19 diagnosis. The antigen test can provide more rapid results vs. the PCR testing method, though there is a higher rate of false negatives.

- **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.”

- **Point of Care Testing**: FDA approved an Abbott Labs point-of-care COVID-19 test, offering results within several minutes. However, a new analysis has indicated a high incidence of false negatives, which may miss a third of positive results detected by other assays. Despite the study not yet peer reviewed, the FDA issued an alert.
• FDA has also authorized a home sample collection kit to facilitate testing within the home environment.

• **False Negatives:** A study has found that PCR tests are particularly likely to be falsely negative early in the course of infection, when patients may be most contagious. Negative tests shouldn’t be used to remove precautions when suspicion for infection is high.

• **Antibody Test Approved.** The FDA authorized the first COVID-19 antibody test on April 1, and there are now 12 serology tests approved. Quest and Labcorp are providing their own serology testing. The FDA now requires test makers to submit validation data within 10 business days from the date they notified the FDA of their validation testing or from the date of this policy, whichever is later.

• 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. There also appears to be wide variability in the performance of existing antibody tests.

• 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:
  o Prioritize patients with serious, unexplained respiratory illness as well as those who are symptomatic with contacts of known cases.
  o 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 …”

• **Concerns with Antibody Testing:** Because serologic testing may be wrong half the time, new CDC guidance indicates that serologic testing should not be used to guide decisions regarding who is safe to return to work and other congregate settings.

• **Diagnostic Accuracy of SARS-CoV-2 Antibodies:** A Cochrane review has found that “The sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role for the diagnosis of COVID-19 … Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. However, the duration of antibody rises is currently unknown, and we found very little data beyond 35 days post-symptom onset.”

• **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.

• 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 (e.g., min bronchial 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.
- **Pooled Testing:** Testing groups of individuals together is an emerging strategy for maximizing current testing capacity, though some data indicate reduced sensitivity with batch testing.
- **Testing Guidelines from the IDSA:** The IDSA recommends testing “all symptomatic individuals suspected of having COVID-19 [and] asymptomatic individuals with known or suspected contact with a COVID-19 case. Testing asymptomatic individuals without known exposure is suggested when the results will impact isolation/quarantine/personal protective equipment (PPE) usage decisions, dictate eligibility for surgery, or inform administration of immunosuppressive therapy.”

## 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 for COVID-19 based on the medications’ cellular interaction with the virus and in vitro data.
  - CDC guidance, Emergency Use Authorization and Controversy: Initial anecdotal evidence suggested the medication helps with shortening disease course and improvement of lung imaging. This led to the CDC suggesting the use of Hydroxychloroquine. Controversy ensued given its potential for cardiac complications and soon medical experts advocated caution. Subsequently, the CDC removed its guidance on the use of Hydroxychloroquine. The FDA has made the medication available via an Emergency Use Authorization for hospitalized patients unable to participate in a clinical trial but has issued a safety communication.
  - Supportive Evidence for Hydroxychloroquine: Small randomized trials—not yet peer reviewed—seem to show modest benefit from Hydroxychloroquine. In one study, investigators showed significant improvement in time to clinical recovery, symptoms and pneumonia (by CT scan) when compared to the control arm. In another study, investigators found those with mild-moderate disease had modest alleviation of symptoms but no difference in seroconversion. A systematic review/meta-analysis of seven studies revealed that Hydroxychloroquine may improve symptoms and decrease radiological progression of lung disease but no difference in death or clinical worsening of disease. Notably the authors note no difference in safety. The authors advocated for more studies.
  - Evidence Against Hydroxychloroquine/Chloroquine: One study failed to demonstrate a benefit among patients hospitalized with an oxygen requirement. A retrospective VA analysis concluded no reduction in risk of mechanical ventilation and in fact found an association of increased overall mortality with use...
of Hydroxychloroquine. Further adding to the potential harm of these medications, one study showed cardiac adverse events when using a higher dosage of chloroquine. In a large, observational study, investigators in New York found no significant association with the medication and intubation or death. In an RCT of 821 asymptomatic participants, investigators concluded there was no difference in the incidence of new illness between placebo and hydroxychloroquine. The study did not suggest any evidence of adverse cardiovascular effects.

- **Combining with Azithromycin:** A small non-randomized study—which received an expression of concern from the sponsoring society—has suggested a benefit of combining hydroxychloroquine with azithromycin for treating COVID-19. Experts have expressed caution in combining these medications, given the potential for adverse cardiac events.

- **Questionable Science:** A recent, large multinational registry analysis of 96,000 hospitalized patients showed hydroxychloroquine or chloroquine with or without a macrolide was independently associated with in-hospital mortality. The death rates of the greeted groups were: Hydroxychloroquine 18%, Chloroquine 16%, and control group 9%. The investigators also found an increase in cardiac complications. This led to the WHO temporarily suspending trials and France banning the medication in the use of COVID-19 patients. However, the validity of the database used to publish the data is being questioned. As such the original article has now been retracted.

- **Hydroxychloroquine Use for Prevention:** Major media outlets have reported Hydroxychloroquine does not prevent COVID-19. This is based on a randomized, double-blind placebo controlled trial of 821 asymptomatic participants in which the investigators concluded there was no difference in the incidence of new illness between placebo and hydroxychloroquine. Some have argued, however, the study may not be definitive, because the participants self-reported symptoms and there was no testing, raising the question of the trial design.

- **Ineffective in Hospitalized Patients, FDA authorization revoked:** Recent robust evidence shows Hydroxychloroquine is ineffective, as a large randomized ongoing study in the UK showed no clinical benefit in hospitalized COVID-19 patients. The FDA has now revoked its emergency use and the WHO halted its Hydroxychloroquine trial.

- **Favipiravir:** In a randomized study of two influenza drugs, Favipiravir versus Arbidol, in moderate severity patients, there were better outcomes with Favipiravir. While Japan has been testing Favipiravir, early data from a Russian trial has prompted Russia to approve the medication for hospital use. India has been conducting its own trial, and plans to approve the medication as well. The medication is not available in the United States but is currently being investigated. Early data from a Russian trial has prompted Russia to approve the medication for hospital use. The medication is not available in the United States but is currently being investigated.

- **Lopinavir-Ritonavir:** This HIV protease inhibitor is being investigated with early studies failing to show improvement over standard of care. An open-label, randomized phase II trial, however, showed some benefit when combing with ribavirin and interferon.
beta-1B. The study showed triple therapy was associated with “shorter median time to complete alleviation of symptoms” of 4 days vs. 8 days and “shorter median hospital stay” of 9 days vs. 14.5 days.

- **Remdesivir:**
  - **Severe Disease:** A large, randomized, placebo-controlled NIH sponsored trial published their preliminary findings, because they showed statistically significant recovery time for those given Remdesivir in severe disease (11 days vs. 15 days). Additionally, a study has shown 5 days of treatment is as effective as 10 days. These studies led to an FDA emergency use authorization for the drug to be used for severe, hospitalized patients. Gilead has donated supplies and U.S. government has prioritized regions and hospitals to receive the donated medication. Of note, a smaller, randomized, placebo controlled trial failed to demonstrate benefit.
  - **Moderate disease:** While not yet published, Gilead released data from a randomized control trial showing hospitalized patients with moderate disease were 65% more likely to have clinical improvement at 11 days vs. standard care.

- **Colchicine:** A small RCT has suggested a benefit of colchicine in COVID treatment.

- **Statins for Hospitalized Patients:** A retrospective analysis has found that statin use among hospitalized patients is associated with substantially lower mortality, though these findings require further evaluation in a randomized trial.

- **Convalescent plasma:** Convalescent plasma has been studied in the SARS outbreak, H1N1 Influenza pandemic, MERS epidemic and Ebola epidemic. Because of this, convalescent plasma has been utilized in severe cases with some early small studies—not randomized—suggesting benefit. FDA allows for expanded access and single patient emergency investigational use based on strict criteria. Despite convalescent plasma available in many institutions not all research has been favorable. In fact, a recent Cochrane review of 8 studies shows uncertainty as to whether plasma is effective with current available studies being at risk for bias. The FDA currently allows use of convalescent plasma based on strict criteria.

- **Immunomodulators:** Because a cytokine storm may be the catalyst for severe disease, clinicians are investigating immunosuppressants.
  - **Tocilizumab** (Actemra) targets IL-6 and its potential use has been advocated with two major studies now underway.
    - Non-randomized studies support the use of Tocilizumab in severe COVID-19 cases. In a small retrospective study, patients were found to have improved clinical manifestations, lung imaging, and lab markers, with all patients discharged on average 15 days after administration of the medication. The authors suggest the medication is effective to reduce mortality and improve clinical outcome. In another small retrospective analysis, it was again found that Tocilizumab improved lung imaging and inflammatory markers. Authors noted the medication also reduced the requirement for ventilatory support.
    - Preliminary results of a randomized trial showed patients with moderate or severe COVID-19 pneumonia had significantly reduced number of deaths or life support interventions when treated with Tocilizumab compared to a
control group. More research is needed to validate these findings and explore the medication’s potential side effects.

- In a non-randomized study, researchers compared 78 intubated patients who received tocilizumab with 76 who did not receive the medication. They found a 45% reduction in hazard of death and improved status, despite higher risk of superinfection occurrence. This study is not yet peer-reviewed.
  - Sarilumab (Kevzara) also targets IL-6 and is currently involved in a large clinical trial. Preliminary results, however, are not promising.
  - News broke recently that Tocilizumab did not help patients with early stage COVID-19 pneumonia, however a large retrospective study showed reduced risk of invasive mechanical ventilation or death in patients receiving tocilizumab vs. standard care. A large randomized placebo controlled trial and a study combining the medication with Remdesivir is in the works.

- Dexamethasone for Severe Disease: The UK is in the midst of a large randomized trial involving 11,500 patients called the RECOVERY Trial, investigating the use of Hydroxychloroquine, Lopinavir-Ritonavir, Convalescent Plasma, Tocilizumab, and Dexamethasone. The study has shown that Dexamethasone reduces mortality in patients with severe disease. While not peer reviewed, the study showed a one third reduction in mortality for those requiring mechanical ventilation with a number needed to treat of 8. There is also a statistically significant improvement in mortality for those requiring supplemental oxygen with a NNT of 25. There is cause for caution, however, as there was a trend toward worsened mortality for those not requiring oxygen and there are unknown outcomes for approximately. Nevertheless, hospitals are now seeing a shortage of Dexamethasone.

- Blood purification device: Despite limited data, the FDA issued an emergency use authorization for a blood purification device that filters inflammatory mediators.

- Adjunct Care: 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 initiating if at increased risk for clinical atherosclerotic cardiovascular disease.
  - Famotidine: An epidemiologic study, not yet peer reviewed, found that famotidine use was associated with a hazard ratio of death of 0.29. However, a randomized trial will be needed to evaluate the potential role of famotidine for COVID-19 treatment. Observational studies for hospitalized patients not initially in an intensive care setting showed that the heartburn drug famotidine was
associated with a two-fold reduction in clinical deterioration leading to intubation or death.

○ 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.

○ Vitamin D: There is some suggestion that vitamin D repletion may reduce complication rates. According to a new analysis, “based on retrospective data and indirect evidence [there is] a possible role of Vit D in reducing complications attributed to unregulated inflammation and cytokine storm.” However, a randomized trial of vitamin D supplementation would be needed to evaluate this hypothesis.

**Expert Recommendations on 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

- **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. A systematic review has found that chest CT is sensitive but not specific for COVID-19 pneumonia.

- **Prone positioning for nonintubated patients:** A new cohort study suggests a benefit of prone position among patients with COVID-19 in improving oxygenation and preventing intubation, however the findings will require confirmation in a randomized trial.

- **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. The American Society of Hematology has attempted to issue some guidance and some institutions have created their own management algorithms for VTE prevention and treatment.

- **Lupus anticoagulant:** COVID-19 may be associated with lupus anticoagulant positivity, which may explain with the observed hypercoagulability and thromboembolic disease.

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

- **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.
  - 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.
  - A large observational study spanning multiple countries and including 8910 patients showed no association between ACEIs/ARBs with mortality.
  - Another population-based case-control study of 6272 patients showed no evidence that ACEIs/ARBs affect the risk of COVID-19.
  - A systematic review showed ACEIs/ARBs not associated with more severe COVID-19 disease.
  - Another large epidemiologic analysis has failed to identify an association.
  - There are now clinical trials further investigating ACEIs/ARBs and their role in
COVID-19.

**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 with implications for resource availability.
- Useful overviews in: NEJM; 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.
  - **Cerebrovascular complications:** There are increasing reports of cerebrovascular complications of COVID-19, including among younger individuals.
  - 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, delirium, and corticospinal tract signs.
- **Clinical markers** include: elevated C-reactive protein, LDH 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 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:**
  - Critical Care Medicine paper (5/26/20) from Atlanta: ICU and ventilator mortality
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 as a risk factor**: A retrospective study looking at a single center E.D. experience found BMI to be an independent risk factor in individuals younger than 60 years. A single center retrospective cohort study found obesity to be a risk factor in disease severity. A single center large retrospective study of 3400 patients found obesity to be independently associated with mortality in patients younger than age 50. Another analysis among hospitalized patients with diabetes showed that “BMI, but not long-term glucose control, was positively and independently associated with tracheal intubation and/or death.” 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 rate unknown, estimated between 0.1-0.6%
  - For **symptomatic infections in the U.S.**, the rate is estimated at 1.3%.

**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.’” 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.”

- A JAMA viewpoint concludes that: “existing limited data on antibody responses to SARS-CoV-2 and related coronaviruses, as well as one small animal model study, suggest that recovery from COVID-19 might confer immunity against reinfection, at least temporarily. However, the immune response to COVID-19 is not yet fully understood and definitive data on post infection immunity are lacking.” Another JAMA viewpoint highlights that there is not currently sufficient evidence to support “immunity certification” programs, but this may change as further data emerge.

- **Update on the South Korean Patients Reported to Have been Reinfefted:** A new report from South Korea suggests that the repeat positive tests among some patients who had previously recovered from COVID-19 infection was likely the result of residual virus rather than a repeat infection -- providing reassurance that previously infected individuals will have at least short-term immunity. These findings highlight that a positive PCR test
does not always indicate active contagious infection, and that negative tests likely should not be required before those who have been infected can safely end their isolation.
Nevertheless, there are now new reports of U.S. sailors who may have been reinfected.

- There does seem to be immunity in other primates.

**Pediatric Populations**

- Pathogenesis
  - Children appear to have a lower likelihood of infection with SARS CoV2 and a milder course when infected. Reasons include:
    - **Children’s lower risk** may be due to low ACE2 gene expression (receptor for SARS CoV2) in nasal epithelium - especially those<10 years - gene expression increases with age
    - **Cross immunity** related to high prevalence of prior infection with other types of human coronavirus may explain why children have milder effects of COVID-19.
    - Another factor may be **children’s healthy arterial endothelium** that reduces the risk of clotting seen in older persons.

- Prevalence and Clinical Course
  - The WHO has issued a preliminary case definition for multi-system inflammatory syndrome in COVID-19 infected children with features of toxic shock and atypical Kawasaki disease. The CDC also has issued a health advisory.
  - Among 17 children admitted with Kawasaki disease over 10 days in Paris, 82% had SARS CoV2 infection - all had marked gastrointestinal symptoms initially and high levels of inflammatory markers and all recovered.
  - **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) limited data on clinical course but generally mild.
  - A study of 582 hospitalized children with COVID-19 from 25 European countries finds 25% had comorbidities which increased risk for ICU as well as: age<1 mo, males, and lower resp sx at admission.
  - Among 48 children with COVID-19 in pediatric ICUs in the US and Canada, 40 (83%) had chronic conditions, 2 died (4%) while 16 were still hospitalized.
  - In Italy, a **30-fold increase in incidence** of severe Kawasaki disease in children-cardiac disease observed.
  - **Clinical course** described in 35 children in Southern California: most symptomatic, association of viral load and disease severity in children <5 years.
  - **50 hospitalized children in NYC,** 80% lung sx or fever; obese children aged 2+ more likely to need respiratory support; 1 child died but no severe disease in infants or immunocomprised children

- Transmission
  - In an analysis of 1,245 contacts of 636 individuals in Wuhan, and 1,296 contacts of 557 individuals in Shanghai, children were ⅓ as likely to develop COVID-19 but, when schools were open, children had 3x the N of contacts as adults. They conclude proactive school closures can reduce peak incidence by 40-60% and delay the epidemic.
○ In a study of 391 SARS-CoV-2 cases and 1,286 close contacts, 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.

● Teens
○ A survey of 770 teens reported that 68% were not social distancing but a greater understanding of the severity was associated with distancing

● 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.
○ The American Academy of Pediatrics issued an initial guidance on the care of newborns of COVID-19 mothers that varies based on access to testing and PPE.
○ The CDC reported that receipt of routine pediatric vaccinations and well child visits has declined sharply, endangering children with contracting vaccine-preventable infections such as measles.

Pregnant Women and Breastfeeding
● Clinical course and management of pregnant women
○ CDC study of 8,207 pregnant women in the US finds COVID-19 affects especially Hispanic pregnant women. Pregnant women are more likely to be hospitalized and develop severe disease but not to die.
○ A systematic review of 9 studies finds that women with COVID-19 are less symptomatic than the general population but adverse birth outcomes (eg. preterm, low birthweight) are higher.
○ Comparison of 28 pregnant and 54 reproductive age women had a similar clinical course: severity of disease, virus clearance time - None of 23 neonates infected.
○ Among 427 pregnant inpatients with COVID-19 in the UK, 56% were black or other minority race, 36% had other comorbidities, 5 died. Among 266 deliveries, 73% were term but 12 were + for SARS CoV2 (6 within 12 h of birth).
○ Summary of international guidelines for 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. However, in WA state, there was low prevalence in 188 pregnant/postpartum women (2.7%).

● Birth outcomes
○ Preterm delivery in ~50% of pregnant women (n=32) hospitalized with COVID-19.
○ In MERS, SARS increased fetal loss for first term infection and increased preterm birth for later infection.
Maternal-child transmission
- Among 6 C-section deliveries 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.
- A systematic review reported that, among 666 neonates of COVID-19 mothers, 28 were infected and usually not symptomatic, and the risk was similar regardless of type of delivery or breast/bottle fed.

Testing and Management
- In NYC, 15% of 155 asymptomatic maternity patients tested positive for SARS-CoV-2 despite having screened negative on a telephone screening tool.
- American Academy of Pediatrics has issued recommendations for the care of infants of COVID-19 positive or suspect mothers--bath after birth, protective clothing for health care workers.

Breastfeeding and Pregnancy
- CDC recommendations: CDC concurs that pregnant women have a similar disease course to nonpregnant women. Women with or suspected to have COVID-19 -- express milk and someone who is healthy feed the infant.
- WHO recommendations: Breastfeeding with precautions (hand washing, masking) but not to breastfeed if severely ill.

The Elderly
- Case fatality rates rise with increasing age, especially over 60 years. Comorbidities further increase risk of death.
- General resources
  - CDC resources for and about elderly
  - CDC guidance for retirement communities.
  - CDC guidance for testing in nursing homes.
- 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 for 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% ≥65); 3,066 (53.8%) still hospitalized (48.5% ≥65).
  - Among 388 inpatients with COVID-19 in Italy (median 66 years) odds of mortality increased by 10%/year of age.
- Comorbidities
  - In CDC study of 7,162 COVID-19 cases 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: among COVID-19 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)
- In >400 hospitalized patients in Wuhan, 20% had cardiac injury with elevated cardiac biomarkers (e.g., HS-troponin), older age (mean 74 vs 60 years), and among those with cardiac injury, 50% died.
- Among 5 patients with COVID-19 complicated by Guillain-Barre syndrome, 3 patients were 60+ years of age.
- Among 362 hospitalized patients in Milan, Italy with COVID-19 (median age 66), 7.7% had a venous or arterial thromboembolic event.

**Predictors of hospitalization**
- Among 220 hospitalized and 311 non hospitalized adults in Atlanta, Georgia risks for hospitalization (all AORs >=1.9) were age ≥65, black race, male, diabetes, obesity, uninsured, smoking.

**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.
- In a skilled nursing facility, surveillance found more than half testing positive were asymptomatic initially, contributing to transmission.
- 167 confirmed cases in Washington State nursing homes: 101 residents (mean age 83; 34 [33.7%] died), 50 health care personnel (no deaths), 16 visitors (mean age 62.5; 1 [6.2%] died).
- 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.
- COVID-19 in 1,128 surgical patients resulted in 51% pulmonary complications and, of these, 38% died; highest mortality in men aged 70+.

**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:

- **Duty to Plan**: From pandemics of the past, WHO and CDC developed ethical guidance for Pandemic Influenza, Society of Critical Care Medicine’s Ethics of Outbreaks Position Statements, AMA’s Code of Medical Ethics: Guidance in a Pandemic
- **Proposed ethical framework for healthcare institutions**
- **Fair resource allocation**: A volunteer committee of respected clinicians and leaders can assist in decision-making, 6 recommendations for allocation, Italy’s SIAARTI’s Ethics Section: Recommendations for intensive care, a guide statewide allocation of ventilators, experts have highlighted that government must discourage hoarding, AMA’s recommendations, ACS’s ethical framework recommending mortality prediction tools, AGS’s position, maximizing use of available resources, general public vaccine rationing should prioritize groups structurally and historically disadvantaged, despite overall lower life years gained.
- **Physical distancing**, civil liberties and economic hardship
- **Right to Health**: Shelter-at-home orders are further impoverishing vulnerable communities, widening health inequities, requiring a coordinated human-rights based response. A report highlights that access to high quality care for vulnerable patients globally is both ethical and necessary, including older adults, low-SES minorities, LGBTQ+ populations, the incarcerated and the homeless. Ensuring access to technology for marginalized populations during social isolation.
- Ethics of universal masking and herd immunity
- **Research considerations**: Pressures of a crisis, may lead to reliance on anecdotes over evidence-based approaches. Ethical commencement of a controlled trial requires “no treatment preference.” Recommendations that studies on COVID be considered highly sensitive and protect the wellbeing of participants. Ethical framework for SARS-CoV-2 human challenge studies. ‘Natural’ or ‘unplanned’ experiments during a pandemic have high power but require responsibility. Concerns when pausing current research includes human cost and needs to divert talent.
- **Right to Try**: outside of a clinical trial.
- Privacy infringement via mobile phone applications for contact tracing
- **Duty to Treat** despite personal & family risk, noting moral professional, legal obligations
- **Immunity passports**
- **Shared ventilation**
- **Consenting** patients during periods of limited resources
- **AMA guidance Students graduating early, Providing remote care, obligations to protect healthcare professionals**, use of public registries, and physicians in the media

Palliative Preparedness:

- **Triage Planning**: During pandemics, a triage plan should include training of underutilized palliative care. ClevelandClinic provides an enterprise-wide example
- **Modes of Communication**: Video consultations are effective, accessible, acceptable, and cost-effective, Virtual reality and 360°-camera utilization
- **Crisis Standards of Care**: A discussion paper for COVID Crisis Standards of Care, CAPC’s Specialty Palliative Care Crisis Service Design.
• **Immediate and Long-Term preparedness** for palliative care. NYC piloted a 24-7 **PAlliaTive Care Help line (PATCH-24)** and a public hospital system **TelePalliative Medicine Volunteer service**
• Need for surgeons to embrace palliative care

**Prognostication:**
• **Mechanical ventilation:** A case series analysis of 5700 patients reported that among 1151 patients requiring mechanical ventilation, 3% had recovered and had been discharged from the hospital, 25% died, and 72% were still alive in the hospital. A **smaller retrospective observational study** of 52 critically-ill patients in China showed 81% of those requiring mechanical ventilation died by day 28.
• **Nursing home residents:** In a case-series of 21 critically-ill older adult nursing home residents in Washington state with a mean age of 70, the mortality rate was 67%, 24% remaining critically ill, and only 9.5% discharged from the ICU.
• **Hospitalized:** In a NEJM observational evaluation of 169 international hospital databases, of 8910 COVID-19 patients overall in-hospital mortality was 5.8%.
• **Outcomes after CPR:** A 136 patient study in Wuhan who underwent CPR on an acute care floor rather than in the ICU, 13% had restoration of spontaneous circulation with only 2% alive at 30 days, with 1 having a favorable neurologic outcome.

**Advance Care Planning:**
• Importance of advance care planning and a framework for informed assent.
• ACC’s recommendation for ACP and management in heart disease
• GEDC recommends ED physicians understand patient's goals, nursing home capabilities
• In primary care, group visits improve ACP documentation
• In nursing homes, ensure updated and appropriate ACP and Advance Directives.
• **Communication Tools:** Toolkits include **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
• POLST: complete for COVID when appropriate, POLST in **Crisis Standards or Care**

**Symptom Management:**
• Nonpharmacologic **dyspnea** management, Pharmacologic management of **psychological distress**, management of **nursing home** symptomatology
• Delirium may be caused by pain, hunger, fear, frustration, boredom, hallucinations, overstimulation, environment/routine changes, unfamiliarity with PPE
  ○ Alzheimer's Association recommends a HIPPA-compliant **personal information form and strategies to respond** to the behaviors
  ○ Change to usual guidelines proposed
  ○ Recommendations for **communication with mask**
Section 4: Preventing Spread in Healthcare Settings

Infection Prevention and Personal Protective Equipment

- **Review paper in Annals** on exposure and healthcare workers, Use of PPE and infection control training are associated with decreased infection risk and certain exposures such as intubation are associated with increased risk.
- **Meta-Analysis of Preventive Measures**: A meta-analysis of observational studies found the following odds ratios for various preventive measures: OR 0.18 for physical distancing of at least 1 meter; OR 0.15 for face mask use; and OR 0.22 for eye protection.
- More discussion on aerosolization in a **AMA paper** a pre-print and related op-ed
- **Paper emphasizing importance of fit for N95 protection**, dome shaped N95s better than duck-bill shaped, with extended use fit should be re-evaluated
- **Updated infection prevention advice for facilities (as of May 18th) from CDC specific for COVID**
- **Updated advice from CDC as of 21st May on transmission of COVID**
- **A small simulation study of intubation in ED** found particles on necks of team members suggesting body suits may be necessary, supported by a research letter in JAMA
- **New short paper in Nature** on aerosolization of COVID, cleaning of staff rooms and decontamination of PPE before donning suggested, plus more evidence for mask wearing
- **Paper published in CDC journal** 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** suggests face masks may be useful in preventing spread from asymptomatic individuals and **BMJ analysis favoring masks for general public**
- Further short report on infection in health care workers supporting masks for all
- General **infection precaution advice** 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.
- **Cochrane review of PPE** emphasizes training
- **Before/After Work**: coming home from work guide on how to stay safe American College of Emergency Physicians
- **CDC infographic** on donning and doffing PPEs.
- HCW need to be prioritized for testing and care else healthcare systems risk **absenteeism**
- **Equipment Supplies**: CDC suggested strategies 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 to decontaminate N95 masks and allow for their reuse, which they are currently evaluating; others are developing decontamination protocols as well. A website is collating data about different decontamination practises for N95 masks. **Microwaving N95s using household props**
glass container, elastic band, mesh produce bag and appears to be effective in
decontamination.

- **Extended N95 Associated with Reduced Efficacy**: Per new JAMA research letter.

**Hospital Precautions**

- **Studies of contamination in a Wuhan COVID hospital** found no virus in the air in high
  risk areas, but significant contamination in medical areas of high touch surfaces, beepers
  (50.00%), water machine buttons (50%), elevator buttons (40%), telephones and
  computer mouse (40%), Keyboards (33%) stressing the need for good environmental
  standards and frequent handwashing
- **With appropriate adherence to evidence-based infection control practices**, in-hospital
  COVID-19 transmission among patients and healthcare workers appears to be **low**.
- Nevertheless, a **study** describes transmission of COVID-19 from a patient with an
  unrecognized infection to 3 healthcare workers, and **another** reports on the characteristics
  of infected healthcare workers.
- Nevertheless, there are reports out of Italy, **Spain** 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

- Guidelines from major UK societies on managing intubation including systems to prevent infection for health-care workers
- 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**
- One proposal argues for rotating staff schedule of a 4 days on, 10 days quarantine off to help minimize spread of the virus in the absence of extended testing
- 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 corp 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

Keck School of Medicine of USC
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.
An evidence review provides reassurance that many clinical situations can effectively be managed via telehealth, both during COVID-19 and subsequently.

Medicare Promotes Home-Based Care for Medicare Recipients: A new Medicare emergency policy waiver will allow hospital outpatient departments to relocate services to off-campus sites, including beneficiaries’ homes. These services will be reimbursed at the higher outpatient prospective payment system rates rather than the typical physician fee schedule rates -- an increase of approximately 40% for similar outpatient services.

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.
Reduced ED Utilization During the Pandemic: A CDC report has found that “in the 10 weeks following declaration of the COVID-19 national emergency, ED visits declined 23% for heart attack, 20% for stroke, and 10% for hyperglycemic crisis.”

Surgery and Procedures

A study from the Netherlands reported a decrease in cancer diagnosis since the COVID-19 guidelines were instituted, especially for skin cancer, with the implication that COVID-19 may be leading to delays in cancer diagnoses.

Reduction in Myocardial Infarction: Since the pandemic began, there has been a reduction in the incidence of myocardial infarction. The explanation for this is uncertain.

Cardiac Death Rates Stable: A new report found that despite the reduction in hospital admissions for MI during the pandemic, overall cardiac death rates have not changed.

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.

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.

**Kaiser Permanente’s Plans to Combat COVID**: In a [NEJM Catalyst piece](https://www.nejm.org/doi/full/10.1056/NEJMc2011140), Kaiser leaders describe key measures that they and other health systems can take to support public health efforts to suppress infection rates. These include: 1) Increasing testing capacity; 2) contact tracing; 3) community healthcare (rather than just providing care for assigned patients); 4) promoting innovations in home-based care; 5) developing surge capacity; 6) safely reopening healthcare facilities based on public health priorities; 7) supporting research efforts; and 8) educating the public through communication.

**Supplemental Resources**

- HHS [COVID healthcare emergency preparedness information gateway](https://www.hhs.gov/coronavirus/) (Tracie)
- WHO: [Pandemic influenza risk management](https://www.who.int/influenza/pandemics/)
- BMJ: [COVID-19 Remote Assessment in Primary Care](https://www.bmj.com/)
- JHU Center for Security: [Top Priorities for Pandemic Preparation](https://www.centerforsecurity.jhu.edu/)
- CDC: [Hospital Preparedness Checklist for COVID-19](https://www.cdc.gov/)
- FEMA: [Incident Command System](https://www.fema.gov/)
- ASPR: [Hospital Pandemic and Emergency Planning Checklist](https://aspr.hhs.gov/)

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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 also suggests direct transmission from horseshoe bats to humans. Moreover, other bat coronaviruses have the predicted necessary characteristics to suggest additional future transmissions from bats to humans are likely. Possibility that SARS-CoV-2 was a lab accidental release is considered extremely unlikely but has not been ruled out.

- **RNA replication and mutation rates:** SARS-CoV-2 is a large RNA virus of 30,000 nucleotides. As is common with RNA viruses, it is mutating over time and can undergo recombination.

- 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 the nucleoside analog remdesivir, or the target of other candidate drugs such as EID-2801 that 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. TMPRSS2 expression is increased by androgens, which could explain why men are more susceptible and why androgen-deprivation therapy in prostate cancer is associated with reduced susceptibility and severity of COVID-19.

- Entry also requires low pH (endosome) which hydroxychloroquine blocks, so proposed as drug.

- Spike protein acquires a mutation D614G over time in multiple populations, leading to speculation that this change makes the virus more transmissible, for example, by creating a better functioning Spike protein, or by conferring an immunological advantage. Lab studies show that the G614 variant is more infectious in vitro.

- **Main viral protease:** The main protease (Mpro or 3CLpro) cleaves the viral polyprotein, deubiquitinates viral and cellular proteins, and antagonizes the interferon (IFN) response (data from SARS). Structure of Mpro is being used to suggest drugs that could inhibit it.

- A trial is underway to test if heartburn drug famotidine could inhibit Mpro following observations from Chinese COVID patients taking the drug, and computational modeling. In observational studies for hospitalized patients not initially in an ICU, famotidine was associated with a 2-fold reduction in clinical deterioration leading to intubation or death.

- **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.
A study identified human cell partners of 26 of the 29 unique coronavirus proteins, and lists 69 potential drugs that could target those interactions. Proteomics studies of SARS-CoV-2 infected cells showed that viral infection alters phosphorylation of host proteins, resulting in production of cytokines, cell cycle arrest and induction of cell protrusions containing viral particles. Eighty-seven FDA-approved drugs were identified that could block these events including Silmitasertib, which is being evaluated as an anti-COVID therapy.

Vaccine Development

- **Types of vaccines:** Both traditional and newer technologies are being used to make vaccines. mRNA and DNA 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. The WHO maintains a list of vaccines in clinical trials and under development. The NY Times has a useful coronavirus vaccine tracker.

- **Vaccine development challenges:**
  - Efficacy - will it induce the right type of immunity, with an effective combination of either neutralizing antibodies or T cell responses?
  - Safety - concern it could make coronavirus infections worse through antibody-dependent enhancement (ADE) of entry into cells.
  - Time and scalability - ease of manufacture varies for different vaccine technologies.
  - How to select the candidate vaccines to test.

- **Vaccines update:** According to the WHO, there are now 17 vaccines in human clinical trials, including trials in the US (Moderna, Pfizer, Inovio and Novavax), China and Europe (Oxford University), with >114 candidates in pre-clinical trial stages.

- The Coalition for Epidemic Preparedness Innovations (CEPI) is funding several trials.

- The Gates Foundation planning how to scale production capacity.

- The US government’s Operation Warp Speed plan has selected 5 vaccine candidates to champion.

- **RNA vaccines:** Moderna’s first-in-human trial (mRNA-1273), started 3/16/20 in Seattle. Injected mRNA makes the spike protein inside the body. An initial report suggests that the first few participants analyzed developed neutralizing antibodies against Spike. Moderna plans to initiate phase 2 trials and phase 3 trials as soon as the summer.

- Pfizer and BioNTech started a Phase 1/2 clinical trial in Germany of a mRNA vaccine (BNT162) and will start in the U.S. soon. If successful, expect to supply millions of vaccine doses by the end of 2020, and hundreds of millions in 2021.

- **Killed virus:** injection with killed virus vaccine (PiCoVac) protected macaques from challenge. Human trials began April 16.

- **Adenovirus vector** vaccine expressing Spike and developed at the University of Oxford, which showed efficacy in macaques, began a Phase 1 trial (1,100 people) in April and will start a combined Phase II/III trial (5,000 people) in May. A Lancet study reports that this vaccine is immunogenic and tolerable at 28 days.
- J&J will partner with US DHHS to start trials by September, deliver first emergency-use vaccine early 2021, and supply one billion doses worldwide for emergency pandemic use.

- **DNA vaccines** expressing Spike given to 25 macaques induced both antibody and cellular responses and cellular responses, including neutralizing antibody titers comparable to those found in COVID patients. Eight vaccinated animals had no detectable virus following challenge, and the others had only low levels of virus.

- **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 with monoclonal antibodies**: Screens are being carried out to identify neutralizing antibodies in patients that could then be synthesized and used as a therapy. Tobacco plants are being evaluated to make this type of vaccine, using a rapid and large-scale technology that was previously effective for a monoclonal antibody-based Ebola vaccine. Eli Lilly has started a trial of antibody LY-CoV555.
Section 7: Public Health Considerations

Simulation Modeling

- **More than a dozen simulation models** forecast the number of short-term and long-term COVID cases and fatalities, relying on various techniques including traditional epidemiological SEIR models, machine learning, and statistical curve fitting. In general, the models predict about 5,500 to 6,500 deaths per day in late June and July, relatively steady after a decline from 9,000 to 13,000 deaths per week mid May. The models project that by Mid August, the US will have recorded between 150,000 to 160,000 total deaths.

- Without interventions, deaths would have been much higher
  - An early and highly influential model from Imperial College London suggested that 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.
  - Another model suggests that by May 17 with current policies in place there have been 87,000 deaths, but without stay-at-home policies, we would have had over 1.3 million deaths.

- 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%.

Health Care Capacity

- 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.
- **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.”

**Policy Approach - Physical Distancing**
- **Monitoring R:** Experts are increasingly suggesting the need for regular tracking and public reporting of $R_t$ -- the number of secondary infections per primary infection -- in different communities as a metric to assess how well social distancing is working.
- **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.
- **Stay-at-Home policies may not be responsible for distancing.** An analysis of differences in state policies shows that distancing occurred even without strong policies, and increased when states made emergency declarations, but not as a result of stay-at-home policies.
- **Paid Sick Leave:** An analysis of the temporary federal paid sick leave mandate showed that the policy led to a large and significant increase in staying at home (about 7.5% increase) as determined by cell phone data.
- **Evidence to Support Distancing Restrictions:** A new JAMA analysis suggests clear benefits of distancing policies on reducing spread of SARS-CoV2.
- **The Benefits of Early and Aggressive Physical Distancing:** A Columbia University model suggests that if distancing regulations had been implemented 1-2 weeks earlier, the U.S. COVID-19 death toll may have been substantially lower.
- **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.”
- **U.S. domestic travel more important than international travel in disease spread:** A genetic analysis (not yet peer reviewed) showed that U.S. domestic travel was responsible for more spread than international travel.
- **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.

● **Projections on duration of social distancing:** Absent a vaccine, a new projection suggests that physical distancing may be required until 2022 or beyond.

### Policy Approaches to Easing Physical Distancing Restrictions/Reopening the Economy

● **Report on “Return to Work” Policies:** A NEJM report recommends a number of policies to ensure safety of the workplace, including masks, hygiene practices, symptom checklists and physical distancing protocols.

● **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, staggering of schedules, “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.

● **Spring Break Outbreak:** A CDC report describes outbreak control during a college trip involving contact tracing of travelers, household and community contacts.

● **Serial Testing at a Skilled Nursing Facility:** A case report describes the successful use of serial COVID-19 testing to help control an outbreak at an LA SNF.

● **Mass Testing on College Campuses:** Initial results from campus-wide testing at UCSD identified zero positives among 1,300 students. Enrollment in the study was lower than expected “partly because it involved the discomfort of nasal swabbing … [and because] many students skipped the test because they feared exposing themselves to the virus, or that they might lose their housing if they tested positive.”
- **Municipal Sewage as a Leading Indicator of Infection Rates**: A new analysis has found that “SARS-CoV-2 RNA concentrations [in sewage] were a seven-day leading indicator ahead of compiled COVID-19 testing data and led local hospital admissions data by three days.” Sewage sampling could be a strategy for guiding “decisions to implement or relax public health measures and restrictions.”

- **A JAMA viewpoint** provides a concise update on the public health issues surrounding COVID-19. The article concludes: “For the foreseeable future, fundamental public health measures such as physical distancing, wearing a mask in public, frequent handwashing, and staying at home when symptoms occur, will remain the best tools to prevent COVID-19.”

- **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.

- **Digital Contact Tracing**: A new analysis (not yet peer reviewed) suggests that digital apps may be effective in suppressing COVID-19 via contacting tracing, and that “willingness to install [these apps among the public] is high.” However, according to a (pre-peer review) analysis, the “proportion of transmissions per index case that can be prevented… ranges from above 80% in the best-case scenario (testing and tracing delays of 0 days) to 40% and 17% with testing delays of 3 and 5 days, respectively.” A British study found that to be effective digital tracing tools must be very clear in their message and indicate the public good of participation.

- **Viral Genome Sequencing to Track Spread**: Full viral genome sequencing may help assess transmission dynamics, an approach the CDC plans to promote. An Israeli analysis suggests that “the basic reproduction number of the virus was initially around ~2.0-2.6, dropping by two-thirds following the implementation of social distancing measures [and that] between 1-10% of infected individuals [resulted] in 80% of secondary infections.”

- **Air Disinfection**: Germicidal UV fixtures have been suggested as a tool for air decontamination in high risk spaces, such as waiting rooms, emergency departments, ICUs, endoscopy and bronchoscopy suites.

- **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.

- **The Public’s Willingness to Take a New Vaccine**: A Pew survey showed that 72% of Americans would get a SARS-Co-V-2 vaccine. The number was lower for African Americans, Evangelicals and Republicans.

- **Public Attitudes Toward Stay-at-Home Orders**: According to a new CDC survey, “among adults in New York City and Los Angeles and broadly across the United States [there is] widespread support of stay-at-home orders and nonessential business closures and high degree of adherence to COVID-19 mitigation guidelines.”
• **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.
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