

Keck School of
Medicine of USC

May 20, 2020

Keck School of Medicine of USC
COVID-19 Evidence-Based Summary

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Section 1: What's new this week?

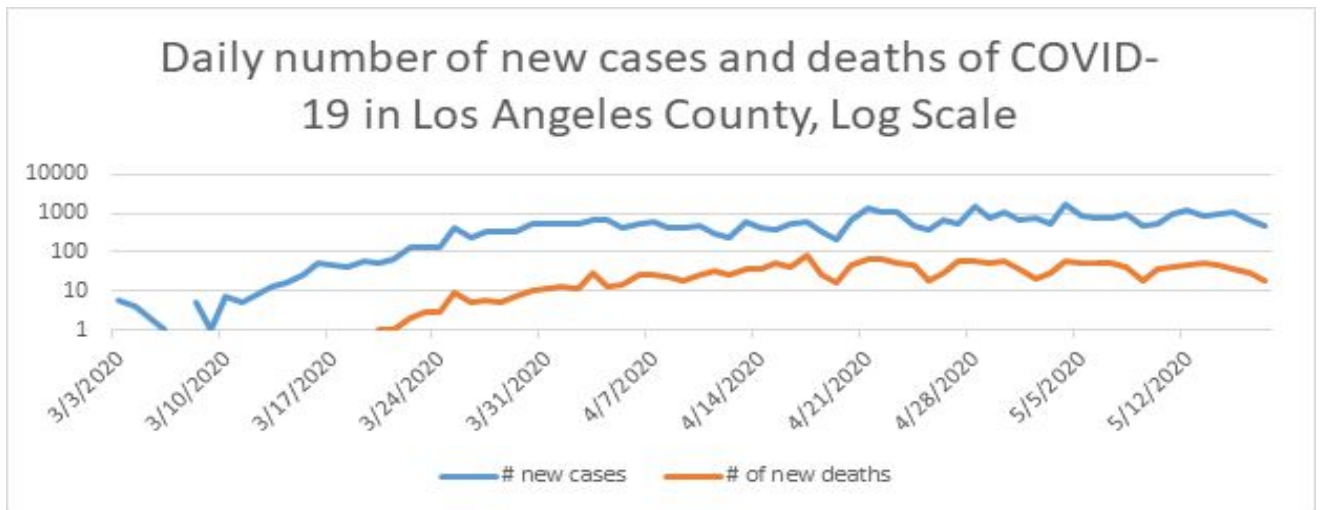
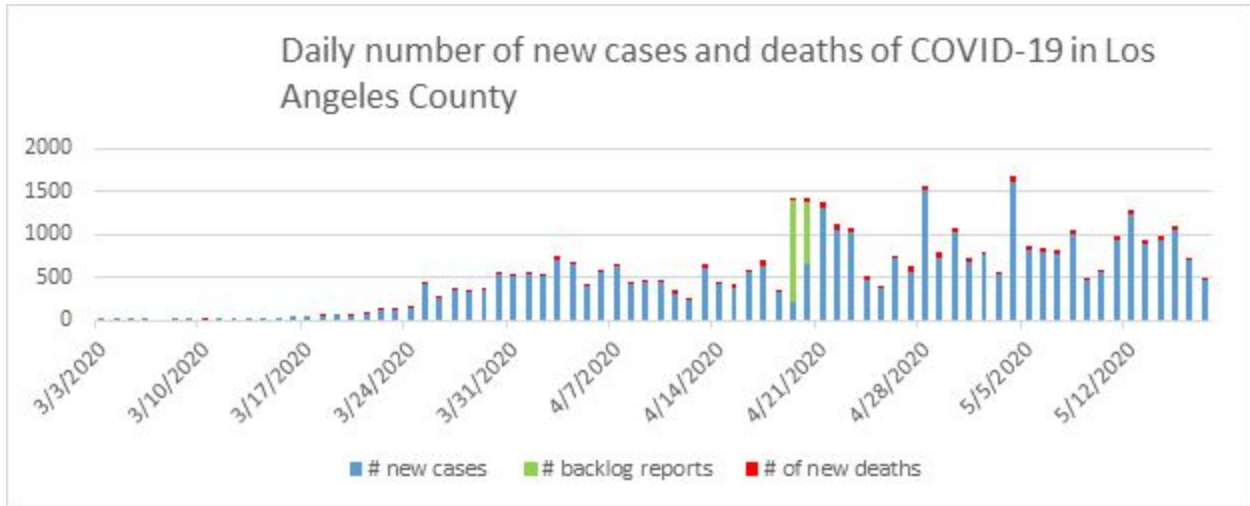
- **Moderna Vaccine:** An initial non-peer reviewed [report](#) suggests that at least some study participants in a phase 1 trial develop neutralizing antibodies against SARS-CoV-2. Moderna now plans to initiate phase 2 trials and phase 3 trials as soon as the summer.
- **COVID-19 Systematic Review:** A newly published [systematic review](#) concluded:
 - SARS-CoV-2 is mainly transmitted via inhalation of respiratory droplets containing the virus and had an incubation period of four to six days;
 - Commonly reported symptoms were fever (80%) and cough (60%), however using these symptoms in isolation will miss a proportion of cases;
 - While several treatments are in development or in clinical trials for COVID-19, supportive home care for mild/moderate cases and supportive hospital care for severe and critical cases remain the recommended management.
- **Update on the South Korean Patients Reported to Have been Reinfected:** 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.
- **Seroprevalence in LA County:** The results of the LA County seroprevalence analysis have now been [published](#), and indicate that the “prevalence of antibodies to SARS-CoV-2 was 4.65%. The estimate implies that approximately 367 000 adults had SARS-CoV-2 antibodies, which is substantially greater than the 8430 cumulative number of confirmed infections in the county on April 10.”
- **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.
- **SARS-CoV-2 found in stool of Patients with severe COVID-19:** 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.
- **Vitamin D:** 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.
- **Evidence to Support Distancing Restrictions:** A new [JAMA analysis](#) suggests clear benefits of distancing policies on reducing SARS-CoV2 spread.
- **Multisystem Inflammatory Syndrome in Children:** The CDC has issued a [health advisory](#) about a possible inflammatory syndrome similar to Kawasaki's disease that may be triggered by SARS CoV-2. Little is known about this potential association, however.
- **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.
- **Telehealth:** An [evidence review](#) provides reassurance that many clinical situations can effectively be managed via telehealth, both during COVID-19 and subsequently.

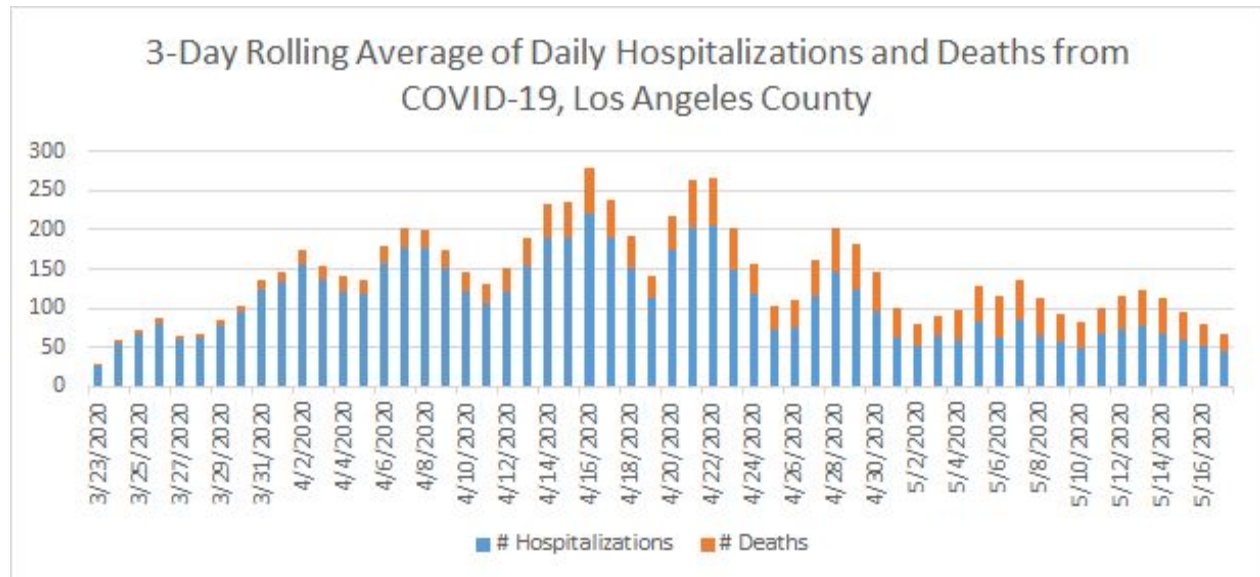
Section 2: Epidemiology, Incubation and Transmission

Infection Burden

- L.A. County: [Current LA County Numbers](#), [interactive city and community level map](#) and [projections to when to ease social distancing](#). There is a new LA County [DPH interactive portal](#).
 - As of May 18: LA County has 38,451 COVID-19 positive tests and 1,839 deaths, with 6,263 (18%) ever hospitalized (decreasing from 20% last week) and 16% of ever hospitalized cases ever intubated.
 - The cumulative incidence rate in Los Angeles County is 380.5/100,000 compared to 143/100,000 in the Bay area and 2,301/100,000 in New York City. The cumulative 2-week case fatality rate in Los Angeles County is 4.76% compared to 3.53% in the Bay Area and 9.92% in New York City.
 - **Skilled Nursing Facilities (excluding other Institutional Settings):** There is at least one COVID-19 case at 243 skilled nursing facilities in Los Angeles County. Cases among staff and residents account for 17% of total Los Angeles County cases and 43% of all deaths.
 - **Age:** Characteristics of cases with known age: 4% ages 0-17 yrs, 35% ages 18-40 yrs, 40% in ages 41-65 yrs, 21% in ages >65 yrs. 50% of cases but 56% of the deaths are in males. All 1,698 deaths had known age: 0%< in ages 0-17 yrs, 3% in ages 18-40 yrs, 19% in ages 41-65 yrs, 78% in ages >65 yr.
 - **Race/Ethnicity:** Characteristics of the 25,390 cases with known race/ethnicity: 11% Asian, 7% Black, 54% Hispanic/Latino, 21% Non-Latino White, 1% American Indian, Alaskan Native, Native Hawaiian, Other Pacific Islander, and 6% Other.
 - Of the 1,824 deaths with known race, 1% were Native American/Pacific Islander, 1% were Other, 13% were Black, 17% were Asian, 38% were Latino, and 30% were non-Latino white.
 - **Underlying comorbidities were present in 93% 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.
 - [New data from the New York City Health Department](#) indicates that the most important comorbidities predicting disease severity, in order, are hypertension, diabetes, high cholesterol, coronary artery disease, dementia, and atrial fibrillation. [A recent paper](#) noted that asthma and COPD are underrepresented among conditions predicting risk and severe disease.
 - **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.
 - **Two ecological studies show BCG may decrease deaths:** Two studies ([Berg et al.](#) and [Miller et al.](#)) that compared rates of cases and deaths due to COVID-19 in countries according to BCG vaccine status showed an association between current BCG vaccination policy in effect and a decrease in both cases and deaths.

- **Contact patterns shaped the COVID-19 outbreak in China:** Analyzed contact surveys data for Wuhan and Shanghai before and during the outbreak and contact tracing information from Hunan Province. Daily contacts reduced 7-8 fold with most interactions restricted to the house. Children 0-14 years were less susceptible and adults > 65 were more susceptible to SAR-CoV-2 infection than adults 15-64 years. Social distancing alone was sufficient to control COVID-19. Proactive school closure alone didn't interrupt transmission, however peak incidence was reduced by 40-60% and delayed the epidemic.
 - **[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.
 - **Domestic travel was more important for US spread than international travel:** A phylogenetic study traced outbreaks to domestic travel introductions and found that international travel did little to increase spread.
 - **[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. Services were held twice indoors for 1-1.5 hours. Highest attack rates were in persons aged 19–64 years (59%) and ≥ 65 years (50%). 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. Among the 35 persons with laboratory-confirmed COVID-19, seven (20%) were hospitalized; three (9%) patients died. An additional 26 cases linked to the church occurred in the community, including one death.
 - **Introduction of [COVID-19 in French Alps:](#)** Index case tourist stayed in Swiss chalet with 15 tourists and resident French family of 5. 7/16 tourists and the entire family was infected. A child with simultaneous COVID-19, picornavirus and flu attended school but did not transmit infection to others. One asymptomatic case had a viral load similar to a symptomatic patient, suggesting asymptomatic transmission. Moreover, 64% of the tested contacts had either flu or the picornavirus, suggesting that these are more infectious than COVID-19.
 - **Comparison of COVID-19 cases in [cross border counties with different mitigation:](#)** Compared daily changes in 8 Iowa border counties with no stay-at-home orders to 7 Illinois border counties with orders in place. Trends in cumulative cases were similar in the two states before stay-at-home orders were imposed in Illinois. After orders were imposed, the Iowa counties had an excess of up to 217 cases after one month, representing a 30.4% excess. Although caveates of ecological studies apply, the results suggest that stay-at-home orders decreased the case burden in Illinois.
- California as of 05/17/20: 80,430 cases and 3,302 deaths: [CDPH](#)
 - U.S. as of 05/18/20: 1,480,349 cases & 89,407 deaths: [CDC](#)
 - Worldwide: As of 05/19/20: 4,629,503 cases & 297,380 deaths: [JHU Map](#)





Seroprevalence

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

Disparities, Homelessness and Jails

- A health disparity is emerging**, with Blacks [experiencing](#) a higher burden of severe disease compared to other racial/ethnic groups. In Los Angeles County, the unadjusted case-fatality rates were similar in Blacks and Asians (12.2%). Lower socioeconomic status communities in Los Angeles County are now experiencing the highest increases in cases and deaths. In addition, males comprised 49.6% of cases in Los Angeles County but 59.6% of deaths. 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, with the highest proportion (16.5%).
- Homeless Populations:** A new [CDC](#) analysis reports on clusters of infections in homeless shelters, finding rates of positive residents and staff, respectively, of 17% and

17% in Seattle, 36% and 30% in Boston and 66% and 16% in San Francisco. More details about the Seattle cluster are reported [here](#).

- **Jails:** A [perspective piece](#) covers the unique challenges of COVID-19 within jails.

Incubation

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

Transmission

- **Person-to-person transmission** occurs mainly via **respiratory droplets**, similar to influenza, and thus droplet precautions are [recommended](#).
- **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.
- **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.”

- **Asymptomatic/Pre-Symptomatic Spread and the Challenges of Contact Tracing:** Evidence for substantial [asymptomatic/presymptomatic spread](#) continues to grow, [highlighting the challenges](#) of contact tracing for COVID-19.
- **Close contact is probably necessary for transmission**, according to a [study](#) of a call center in South Korea, where 97 people out of 1,143 tested positive and 94 of these were working in a small area on the same floor. The secondary attack rate (to their families) was 16.2%. Four out of 97 positives remained asymptomatic and none of their family members were infected.
- **COVID-19 Infectiousness May Peak at Time of Symptom Onset:** A [study](#) of viral shedding found “the highest viral load in throat swabs at the time of symptom onset” suggesting that “infectiousness peaks on or before symptom onset.” The study also suggested that 44% of 77 secondary viral transmissions occurred during the presymptomatic period.
- **Seasonal Variation:** A [National Academy of Sciences](#) report finds that data are insufficient to indicate whether COVID-19 will dampen in hot/humid summer months. A [case study](#) suggests that COVID-19 is transmitted even in hot and humid conditions.
- **Evidence for community spread in the U.S. in February:** A [Northeastern University model](#) indicates there may have been [tens of thousands of cases](#) of COVID-19 in the U.S. by February 2020, long before community spread had been recognized; these findings have not yet been published in a peer-reviewed journal.
- **Facemask use by the general public:** After considerable debate, the [CDC has begun recommending](#) voluntary use of cloth face coverings by the public, particularly in areas where there is substantial community spread. There is mechanistic evidence to support this recommendation, as well as some [experimental evidence from the SARS epidemic](#).
- **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.
- **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 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.”
- **CDC Guidance on Discontinuation of Transmission Precautions:** The latest [CDC guidance](#) 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. There is also growing concern that [fecal-oral transmission](#) may occur, though this remains uncertain. LFT abnormalities were present in a third of hospitalized patients in one [analysis](#).
- **Anosmia:** A study from [Italy reports at least one taste or olfactory disorder in 33% of patients](#) with SARS-CoV-2infection. [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 List 6 New COVID-19 Symptoms:** The CDC has added [six new symptoms](#) to its list to watch for: chills, repeated shaking with chills, muscle pain, headache, sore throat and new loss of taste or smell.
- **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:** 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.
- **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.

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.
- **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:
 - Prioritize patients with serious, unexplained respiratory illness as well as those who are symptomatic with contacts of known cases.
 - Because of the incubation period, experts also highlight that “a negative result does not rule out infection, particularly for people with a known exposure [and a] positive result in an otherwise well or mildly ill patient does not require urgent medical attention but does require isolation ...”
- **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 (eg, minibronchial alveolar lavage) are more sensitive than a nasopharyngeal swab ... it is important to emphasize that, depending on the clinical presentation, a negative RT-PCR result does not exclude COVID-19.”

- **False negative test results** may lead to a [false sense of security](#), leading to risk of further viral spread.
- **Batch Testing:** [Testing groups of individuals together](#) is an emerging strategy for maximizing current testing capacity.

Treatment and Management

Treatment Guidelines

- For the vast majority of COVID-19 cases, treatment includes **supportive care**.
- **Hydroxychloroquine/Chloroquine:** Early in the pandemic, Hydroxychloroquine was suggested as a potential antiviral medication based on the [medications’ cellular interaction](#) with the virus and [in vitro data](#).
 - **FDA Approval and Controversy:** Initial [anecdotal evidence](#) suggested the medication helps with pneumonia in regards to shortening of disease course and improvement of lung imaging. This led to the [CDC suggesting](#) the use of Hydroxychloroquine and the FDA enacting its emergency use without rigorous clinical trials. This has led to much [controversy](#) given potential for [cardiac complications](#), prompting [medical experts to advocate for caution](#). The FDA issued a [safety communication](#) cautioning “against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.
 - **Supportive Evidence for Hydroxychloroquine:** Small randomized trials--with inherent weaknesses--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](#).
 - **Combining with Azithromycin:** A [small non-randomized study](#) -- which subsequent to publication [received an expression of concern](#) from the sponsoring

society -- has suggested a benefit of combining hydroxychloroquine with [azithromycin](#) for treating COVID-19. Caution has been expressed in light of [adverse cardiac events](#).

- **HIV protease inhibitors:** Lopinavir-Ritonavir (Keletra) is being investigated, but [studies to date](#) have [failed to show](#) improvement over standard of care.
- **Other antiviral drugs:** Randomized [study](#) of two influenza drugs, Favipiravir versus Arbidol, in moderate severity patients showed better outcomes with Favipiravir.
- **Combination Therapy:** [Preliminary results](#) of a randomized trial found that treatment with combination antiviral therapy consisting of lopinavir, ritonavir, ribavirin and interferon beta-1b vs. lopinavir/ritonavir alone 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.
- **Famotidine:** An epidemiologic [study](#) among hospitalized patients, not yet peer reviewed, found that famotidine was associated with a hazard ratio of death of 0.29. However, a randomized trial will be needed to rigorously evaluate famotidine as a treatment option.
- **Remdesivir:** Preliminary results from an [NIH randomized control study](#) of 1063 patients showed a median time to recovery of 11 days with remdesivir vs. 15 days with placebo (P<0.001). Gilead also announced results from their own Phase 3 trial [evaluating 5-day vs 10-day dosing duration](#), which suggested that 5 days of treatment may be as effective as 10 days. Based on these findings, the [FDA issued emergency use authorization](#) for the drug to be used for severe, hospitalized patients. Gilead [donated supplies](#) to treat approximately 100,000-200,000 patients to the federal government. The [U.S. government will prioritize](#) regions and hospitals to receive the donated medication. Despite the encouraging news, these two promising studies are preliminary and have not yet been peer-reviewed. Many are [calling for the release](#) of the full data-set. Additionally, not all the news for remdesivir has been favorable. Another placebo controlled [trial](#) in the Lancet failed to demonstrate benefit.
- **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](#).
 - Two [major studies](#) are now [underway](#).
 - In a [small retrospective study](#), Tocilizumab was given to patients with severe or critical COVID-19. These 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 but more rigorous studies are needed. Another [retrospective analysis](#) also suggested benefit.
 - Promising data for the use of Tocilizumab was recently reported from preliminary results of a randomized control trial. [French investigators](#) enrolled 129 hospitalized COVID-19 patients with moderate or severe pneumonia and showed Tocilizumab led to significantly reduced number of deaths or life support interventions when compared to a control group. More research needed to validate these findings and explore the medication’s potential side effects.
 - Sarilumab (Kevzara) also targets IL-6 and is currently involved in a [large clinical trial](#). Preliminary results, however, [are not promising](#).

- **Convalescent serum:** In response to [new](#) encouraging but small and uncontrolled [studies](#), the FDA has approved [convalescent serum](#) for COVID-19 treatment under an emergency Investigational New Drug (IND) application. [Not all studies](#) of convalescent plasma have been favorable, however.
- **Synthetic Monoclonal Antibodies:** A [number of biotech companies](#) are developing synthetic monoclonal antibodies as another treatment option.
- **Blood purification device:** Despite limited data, the [FDA issued an emergency use authorization](#) for a blood purification device that filters inflammatory mediators.

Expert Recommendations on Treatment

- **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.

- **Management recommendations for MI amidst COVID:** [Recommendations](#) highlight special considerations to ensure infection control for patients and staff.
- **Venous Thromboembolism Prevention:** Literature continues to emerge highlighting the VTE risk in COVID-19 patients. In one Chinese study, the [incidence of VTE was high in ICU patients](#) and potentially related to poor prognosis. In a retrospective French study, a high incidence of VTE in ICU led to suggestions of [systematic screening of VTE](#) and therapeutic anticoagulation in severe cases. Studies like these have led many to advocate for [close attention to VTE risk](#) in COVID-19 patients. 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.
- **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.
 - There are now [clinical trials](#) further investigating [ACEIs/ARBs](#) and their role in COVID-19.
- **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 depletion may reduce complication rates.

Intensive Care Unit (ICU)

- The ICU lies on a continuum of care (community, outpatient, inpatient ward/telemetry/ICU, discharge or death). Prevention and treatment in one part of the continuum have effects throughout the continuum [with implications for resource availability](#).
- Useful overviews in: [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, agitation/confusion and corticospinal tract signs.
- [Clinical markers](#) include: elevated C-reactive protein and ferritin
- [Current management](#) largely involves supportive care:

- [Invasive Ventilation/Personal Protective Equipment](#)
- ARDSnet lung protective ventilation [protocol](#)
- Conservative fluid resuscitation, Early vasoactive support.
- Prone Positioning
 - A recent [small study](#) has shown the potential benefit of prone positioning for ventilated COVID-19 patients with ARDS.
 - [Prone positioning in non-ventilated patients](#) with moderate ARDS (non COVID in a recent paper) supported by high flow O2 or NIV reduced need for intubation
 - [Increasing use of prone positioning in the non-ventilated patient - management guidelines](#) including useful flow chart
- [Considerations](#) for extracorporeal membrane oxygenation (ECMO)
- [Resources from European ICU](#) including papers and blogs from Italian ICUs
- Published resources:
 - [JAMA paper \(4/6/2020\) from Italy](#): baseline characteristics and outcomes
 - [JAMA paper \(3/19/2020\) from 21 ICU patients in Washington State](#)
 - [NEJM case series \(3/30/2020\)](#) from Seattle of ICU patients
- Guidelines include:
 - [“Surviving Sepsis campaign” guidelines](#) for management of the adult ICU patient with COVID (3/27/2020)
 - [JAMA Clinical Guidelines Synopsis \(3/26/2020\)](#)
- Interviews with:
 - Maurizio Cecconi (EICSM) from Italian centers: practice PPE before you need to do it in real life and ICU management - [JAMA interview](#) (3/16/2020)
 - Derek Angus - Update on Critical Care management: [JAMA interview](#) (4/1/2020)

Prognosis and Outcomes

- **Prognostic indicators:** [Models are being developed](#) to assist in predicting disease severity and mortality.
 - **Elderly Age and Comorbidities:** A [review article](#) of 53,000 patients found that the strongest predictors of disease severity were age ≥ 50 , smoking, and co-morbidities, particularly CKD, COPD, and cerebrovascular disease. Age >60 , CVA, HTN, and DM were found to be independent prognostic factors for death. Another review article, [found elderly male patients](#) were more likely to develop into critically ill patients. In a single-center, cross-sectional analysis, [elderly age \(age \$>65\$ \) and heart failure](#) were strong risk factors for hospitalization.
 - **Obesity a risk factor for severe disease:** Studies from [NYU](#) and [France](#) show higher rates of ICU admittance of obese patients. CDC now lists [severe obesity as a risk factor](#).
 - **Lab Data:** [Elevated D-dimer](#) on admission has been found to be both a predictor of severity and [mortality](#). [Elevated CRP](#) has been found to be associated with severe COVID-19. [Lymphopenia](#) may also indicate disease severity.
- **Morbidity Data for U.S. Patients:** [CDC data](#) continue to suggest that older patients with comorbidities are more likely to develop COVID-19 complications, though younger, healthy patients can experience serious illness: “The percentage of COVID-19 patients

with at least one underlying health condition or risk factor was higher among those requiring intensive care unit (ICU) admission (78%) and those requiring hospitalization without ICU admission (71%) than that among those who were not hospitalized (27%).” A CDC [report](#) also found that case-fatality percentages increased with increasing age with the highest percentages (6%–27%) among adults aged ≥ 85 years.

- Illness severity varies considerably. In China, [mortality rates](#) have been reported ranging from 0.7% (other areas in China) vs 5.8% (Wuhan).
- **COVID in the Kaiser Population:** In a [cohort analysis](#) of more than 9.5 million Kaiser members, the cumulative incidence of a COVID-related hospitalization ranged from 10.6-12.4 per 100,000 (depending on the region); among hospitalized patients, 41.9% required ICU care the mortality rate was 17.8%; the effective reproductive number dropped substantially from March 1-20 in conjunction with social distancing.
- [Distribution of China’s Cases](#) (n=72,134):
 - Mild (no or mild pneumonia): 81%
 - Severe disease (dyspnea, hypoxia, or >50 % lung involvement on imaging): 14%
 - Critical disease (respiratory failure, shock, or multiorgan dysfunction): 5%.
- [Hospitalized Patients:](#)
 - 10-20% admitted to ICU
 - 3-10% require intubation
- [Case Fatality Rate](#)
 - Overall 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.
- There does seem to be [immunity in other primates](#).

Pediatric Populations

- Prevalence and Clinical Course
 - [CDC data from Feb 12–April 2, 2020](#) reported 2,572 (1.7%) of 149,760 lab confirmed COVID-19 cases in the U.S. were aged <18 years (median 11 years) limited data on clinical course but generally mild.
 - Among [2,143 Chinese children](#) with likely COVID-19, few developed severe infection:
 - 55% asymptomatic-mild (4% asymptomatic), 39% moderate (pneumonia, dry cough, fever, lung lesions), 5% severe (fever, cough, GI symptoms, shortness of breath, decreased oxygen saturation), and 0.6% critical (respiratory failure, heart failure, multi-organ dysfunction)
 - [Infants \(<1 year\) are more likely to have severe infection \(10.6%\)](#).
 - Characteristics of a cohort of [100 Italian children](#) seen in the emergency room were compared to cohorts from China and US, fewer had moderate/severe disease
 - 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.
 - In Italy, a [30-fold increase in incidence](#) of severe Kawasaki disease in children-cardiac disease common.
 - Among [17 children admitted with Kawasaki disease](#) over 10 days in Paris, 82% had evidence of SARS CoV2 infection - all had marked gastrointestinal symptoms initially and high levels of inflammatory markers and all recovered
 - 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.
- Transmission
 - In [an analysis](#) of 1,245 contacts of 636 individuals in Wuhan, and 1,296 contacts of 557 individuals in Shanghai, children were 1/3 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.
- 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.
 - [Recommendations](#) for COVID-19 in children by severity of disease.
 - [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
 - Among [118 pregnant women with Covid-19](#) in Wuhan, 92% had mild disease and 21% of deliveries were premature. The authors conclude that COVID-19 may be less severe than flu for pregnant women.
 - [Comparison](#) of 28 pregnant and 54 reproductive age women, shows similar clinical course: severity of disease (OR=0.73, 95% CI=0.08-5.15; $p = 0.76$), virus clearance time (HR=1.16, 95% CI=0.65-2.01; $p = 0.62$). None of 23 neonates were infected.
 - In review of [6 studies of pregnant women from China](#), 46/48 delivered by C-section but this practice was questioned; 1 fetal death in critically ill pt.
 - [Recommendations](#) for the care of pregnant women: [flowchart](#) of steps in care.
 - In areas of high COVID-19 prevalence such as New York City, [universal screening of women](#) admitted for delivery is recommended due to frequent asymptomatic infection.
- Birth outcomes
 - [Preterm delivery](#) in ~50% of pregnant women (n=32) hospitalized with COVID-19.
 - Similar coronavirus infections ([MERS, SARS](#)) found increased fetal loss for first term infection and also observed increased preterm birth for later infection.
- Maternal-child transmission
 - Among 6 babies delivered by C-section to women with COVID-19, all had anti-COVID antibodies (IgG) and two had IgM (which does not usually cross the placenta), [raising concern about transplacental infection](#).
 - However small studies (N=19) [report no maternal-child COVID-19 transmission](#) to newborns.
- Management
 - [American Academy of Pediatrics](#) has issued recommendations for the care of infants delivered by COVID-19 positive or suspect mothers including bath after birth, protective clothing for health care workers
- Breastfeeding
 - [CDC recommendations](#): Breastfeeding women with or suspected to have COVID-19 are recommended to express milk and feed the infant by someone who is healthy.
 - [WHO recommendations](#): Breastfeeding with precautions (hand washing, masking) but not to breastfeed if severely ill.

The Elderly

- Experience worldwide shows increasing case fatality rates with increasing age, especially over 60 years. Comorbidities further increase the risk of death.
- General resources
 - [CDC resources](#) for and about elderly

- [CDC guidance for retirement communities.](#)
- Mortality rate by age
 - [Mortality](#) for persons >59 yrs in Wuhan was 5.1 times that of persons 30-59 years
 - Among [191 hospitalized adults](#), 54 decedents were older with mean age 69 vs 52 years for discharged survivors. Adjusted odds of death rose by 10% per year of age (p=0.004).
 - Among [1,625 deaths in Italy](#): mean age 81+ years and 2/3 had diabetes, cardiovascular disease, cancer, or smokers. The case fatality rate among persons <60 was 1% or less versus 8% for 70-79 and 20% for 80+ years.
 - Among [5,700 patients hospitalized with COVID-19 in New York](#), 553 (9.7%) died (of these 75.8% ≥65); 2,081 (36.5%) discharged alive (32.5% were ≥65); 3,066 (53.8%) still hospitalized (48.5% were ≥65).
 - Among [388 inpatients with COVID-19 in Italy](#) (median age 66 years) the odds of mortality increased by 10%/year of age.
- Comorbidities
 - [CDC study of 7,162 COVID-19 cases](#) found that 71% of 1,037 hospitalized and 78% of 378 in ICU had 1+ comorbidity vs 27% of 5,143 not hospitalized (commonly diabetes, cardiovascular, and chronic lung disease).
 - A [CDC report](#) found that “among COVID-19–associated hospitalizations in older adults, nearly 90% had one or more underlying medical conditions.”
 - [Comorbid cardiovascular disease increases risk of death](#) (acute coronary syndrome due to inflammation, depressed myocardial function, arrhythmias)
 - [Out of hospital cardiac death increased](#) in Lombardy, Italy by 58% in 2/21/2020-3/21/20 compared the same month in 2019; 103 likely had COVID, contributing to increase; mean age 77 years at death.
 - [In >400 hospitalized patients in Wuhan](#), 20% had cardiac injury with elevated cardiac biomarkers (e.g., HStroponin), older in age (mean 74 years vs 60 years), and amongst those with cardiac injury, 50% died.
 - Among 5 patients with COVID-19 [complicated by Guillain-Barre syndrome](#), 3 patients were 60+ years of age.
 - Among [362 hospitalized patients](#) in Milan, Italy with COVID-19 (median age 66), 7.7% had a venous or arterial thromboembolic event.
- 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.
 - Resident screening in a [Washington state nursing home](#) found 2/3 infected and 1/2 of these were asymptomatic but most become symptomatic later.

- Poor outcomes from ICU care: Among 1,689 patients (median age 64 years) admitted to the ICU with an outcome reported, 51% died after an average of 6 days ([ICNARC report](#), 10 April 2020).
- Limited ventilator supply may [restrict use to younger patients](#).
- [Acute kidney disease with COVID-19](#) is placing demands on limited dialysis units and dialysis units are at risk for spread of infection.
- Social issues
 - [Recommendations to assist older, isolated persons](#) living at home.
 - Despite the increased risks among the elderly, another [study](#) found that “many adults with comorbid conditions lacked critical knowledge about COVID-19 and, despite concern, were not changing routines or plans.”

Palliative Care and Ethical Considerations

Ethical Concerns:

- **Learning from past pandemics**
 - [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
- **Fair allocation of resources**
 - [a volunteer committee of respected clinicians and leaders](#) can assist in decision-making, [6 recommendations](#) regarding allocation of resources, Italy’s SIAARTI’s Ethics Section: [Recommendations](#) for intensive care treatments, a [guide statewide allocation](#) of ventilators. Mask shortages, [experts have](#) highlighted the government to discourage hoarding. [AMA’s recommendations](#), [ACS’s ethical framework](#) recommending mortality prediction tools
- **Physical distancing, [civil liberties](#) and [economic](#) hardship**
- **Proposed [ethical framework](#) for healthcare institutions**
- **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 [controlled human infection studies](#). “[Right to Try](#)” outside of a clinical trial.
- **Health Equity:** A [report](#) highlights that providing high quality care for [vulnerable patients](#) globally is both [ethical and necessary](#) to ensure Americans’ health. [Ensuring access to technology](#) for marginalized populations during [social isolation](#).
- **[Immunity passports](#)**
- **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 [palliative care](#).
- **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. In NYC, a 24-7 [Palliative Care Help line](#) (PATCH-24) with real-time adjustments.

- 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.
- Communications Tools: [VitalTalk: COVID-Ready Communication Skills, Respecting Choices](#) [Guide for proactive care planning for COVID-19](#), Serious-Illness [Conversation Guide](#) for Inpatient and Outpatient Care, [Best case/Worst Case](#): ICU conversations
- 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
- Dementia-related behaviors 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
 - Recommendations for [communication with masks](#)

Section 4: Preventing Spread in Healthcare Settings

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.
- [Updated infection prevention advice from CDC specific for COVID](#)
- [A small simulation study of intubation in ED](#) found particles on necks of team members suggesting body suits may be necessary
- [New short paper in Nature](#) on aerosolization of COVID, cleaning of staff rooms and decontamination of PPE before doffing suggested, plus more evidence for mask wearing
- [Paper published in CDC journal](#) 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.

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

- 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](#)

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

Surgery and Procedures

- 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.
- **Implications of COVID-19 on cancer screening:** A [study](#) from the Netherlands reported a decrease in cancer diagnosis since social distancing began, especially for skin cancer, suggesting that COVID-19 may lead to delays in cancer diagnoses.
- The [American College of Surgeons](#) and AAP has called for surgeons to [cancel elective cases](#), with guidelines for [triage](#) of various [procedures](#). [CMS](#) has called for delaying all elective surgeries, non-essential medical, surgical, and dental procedures.
 - Specific guidance from other specialty societies below:
 - [American College of Obstetricians and Gynecologists](#)
 - [American Society for Reproductive Medicine](#)
 - [Children’s Hospital Association](#) and [American Academy of Pediatrics](#)

Reopening Health Systems

- As of April 22, Governor Newsom (CA) allowed [partial re-opening of hospitals](#) for procedures “foundational to people’s health” including cancer surgeries, colonoscopies, heart valve surgeries, and surgeries related to diabetes. Purely cosmetic procedures are prohibited.
- The [White House](#) with the CDC has issued a gated strategy for re-opening healthcare systems
 - **Symptoms** - downward trajectory of reported ILI (influenza like illness) within a 14 day period AND downward trajectory of covid-like syndromic cases reported in a 14 day period

- **Cases** - downward trajectory of confirmed COVID cases in a 14 day period OR downward trajectory as a function of total tests in a 14 day period (flat or increasing volume of tests).
- **Hospitals** - treat all patients without crisis care AND robust testing in place for at-risk healthcare workers, including emerging antibody testing
- Critics have noted these criteria lack metrics or specificity. It is unclear how much of a downward trajectory is required for reopening.
- **CMS** suggests a [phased re-entry of procedures](#) will start in low COVID areas in conjunction with state DOH depending on projected COVID rates in the near future including likelihood of surges; availability of testing (including swabs/reagents); workforce capacity; and PPE inventory.
- Medical and surgical societies are anticipated to issue guidelines in the coming weeks. Rigorous testing to monitor for potential outbreaks during this time is key. Non-covid care zones (NCCs) in hospitals can facilitate this.
- Guidelines will need to be discussed now about when to ease limitations on semi-urgent and elective procedures. Best practice suggests doing this in 2 week blocks in conjunction with rigorous testing, digital and in-person [contact tracing](#), and tracking of PPE to identify any potential outbreaks and shortage of protective equipment. Limiting low value care is [essential](#).

Supplemental Resources

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

Section 6: Virology, Drug and Vaccine Development

Virology and Drug Targets

- **Coronaviruses:** COVID-19 is caused by the coronavirus [SARS-CoV-2](#). Seven coronaviruses infect humans: 4 cause common colds, while SARS, MERS and COVID-19 are more serious diseases caused by the other 3 human pathogens.
- **Origin:** Many (100s) strains of coronaviruses circulate in animals, with the closest relatives so far to SARS-CoV-2 found in bats. Although possible that bat to human transmission occurred via an intermediate animal host, as happened in SARS (palm civets) and MERS (camels), [bat virus sequence analysis](#) instead suggests direct transmission from horseshoe bats to humans. Moreover, other bat coronaviruses have the presumed necessary characteristics to suggest additional future transmissions from bats to humans is likely. Possibility that SARS-CoV-2 was a [lab accidental release](#) 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 also 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](#).
- Entry also requires low pH (endosome) which chloroquine blocks, hence [possible drug](#).
- Spike protein acquires a [dominant mutation, D614G](#), over time in multiple populations, leading to speculation that this change makes the virus more transmissible. This could occur, for example, by creating a better functioning Spike protein, or by conferring an immunological advantage in the presence of the host antibody response.
- **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 addition, [observational studies](#) for hospitalized patients not initially in an intensive care setting, famotidine was associated with a two-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.
- [Study](#) identified human cell partners of 26 of the 29 unique coronavirus proteins, and lists 69 potential drugs that could target those interactions.

Vaccine Development

- **Types of vaccines:** Both [traditional and newer technologies](#) are being 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. A list of vaccines under development is [here](#).
- **Vaccine development challenges:**
 - Efficacy - will it make the right type of immunity, with an effective combination of either neutralizing antibodies or T cell responses?
 - Safety - some vaccines can make coronavirus infections worse through [antibody-dependent enhancement](#) (ADE) of entry into cells.
 - Time and scalability - ease of manufacture varies for different vaccine technologies. Gates Foundation planning how to [scale production](#) capacity.
 - How to select the candidate vaccines [to test](#).
- The Coalition for Epidemic Preparedness Innovations ([CEPI](#)) is funding 8 vaccine trials.
- First-in-human [trial](#) was Moderna's mRNA vaccine (mRNA-1273), started 3/16/20 in Seattle. Injected mRNA makes the spike protein inside the body. The company announced 5/6/20 that FDA had cleared them to move to a [Phase II trial](#).
- 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.
- [Tobacco plants](#) are being evaluated to make a vaccine, using a rapid and large-scale technology that was previously effective for an Ebola vaccine.
- 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.
- Injection with an "old-fashioned" killed virus vaccine ([PiCoVacc](#)) protected macaques from challenge. Human trials began April 16.
- An adenovirus vector vaccine developed at the [University of Oxford](#), which showed efficacy in macaques, began a [Phase I trial](#) (1,100 people) in April and will start a combined Phase II/III trial (5,000 people) in May.
- **Other vaccine approaches:** The anti-TB vaccine, BCG, non-specifically boosts immunity and is hypothesized to [confer some protection](#). BCG vaccination is being tested in [Australia and the Netherlands](#).
- **Passive immunization:** Screens are being carried out to identify [neutralizing antibodies](#) in patients that could then be synthesized and used as a therapy.

Section 7: Public Health Considerations

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 9,000 to 13,000 deaths per week in the US during May and declining throughout June and July. The models project that by Mid June, the US will have recorded between 110,000 to 125,000 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_0 :** [Experts](#) are increasingly suggesting the need for regular tracking and public reporting of R_0 -- 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.
- **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 importations 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 Social Distancing Restrictions/Reopening the Economy

- **Plans to Reopen the Economy:** Comprehensive plans to reopen the economy from the [Center for American Progress](#) and [American Enterprise Institute](#) focus on criteria needed to reopen and state responsibilities including increasing testing, case isolation, contact tracing, travel restrictions, disease surveillance, increasing availability of PPE in healthcare settings, and use of nonmedical cloth face coverings in the general public. The [Harvard Center for Ethics](#) and [Paul Romer](#) have additional plans that focus only on testing capacity. The [White House](#) has also released a plan.
- **Easing of Social Distancing Measures:** As COVID-19 rates peak in the U.S., experts have begun suggesting validated approaches -- such as “[suppress and lift](#)” policies, [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.
- **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 contact 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.

- **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.
- **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.

Acknowledgements

For questions or corrections, email: mhochman@med.usc.edu

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