

Keck School of
Medicine of USC

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COVID-19 Evidence-Based Summary

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Table of Contents

Section 1: What’s new this week.....	1
Section 2: Epidemiology, Seroprevalence, Incubation and Transmission.....	2
Section 3: Clinical Care.....	12
a. Presentation, Diagnosis, Treatment, ICU Care, Outcomes and Immunity	
b. Pediatrics, Pregnancy, Breastfeeding, and the Elderly	
c. Palliative Care and Ethical Considerations	
Section 4: Preventing Spread in Healthcare Settings.....	33
a. Infection Prevention, Personal Protective Equipment and Hospital Precautions	
b. Airway Management and Intubation and Managing Exposures in Healthcare Settings	
Section 5: Health System Best Practices	36
a. The Four S’s of Disaster Relief Planning	
b. Primary/Outpatient Care (Telemedicine) and Surgery	
c. Supplemental Resources	
Section 6: Virology, Drug and Vaccine Development.....	41
a. Virology and Drug Targets	
b. Vaccine Development	
Section 7: Public Health Considerations.....	44
a. Modeling and Predictions, Simulations using “suppression” and “mitigation approaches”, ICU Needs Estimation	
b. Approaches to Easing Physical Distancing/Reopening the Economy	
Acknowledgments	49

Section 1: What's new this week?

- **Seroprevalence Tracker:** A team has published an [online tracker](#) to monitor seroprevalence of COVID-19 throughout the world.
- **NIH Initiating Synthetic Antibody Trial:** The [NIH](#) is organizing trials of a monoclonal antibody in 220 subjects with mild-moderate Covid and another among [hospitalized patients](#). The trials may eventually test other experimental therapeutics.
- **Household Transmission:** A [meta-analysis](#) has concluded that the secondary attack rate within households is 18.8%.
- **More Evidence for Rapid Antibody Decay:** A study has found that “in non-severe COVID-19 infections, antibody titers against RBD and Spike, but not against the N protein, as well as pro-inflammatory cytokines decreased within a month after viral clearance.” The implications for immunity are uncertain, however the findings suggest the need for “caution in using serological testing to estimate the prevalence of SARS-CoV-2 infection in the general population.” Another [study](#) reported that “antibodies likely wane over a period of months.”
- **T Cell Immunity in Unexposed Humans:** A new [study](#) has suggested that “T cell memory to coronaviruses that cause the common cold may underlie at least some of the extensive heterogeneity observed in COVID-19 disease.”
- **Contagiousness of Those with Asymptomatic Infections:** Based on low level evidence, an [analysis](#) suggests that those with asymptomatic infections “may have a degree of infectiousness which is about 0.40-0.70 that of symptomatics.” Another [study](#) found that “many individuals with SARS-CoV-2 infection remained asymptomatic for a prolonged period, and viral load was similar to that in symptomatic patients.”
- **Duration of Contagiousness:** A new [study](#) suggests “that patients with mild or moderate illness might be less contagious 8 days after symptom onset.”
- **Pediatric Hospitalization Rate:** A CDC [report](#) found that during March 1–July 25, 2020, was 8.0 per 100,000 vs. 164.5 per 100,000 adults.
- **Low Transmission in Schools:** Schools in Australia have remained open throughout the pandemic. A [study](#) reports that “transmission rates were low in ... educational settings during the first COVID-19 epidemic wave.” Similarly, graduated reopening in [Korean schools](#) did not appear to trigger substantial transmission.
- **Automated Monitoring to Support Contact Tracing:** A [report](#) from Maine “found that using automated symptom monitoring as a part of the state’s contact tracing program was well received, with the majority of monitored contacts (96.4%) agreeing to automated symptom monitoring.”
- **Rapid Surveillance Mechanisms:** The WHO has released a [scientific brief](#) on environmental COVID surveillance that reports that environmental surveillance may have value in providing an early warning of rising rates and detecting SARS-CoV-2 in areas with limited clinical surveillance. An [analysis](#) also suggests that “social network data from Twitter [provided] early-warning signals of COVID-19 outbreaks in Europe in the winter season 2020”, highlighting the potential for digital surveillance systems.
- **Successful Elimination of COVID Transmission in New Zealand:** A [case report](#) highlighted the value of “early, decisive government action.”

Section 2: Epidemiology, Incubation and Transmission

Infection Burden

- L.A. County: [Current LA County Numbers](#), [interactive city level map](#) and [projections to when to ease social distancing](#). LA County [DPH interactive portal](#).
 - As of July 29: LA County has 185,872 COVID-19 positive people. The cumulative crude incidence rate (CCIR) is 1,839/100,000; the two-week moving crude incidence rate (CIR) is 380/100,000, down from 417/100,000 July 24.
 - As of July 29, 13,634 cases (7%) have been ever hospitalized, and 2,244 of these have been ever intubated (16%). 207 were hospitalized July 29, and 29 were intubated.
 - As of July 29, there have been 4,552 deaths, with a two-week mortality rate of 5.58%, down from 5.72% on May 22; 93% of people who died had an underlying condition.
 - Percent positivity of tests and people is increasing (9.93% on July 29, compared to 9.34% on July 15, 8.76% on June 29 and 8.35% on May 27).
 - **Characteristics of cases with known age:** 9% ages 0-17 yrs, 25% ages 18-29 yrs, 35% in ages 30-49 yrs, 19% in ages 50-64 yrs and 12% in ages >65 yrs, with higher %'s in cases 18-40 younger cases compared to 2 weeks ago. 4,516 deaths had known age: 0% in ages 0-17 yrs, 1% in ages 18-29 yrs, 7% in ages 30-49 yrs, 16% 50-64 yrs, 76% in ages >65 yrs.
 - **Sex:** 49.5% of cases but 56.7% of the deaths are in males (increased by 2% since the beginning of the outbreak).
 - **Race/Ethnicity:** Characteristics of the cases with known race/ethnicity: 5.4% Asian, 4.9% Black, 54.7% Hispanic/Latino (up from 50% on July 17), 12.7% Non-Latino White, 1% American Indian, Alaskan Native, Native Hawaiian, Other Pacific Islander, and 21.6% Other (increased from 6% on May 24).
 - Of the 4,532 deaths with known race, <1% were Native American/Pacific Islander, 1% were Other, 11% were Black, 15% were Asian, 47% were Hispanic, and 25% were non-Hispanic white. Blacks and Asians overrepresented in deaths relative to population and the distribution of cases.
 - **CDC reported a decrease in transmission with use of masks:** Two hair stylists saw 139 clients for at least 15 minutes while they were infectious with COVID-19. The stylists and clients all wore masks, and there were no detected symptomatic cases among the clients for up to 2 weeks after exposure. 67 of the 139 clients agreed to be tested and all were negative for SARS-CoV-2. The study suggests the use of masks mitigated transmission.
 - A [report](#) finds: "COVID-19 deaths reported in the first weeks of the pandemic captured only two-thirds of excess deaths in the US. Potential explanations include delayed reporting of COVID-19 deaths and misattribution of COVID-19 deaths to other respiratory illnesses or to non-respiratory causes."
 - **Transmission to household and non household contacts:** In a [study](#) from South Korea, 59,073 contacts of 5,706 index cases of COVID-19 were monitored. 11.9% of household contacts and 1.9% of non-household contacts developed

COVID-19. For index cases in children 0-9 years old, the household contact positivity rate was 5.3% and the non-household rate was 1.1%. This is in contrast to children 10-19, for which the household contact rate was 18.6% (highest of all age groups) and the non-household contact rate was 0.9%. Thus, younger children were not efficient transmitters, while older children had transmission rates higher than adults.

- **Closed environments more risky than outdoors:** An [unpublished study](#) in Japan, 27 were primary cases and 83 secondary cases. The risk of transmission was 18.7 times higher in a closed compared to an open environment.
- **Global control:** One of New Zealand’s secrets to its [successful virus response](#) may be a simple one: trust. In a national survey of more than 1,000 people, researchers found that nearly all New Zealanders have adopted hygiene practices, and their belief in the authorities was at almost 100%. To date, the country has had just 1,556 cases and 22 deaths, and has gone 83 days without community transmission of the virus. Other countries that had been successful at controlling the virus are now seeing resurgence upon reopening.
- California as of 08/05/20: 529,980 cases and 9,869 deaths: [CDPH](#)
- U.S. as of 08/06/20: 4,802,491 cases & 157,631 deaths: [CDC](#)
- Worldwide: As of 08/07/20: 19,141,627 cases & 715,802 deaths: [JHU Map](#)

Figure 1. Average number of weekly new cases and deaths from COVID-19

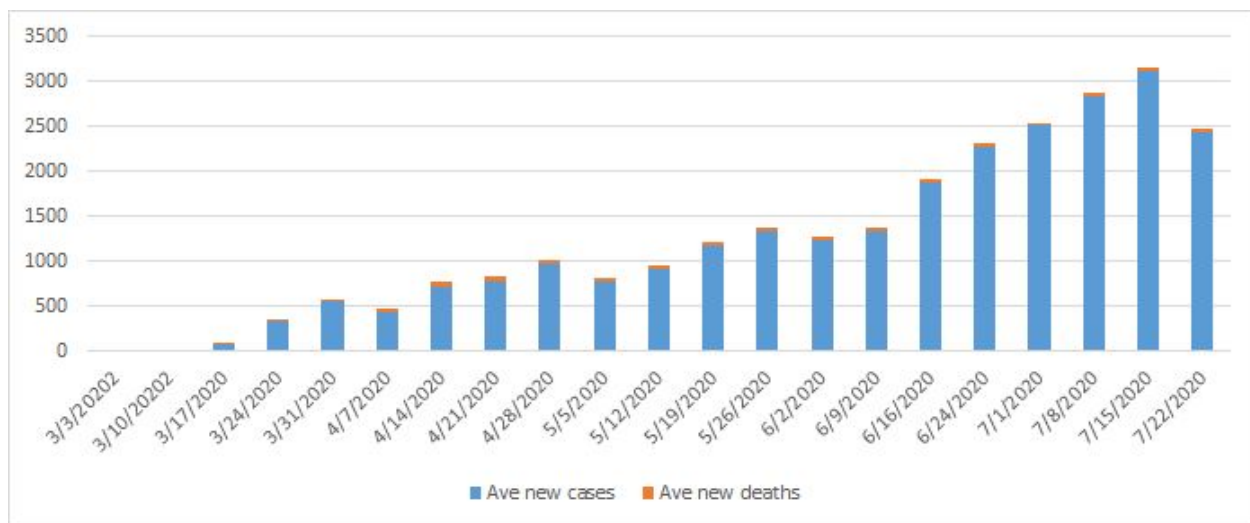


Figure 2. New cases and deaths from COVID-19 (log scale)



Figure 3. Weekly average of new hospitalizations and deaths

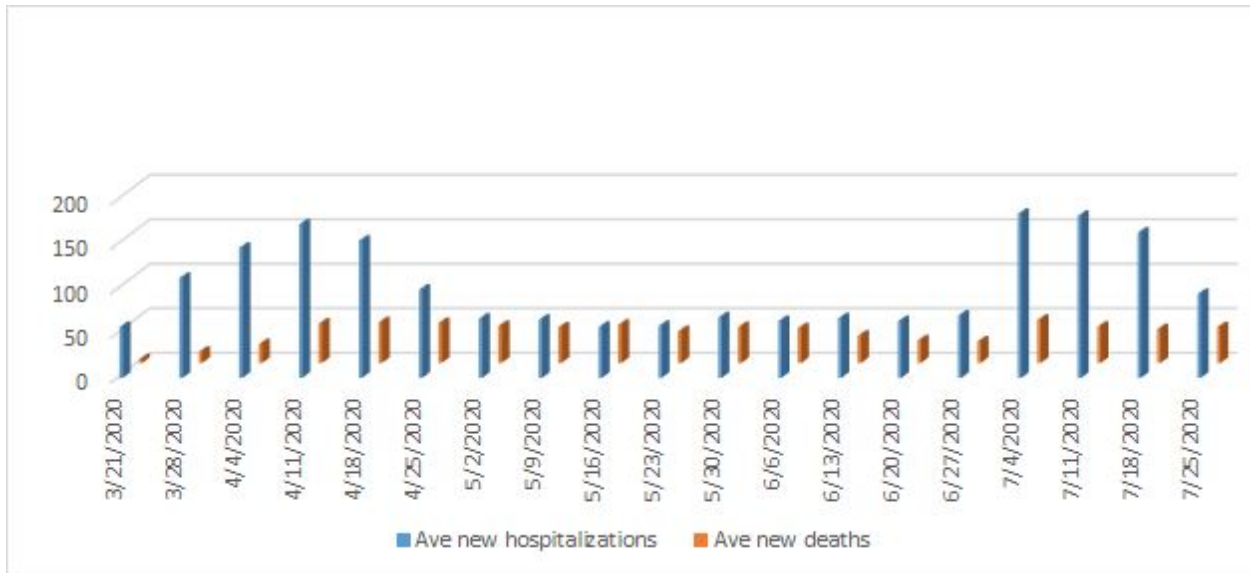
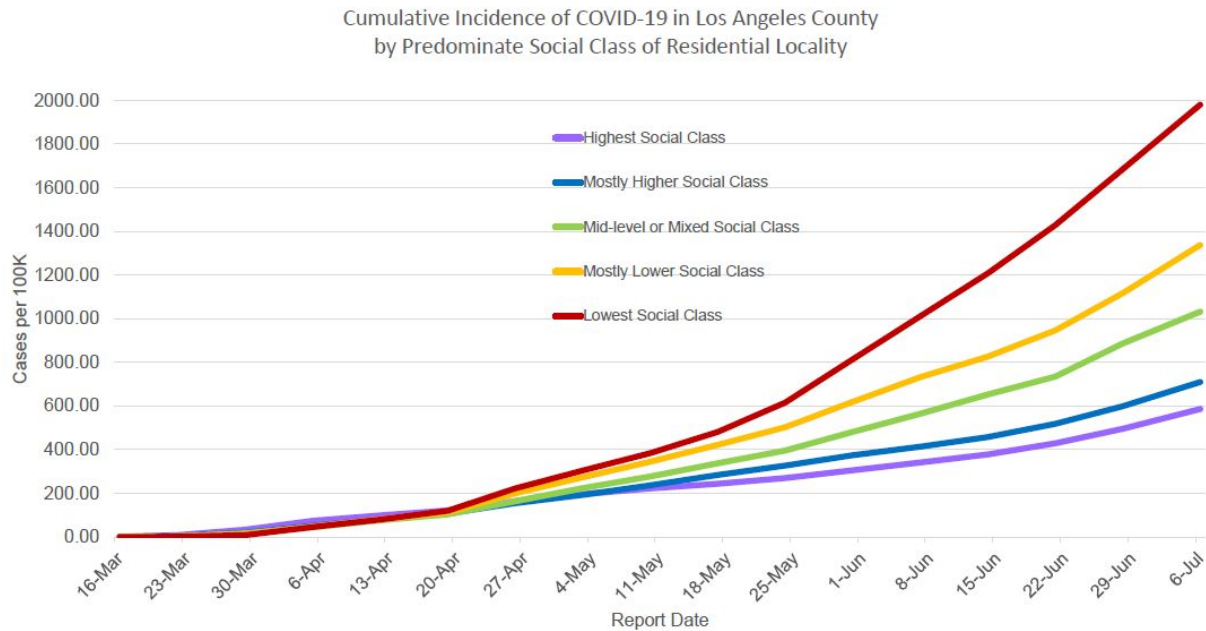


Figure 5. Cumulative COVID-19 incidence in L.A. County by Social Class (T. Mack)

Seroprevalence

- **LA County:** A USC/LA County seroprevalence [study](#) found that the “prevalence of antibodies to SARS-CoV-2 was 4.65%.” However, a follow-up [analysis](#) from this same group, perplexingly, now suggests that just 2.1% of LA County residents have previously been infected.
- A [similar study](#) in Santa Clara County among more than 3,000 residents (not randomly selected) suggests that the prevalence likely ranges from 2.5-4.2% -- about 85-fold higher than the number of confirmed cases. Another [study](#) suggests a rate of 21% in New York City. Based on these estimates, the COVID-19 case fatality rate may be lower than previously believed (as low as 0.1%-0.6%). Nevertheless, these studies have not yet been peer-reviewed and [some experts](#) worry the antibody testing results may not be accurate.
- **Seroprevalence in Geneva:** Repeated seroprevalence estimates were 4.8% (first week), 8.5% (second week), 10.9% (third week), 6.6% (fourth week), and 10.8% (fifth week), according to a [Lancet study](#). In addition, “a significantly lower seroprevalence was observed for children aged 5–9 years and adults older than 65 years, compared with those aged 10–64 years.
- **Seroprevalence in Spain:** Approximately [5%](#).
- **Seroprevalence in Indiana:** A CDC [report](#) has found that “the estimated prevalence of current or previous SARS-CoV-2 infection in late April 2020 was 2.79%. Among persons with active infection, 44% reported no symptoms.”
- **Seroprevalence in Atlanta:** A CDC [report](#) found that “2.5% of the population had antibodies to SARS-CoV-2.
- **Seroprevalence Estimates in the U.S.:** A new [study](#) reports that “the proportion of persons seroreactive to the SARS-CoV-2 spike protein ranged from 1.13% in WA to

6.93% in NYC (collected March 23-April 1) [to] 1.85% (collected April 6-10) for FL to 4.94% for CT (April 26-May 3). The estimated number of infections ranged from 6 to 24 times the number of reported cases in each site.

- **Middle/High Income Countries Most Impacted:** According to a new [analysis](#).
- **COVID-19 Surveillance:** A [report](#) found that respiratory illness was “above the seasonal average in March 2020” and “this surge correlated with COVID-19 case counts across states ... [these findings indicate that] over 80% infected patients [are] undetected.”

Disparities, Homelessness and Jails

- **Blacks are [experiencing](#) a higher burden of severe disease** compared to other [racial/ethnic](#) groups, according to [multiple studies](#).
- **Racial/Ethnic Disparities:** An [analysis](#) has found that “black adults ... were more likely than whites to have health risks associated with severe COVID-19 [however because the white population is older, overall] whites tended to be at higher risk ... with Asians and Hispanics having much lower overall levels of risk.”
- COVID-19 deaths have [disproportionately](#) impacted non-white populations, as has [morbidity](#).
- [Nationally](#), recent [estimates](#) suggest that **Blacks and Hispanics are approximately three times as likely to contract the virus and Blacks are nearly twice as likely to die from the disease.**
- There are significant disparities in [Los Angeles County](#):
 - **Hispanics have the highest rate of cases in LA.** Per 100,000 people there are 102.3 cases among Blacks, 113.6 among Hispanics, 73.2 among Asians and 78.2 among Whites, after adjusting for age.
 - In L.A. County, Blacks are more than twice as likely as Whites to die from COVID. Hispanics and Asians also have a higher risk of dying from COVID.
 - High rates and death-rates reported in [predominantly Latino counties](#).
 - Lower socioeconomic status communities in Los Angeles County are now experiencing the highest increases in cases and deaths.
- **Disparities:** An [analysis](#) of large U.S. metro areas identified an “excess burden of both infections and deaths [within] poorer and more diverse areas, racial and ethnic disparities ... existed beyond those explained by differences in income.”
- A [case series](#) of hospitalized patients with COVID-19 in Georgia reports that “black patients were overrepresented, and their clinical outcomes were similar to those of nonblack patients.” Another [new study](#) found that the number of hospitalizations and deaths in NYC was highest in the Bronx, the area with the lowest SES and highest percent of Blacks, and lowest in Manhattan, in spite of the Bronx having the lowest proportion of adults > 65 (12.8%) compared to Manhattan (16.5%).
- An [analysis](#) suggests Latinos are at increased risk for COVID-19 while another [study](#) suggests African Americans are at elevated risk. An [analysis](#) also suggests that “African Americans, men, and people younger than 55 years were less likely to know how the disease is spread, were less likely to know the symptoms of coronavirus disease 2019, washed their hands less frequently, and left the home more often.”
- **Homeless Populations:**
 - The [homeless in New York face](#) **disproportionately high mortality rates.**

- A new [CDC](#) analysis reports on clusters of infections in homeless shelters, finding rates of positive residents and staff, respectively, of 17% and 17% in Seattle, 36% and 30% in Boston and 66% and 16% in San Francisco. More details about the Seattle cluster are reported [here](#).
- Another [report](#) describes an outbreak at a San Francisco homeless shelter.
- **Jails:**
 - A [perspective piece](#) covers the unique challenges of COVID-19 within jails.
 - COVID-19 cases and deaths in prisons can be tracked [here](#)
 - A [study](#) found that “Aggressive intervention strategies coupled with widespread diagnostic testing of detained and staff populations can limit introduction and mitigate transmission of SARS-CoV-2 infection in correctional and detention facilities.”

Incubation

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

Transmission

- **Person-to-person transmission** occurs mainly via **respiratory droplets**, similar to influenza, and thus droplet precautions are [recommended](#).
- A [systematic review](#) concluded SARS-CoV-2 is mainly transmitted via inhalation of respiratory droplets containing the virus and has an incubation period of four to six days.
- **Fomites:** Transmission via [fomites](#) may be relatively small.
- **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 [experts have suggested airborne](#) transmission by aerosolized particles, [particularly](#) in enclosed spaces, [CDC](#) and [WHO](#) guidelines 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.
- **Airborne Transmission:** In response to feedback from prominent scientists, the WHO issued an updated [scientific brief](#) on airborne transmission: “some outbreak reports related to indoor crowded spaces have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice, in restaurants or in fitness classes.” Still, [data](#) continue to [suggest](#) that [droplet transmission](#) is the predominant form of spread. A [study](#) does, however, suggest that the airborne route may play a role in transmission aboard cruise ships, and [another](#) has found that aerosols generated by infectious patients may be contagious.
- **Preventing Airborne Spread:** While [CDC](#) guidance indicates that SARS-CoV-2 primarily spreads via respiratory droplets that typically don’t travel more than 6 feet, a [new article](#) contends that “SARS-CoV-2 is silently spreading in aerosols exhaled by highly contagious infected individuals with no symptoms.” The authors suggest that

future research should focus on identifying masks that effectively control release of airborne particles at the source, as well as strategies to improve ventilation.

- **Environmental Contamination:** [New CDC paper](#) reports that COVID travels up to 13 feet and frequently contaminates floors in healthcare facilities.
- **Transmission Indoors vs. Outdoors:** As is the case for many other respiratory viruses, transmission [appears to occur](#) more readily indoors vs. outdoors.
- **Outbreaks at Meat-Processing Plants:** Outbreak [reports](#) highlight the impact of close proximity in indoor environments in promoting transmission.
- **Young People Transmitting to Older Adults?** An [analysis](#) in Florida suggests that “younger persons, having first acquired their infections through increasing social contact [have] transmitted their infections to older, less socially mobile individuals.”
- **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).
- **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](#) 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, widespread transmission of SARS-CoV-2 was [in a] skilled nursing facility. More than half of residents with positive tests were asymptomatic at the time of testing and likely contributed to transmission. Infection-control focused solely on symptomatic residents were not sufficient to prevent transmission after SARS-CoV-2 introduction into this facility.”
 - A new [analysis](#) in the Annals of Internal Medicine concludes that “asymptomatic persons seem to account for approximately 40% to 45% of SARS-CoV-2 infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days.” Nevertheless, the WHO reported that the extent of asymptomatic spread remains uncertain.
 - Italian case [study](#) also highlights the role of asymptomatic spread.
- **Asymptomatic/Pre-Symptomatic Spread and the Challenges of Contact Tracing:** Evidence for substantial [asymptomatic/presymptomatic spread](#) continues to grow, [highlighting the challenges](#) of contact tracing for COVID-19.
- **Viral Levels in those without Symptoms:** A Massachusetts [analysis](#) of more than 30,000 people “found strikingly similar distributions of viral load in patients with or

without symptoms at the time of testing during the local peak of the epidemic; as the epidemic waned, individuals without symptoms ... had lower viral loads.”

- **Infection Clusters:** A new [article](#) explains that a disproportionate amount of spread occurs in clusters, highlighting the need to better understand factors associated with “superspreading”. Disease clusters seem to occur when an individual interacts closely in an indoor environment during a period of high infectivity early in the disease course.
- **Preventing Superspreader Events:** An [article](#) describes how addressing superspreading events will be critical for controlling the pandemic.
- **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:** New [models](#) do not suggest a link between temperature, humidity and disease rates, or at least that the relationship is [nuanced](#). In contrast, a JAMA [analysis](#) concludes that “the distribution of ... community outbreaks of COVID-19 along restricted latitude, temperature, and humidity measurements was consistent with the behavior of a seasonal respiratory virus. Another [report](#) concludes that “air temperature and relative humidity are shown to be negatively correlated with COVID-19 transmission throughout the world ... [however] weather conditions are not the decisive factor in COVID-19 transmission.” er modeling, it may be possible to estimate the regions most likely to be at a higher risk of substantial community spread in the upcoming weeks ...” Previously, a [National Academy of Sciences](#) report found that data are insufficient to indicate whether COVID-19 will dampen in hot/humid summer months. A [case study](#) suggested that COVID-19 is transmitted even in hot and humid conditions.
- **SARS-CoV-2 in Animals:** An [analysis](#) has found that “3.4% of dogs and 3.9% of cats had measurable SARS-CoV-2 antibody titers, with dogs from COVID-19 positive households being significantly more likely to test positive.” Another [study](#) reports on SARS-CoV-2 infections on tigers and lions at the Bronx zoo. [Cats](#) appear capable of transmitting the virus, though they do not seem to develop symptoms.
- **Pollution Levels May Accelerate Spread:** Based on [data](#) from subway systems.
- **Evidence for community spread in the U.S. in February:** A [Northeastern University model](#) indicates there may have been [tens of thousands of cases](#) of COVID-19 in the U.S. by February 2020, long before community spread had been recognized; these findings have not yet been published in a peer-reviewed journal.
- **Facemask use by the general public:** After considerable debate, the [CDC has begun recommending](#) voluntary use of cloth face coverings by the public. There is mechanistic evidence as well as some [experimental evidence from the SARS epidemic](#) and other [studies](#) to support this practice.
- **Face covering options:** There is [some evidence](#) that medical masks provide better protection vs. [cloth face masks](#). [Face shields](#) are another potential option.
- **More Data on the Effectiveness of Masks:** From [Italy](#), as well as from a laboratory [study](#) that found “that most home fabrics substantially block droplets, even as a single layer. With two layers, blocking performance can reach that of a surgical mask without significantly compromising breathability.”

- **New Evidence for Face Coverings:** A new [modeling study](#) -- not yet officially published nor peer-reviewed -- indicates that [consistent use of face coverings](#) might dramatically reduce COVID-19 spread. An [analysis](#) among healthcare workers also suggests that face coverings are highly effective in preventing spread.
 - A new [analysis](#) has found that “wearing of face masks in public corresponds to the most effective means to prevent interhuman transmission, and this inexpensive practice, social distancing, quarantine, and contact tracing, represents the most likely fighting opportunity to stop the COVID-19 pandemic.”
 - Another [analysis](#) from Germany suggests that “face masks reduce the daily growth rate of reported infections by around 40%.”
 - Furthermore, [testing results of direct contacts of two infected hair stylists](#) who worked while symptomatic has thus far found that none acquired the infection; since the stylists and their clients wore masks, it supports the effectiveness of masks for preventing spread.
 - Notably, however, a comprehensive Annals [review](#) found insufficient evidence of the efficacy of masks for SARS-CoV-2 prevention.
- **WHO Now Recommending Multi-Layered Cloth Masks for the General Public:** New guidance from the WHO recommends three-layered cloth masks with a water-resistant external layer; a cotton absorbent inner layer; and a middle filtering layer.
- **Multilayered Masks:** A high-speed photography [study](#) suggests that “A three-layer surgical mask was the most effective at limiting droplet spread. A two-layer cloth cotton mask was more effective during coughing and sneezing than one made from a single layer, but even the single-layer mask was better than no mask.”
- **Inexpensive Enhancements to Cloth Masks:** A [study](#) suggests that “the filtration efficacy of cloth masks with either a light or heavy starch can approach the performance of much costlier masks.”
- **Calls for Nationwide Masking:** In response to growing [data](#) supporting mask use to prevent infection spread, [experts](#) are calling for nationwide mask mandates.
- **California Mask Order:** Gov. Newsom issued an [order](#) that all Californians must wear masks in public and high risk settings.
- **Increased Prevalence of Mask Use:** [A CDC study](#) showed an increased mask use from April to May, up from 62% to 76% of those surveyed using masks in public. Usage by U.S. region in May: Northeast (87%), West (80%), Midwest (74%), South (71%). Every racial/ethnic group except Hispanics increased mask use with the highest use among Blacks (82%). Use among Hispanics was relatively stable from 77% in April to 76% in May. Research on barriers to mask wearing is suggested.
- **Transmission Via Toilets?** A [fluid dynamics simulation](#) suggests that toilet flushing may lead to “massive upward transport of virus particles”. The authors recommend consideration of measures such as toilet lids to protect against spread via toilets.
- **Factors Associated with Infection Clusters in Japan:** Japanese researchers [report](#) that “many COVID-19 clusters were associated with heavy breathing in close proximity, such as singing at karaoke parties, cheering at clubs, having conversations in bars, and exercising in gymnasiums.” Japanese policymakers advise avoiding “the “Three Cs”: closed spaces with poor ventilation, crowded places, and close-contact settings.”

- **Singing and COVID Spread:** [Data](#) continue to accumulate about the risks of singing, particularly in indoor environments.
- **Brass Instruments:** A [study](#) has found that “while playing a brass instrument, the propagation of respiratory Aerosols does occur and, to a smaller extent, so do Droplet size particles, but at a lower level than when the subject was breathing without an instrument.”
- **Wind Instruments:** Another [study](#) has found that “the aerosol concentration from different instrument plays exhibits two orders of magnitude variation. Specifically, tuba produces fewer aerosols than normal breathing, while the concentrations from piccolo, flute, bass clarinet, French horn, and clarinet stay within the range of normal breathing and speaking. Trumpet, oboe, and bass trombone tend to generate more aerosols than speaking.”
- **Effectiveness of Simple Measures to Prevent Spread:** A [study](#) of 124 families in China found that masks, disinfection and physical distancing substantially reduces transmission within households. Another [case study](#) at a Wuhan Medical Center found that “standard preventive measures can prevent SARS-CoV-2 exposure in medical staff.”
- **Meta-Analysis of Preventive Measures:** A [meta-analysis](#) of observational studies found the following odds ratios for various preventive measures: OR 0.18 for physical distancing of at least 1 meter; OR 0.15 for face mask use; and OR 0.22 for eye protection.
- **New CDC Guidance for Essential Workers Who Have Been Exposed:** New [CDC guidelines](#) indicate that “to ensure continuity of operations of essential functions, CDC advises that critical infrastructure workers may be permitted to continue work following potential exposure to COVID-19, provided they remain asymptomatic and additional precautions are implemented to protect them and the community.”
- **Factors Associated with Spread:** A new [CDC report](#) offers insights on factors associated with the early rapid spread of COVID-19 during February and March, including “travel-associated importations, large gatherings, introductions into high-risk workplaces and densely populated areas, and cryptic transmission resulting from limited testing and asymptomatic and presymptomatic spread.”
- **Ultraviolet Light to Disinfect:** Though some have suggested the role of UV light to kill the virus on surfaces, [evidence](#) to support this practice is limited.
- **CDC Guidance on Discontinuation of Transmission Precautions:** The latest [CDC guidance](#) 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

- Excellent clinical COVID [review](#).
- Description of [common](#) COVID-19 presentations.
- In a study of [138 hospitalized patients in Wuhan](#), initial symptoms were as follows:
 - Fever in 99% (In another [study](#), however, fever was present in only 44% of patients on admission, though 89% experienced fever during the hospitalization).
 - Fatigue in 70%
 - Dry cough in 59%
 - Anorexia in 40%
 - Myalgias in 35%
 - Dyspnea in 31%
 - Sputum production in 27%
- **GI symptoms:** Contrary to earlier reports, digestive symptoms including diarrhoea may be a symptom in up to [50% of cases](#) (though lower rates have been reported from other studies, particularly those from [China](#)); patients presenting with [GI symptoms](#) may have worse outcomes. Recent evidence suggests that digestive symptoms -- including [anorexia](#) -- may be a common [presenting symptom](#) of COVID-19. LFT abnormalities were present in a third of hospitalized patients in one [analysis](#). A new [meta-analysis](#) has found that “12% of patients with COVID-19 will manifest GI symptoms” and 40.5% will shed virus in their stool. The extent to which the virus spreads via stool is uncertain, however.
- **Anosmia:** A study from [Italy reports at least one taste or olfactory disorder in 33% of patients](#) with SARS-CoV-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](#).”
- **Dermatologic Symptoms:** May have some [diagnostic value](#). Among those with [severe disease](#), manifestations may include “livedo racemosa (skin discoloration) and retiform purpura.”
- **Cardiac Involvement:** A [study](#) has suggested cardiac involvement based on MRI findings in patients recovered from COVID.
- **Lingering COVID Symptoms:** An [analysis](#) concludes: “in patients who had recovered from COVID-19, 87.4% reported persistence of at least 1 symptom, particularly fatigue and dyspnea ... Patients with community-acquired pneumonia can also have persistent symptoms, suggesting that these findings may not be exclusive to COVID-19.” [Fatigue](#) in particular may linger.
- **CDC Updates:** The CDC has updated its [list](#) of conditions associated with increased COVID-19 complication risk; the list now includes sickle cell disease, and those with chronic kidney disease (not just those on dialysis) and those with a BMI 30 or greater

(rather than 40 or greater). The CDC has also added three new symptoms to its [list](#) of common COVID-19 symptoms: congestion/runny nose, nausea and diarrhea.

- **Effects of Age on Prognosis:** An [analysis](#) has found that “susceptibility to infection in individuals under 20 years of age is approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% of infections in 10- to 19-year-olds, rising to 69% of infections in people aged over 70 years.” ICU and mortality [rates](#) are also highest among the elderly.
- **Genome Associations with Severe Respiratory Failure:** An [analysis](#) has found associations between ABO blood group loci and COVID-related respiratory failure. Group O is associated with decreased risk while A with increased risk.
- **Blood Types and COVID Risk:** A [study](#) found that “Blood type was not associated with risk of intubation or death in patients with COVID-19. Patients with blood types B and AB who received a test were more likely to test positive and blood type O was less likely to test positive. Rh+ patients were more likely to test positive.” [Another](#) found that “blood group A was associated with an increased risk of infection, whereas group O was associated with a decreased risk.”
- [Neanderthal DNA sequence](#) with a high prevalence in South Asians may be associated with high risk of complications.
- A [systematic review](#) concluded that commonly reported symptoms were fever (80%) and cough (60%), however using these symptoms in isolation will miss a proportion of cases.
- **Characteristics of Hospitalized Patients:** A [cohort analysis](#) of more than 20,000 hospitalized patients found that the median age of hospitalized patients was 73; median duration of symptoms prior to hospitalization was 4 days; most common comorbidities were cardiac disease, diabetes, pulmonary disease and kidney disease, while 23% had no major comorbidity. Of those hospitalized, 41% were discharged alive, 26% died and the remainder were still receiving care in the hospital at the time of study reporting.
- **Link with out-of-hospital cardiac arrest:** A new [report](#) in the NEJM suggests a potential link between COVID-19 and a rise in out-of-hospital cardiac arrest in Italy.
- **Ambulatory care:** An [analysis](#) of ambulatory patients has found that “the most commonly reported symptoms ... were cough (83%), headache (73%) loss of smell or taste (71%), sinus congestion (71%), and body ache (67%). Symptoms remained common at 3 weeks, including cough (41%), shortness of breath on exertion (24%), loss of smell or taste (23%), sinus congestion (23%), and headache (20%).” A [case series](#) describes the clinical presentation of patients with COVID-19 in an ambulatory setting; anxiety-related dyspnea is more common soon after infection while COVID-related dyspnea occurs more often several days later.
- **Lingering Symptoms:** A CDC [analysis](#) has found that “35% [of those with SARS-CoV-2] had not returned to their usual state of health when interviewed 2–3 weeks [later]. Among persons 18–34 years with no chronic medical conditions, one in five had not returned to their usual state of health.”
- **Diabetes is a risk factor for severe disease/death.** In a [meta-analysis of 30 studies](#), there was a 4.64-fold increased risk of ARDS and a 2.12-fold increased risk of death.
- **Artificial Intelligence to Aid in Diagnosis:** A new [study](#) reports on a digital App that may help predict the probability of COVID-19 based on symptoms patients enter.

- **COVID Triage Tool:** A 9-question [triage tool](#), developed based on a national symptom survey in Israel, may help identify those likely to test positive for COVID-19.
- **Tools to Predict Disease Severity:** A [tool](#) has been developed to predict disease severity among hospitalized patients with COVID-19; [another](#) was recently released as well.
- **Clinical and Immunological Features of Asymptomatic Infection:** A [study](#) has found that asymptomatic individuals may have a longer duration of viral shedding (median duration 19 days) vs. those with symptoms; may be more likely to become seronegative during the early convalescent phase (40% in asymptomatic vs. 12.9% in symptomatic); and that asymptomatic individuals have a weaker immune response.

Diagnostic Testing

- [Summary](#) of diagnostic testing.
- Testing for active COVID-19 generally involves the [reverse transcriptase-PCR](#), typically utilizing a nasopharyngeal sample.
- **New COVID-19 Antigen Test Approved:** The [FDA has approved](#) the first antigen test for COVID-19 diagnosis. The antigen test can provide more rapid results vs. the PCR testing method, though there is a higher rate of false negatives. Another [antigen test](#) has now been approved as well.
- **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.
- **Testing Technology:** A [study](#) reports on an “RT-LAMP test for SARS-CoV-2 in raw saliva that takes about 45 minutes.” [Another](#) found that “home mid nasal swab collection was comparable to clinician-collected nasopharyngeal swab collection for detection of SARS-CoV-2 in symptomatic patients.” Another [analysis](#) reports on a potential serological test to detect neutralizing antibodies to SARS-CoV-2. And [another](#) reports on a rapid point-of-care test utilizing another RNA amplification technique.
- **More Rapid Saliva Tests:** [Studies](#) highlight the rapid race for a rapid [saliva test](#).
- **CRISPR-Based Testing:** A [study](#) has found nearly “perfect concordance between CRISPR- and PCR-based assays.”
- **False Negatives:** A [study](#) has found that PCR tests are particularly likely to be falsely negative early in the course of infection, when patients may be most contagious. Negative tests shouldn’t be used to remove precautions when suspicion for infection is high.
- **Antibody Test Approved.** The [FDA authorized](#) the first COVID-19 antibody test on April 1, and there are now [12 serology tests approved](#). [Quest](#) and [Labcorp](#) are providing their own serology testing. The FDA now [requires](#) test makers to submit validation data within 10 business days from the date they notified the FDA of their validation testing or from the date of this policy, whichever is later.

- There is growing interest in [antibody screening tests](#) to identify immune individuals who can [drive the return to work](#). However, important questions remain -- which are [just beginning to be addressed](#)-- regarding the sensitivity, specificity, and positive/negative predictive value of antibody testing, as well as whether positive antibodies actually indicate immunity. There also appears to be [wide variability](#) in the performance of existing antibody tests.
- According to [one analysis](#) from China, the median duration of IgM detection is 5 days, while IgG is detected at a median of 14 days after symptom onset.
- [Criteria](#) for who should be tested remains controversial:
 - 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 ...”
- **Concerns with Antibody Testing:** Because serologic testing [may be wrong half the time](#), new [CDC guidance](#) indicates that serologic testing should not be used to guide decisions regarding who is safe to return to work and other congregate settings.
- **Diagnostic Accuracy of SARS-CoV-2 Antibodies:** A [Cochrane review](#) has found that “The sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role for the diagnosis of COVID-19 ... Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. However, the duration of antibody rises is currently unknown, and we found very little data beyond 35 days post-symptom onset.” Another [analysis](#) has found that due to their inaccuracy, “available evidence does not support the continued use of existing point-of-care serological tests.”
- **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 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.
- **Pooled Testing:** [Testing groups of individuals together](#) may maximize current testing capacity, though [some data](#) indicate reduced sensitivity with batch testing.

- **Testing Guidelines from the IDSA:** The [IDSA](#) recommends testing “all symptomatic individuals suspected of having COVID-19 [and] asymptomatic individuals with known or suspected contact with a COVID-19 case. Testing asymptomatic individuals without known exposure is suggested when the results will impact isolation/quarantine/personal protective equipment (PPE) usage decisions, dictate eligibility for surgery, or inform administration of immunosuppressive therapy.”

Treatment and Management

Treatment Guidelines

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

- **Combining with Azithromycin:** A [small non-randomized study](#)--which [received an expression of concern](#) from the sponsoring society-- has suggested a benefit of combining hydroxychloroquine with [azithromycin](#) for treating COVID-19. Experts have expressed caution in combining these medications, given the potential for [adverse cardiac events](#).
- **Questionable Science:** A recent, large multinational registry analysis of 96,000 hospitalized patients showed hydroxychloroquine or chloroquine with or without a macrolide was [independently associated with in-hospital mortality](#). The death rates of the treated groups were: Hydroxychloroquine 18%, Chloroquine 16%, and control group 9%. The investigators also found an increase in cardiac complications. This led to the [WHO temporarily suspending trials](#) and [France banning the medication](#) in the use of COVID-19 patients. However, the [validity of the database](#) used to publish the data is being questioned. As such the original article has now been [retracted](#).
- **Hydroxychloroquine Use for Prevention:** [Major media outlets](#) have reported Hydroxychloroquine does not prevent COVID-19. This is based on a randomized, double-blind placebo controlled trial of 821 asymptomatic participants in which the [investigators concluded there was no difference](#) in the incidence of new illness between placebo and hydroxychloroquine. Some have argued, however, the [study may not be definitive](#), because the participants self-reported symptoms and there was no testing, raising the question of the trial design.
- **Ineffective in Hospitalized Patients, FDA authorization revoked:** Recent robust evidence shows Hydroxychloroquine is ineffective, as a large randomized ongoing study in the UK showed [no clinical benefit in hospitalized COVID-19 patients](#). The [FDA](#) has now [revoked its emergency use](#) and the [WHO halted its Hydroxychloroquine trial](#).
- **Favipiravir:** In a randomized [study](#) of two influenza drugs, Favipiravir versus Arbidol, in moderate severity patients, there were better outcomes with Favipiravir. While [Japan](#) has been testing Favipiravir, early data from a Russian trial has prompted [Russia](#) to approve the [medication for hospital use](#). [India](#) has been conducting its own trial, [and plans to approve](#) the medication as well. The medication is not available in the United States but is [currently being investigated](#). Early data from a Russian trial has prompted [Russia](#) to approve the [medication for hospital use](#). The medication is not available in the United States but is [currently being investigated](#).
- **Lopinavir-Ritonavir:** This HIV protease inhibitor is being investigated with early [studies](#) failing [to show](#) improvement over standard of care. An open-label, randomized phase II trial, however, showed some benefit when combining with ribavirin and interferon beta-1B. The [study](#) showed triple therapy was associated with “shorter median time to complete alleviation of symptoms” of 4 days vs. 8 days and “shorter median hospital stay” of 9 days vs. 14.5 days.
- **Remdesivir:**
 - **Severe Disease:** A large, randomized, placebo-controlled [NIH sponsored trial](#) [published their preliminary findings](#), because they showed statistically significant recovery time for those given Remdesivir in severe disease (11 days vs. 15 days). Additionally, [a study](#) has shown 5 days of treatment is as effective as 10 days.

These studies led to an [FDA emergency use authorization](#) for the drug to be used for severe, hospitalized patients. Gilead has [donated supplies](#) and [U.S. government has prioritized](#) regions and hospitals to receive the donated medication. Of note, a smaller, randomized, placebo controlled [trial](#) failed to demonstrate benefit.

- **Moderate disease:** While not yet published, [Gilead released data](#) from a randomized control trial showing hospitalized patients with moderate disease were 65% more likely to have clinical improvement at 11 days vs. standard care.
- **Colchicine:** A [small RCT](#) has suggested a benefit of colchicine in COVID treatment.
- **Statins for Hospitalized Patients:** A retrospective [analysis](#) has found that statin use among hospitalized patients is associated with substantially lower mortality, though these findings require further evaluation in a randomized trial.
- **Convalescent plasma:** [Convalescent plasma](#) has been studied in the SARS outbreak, H1N1 Influenza pandemic, MERS epidemic and Ebola epidemic. Because of this, convalescent plasma has been utilized in severe cases with some [early small studies](#)--not randomized--[suggesting benefit](#). [FDA allows](#) for expanded access and single patient emergency investigational use [based on strict criteria](#). Despite convalescent plasma available in many institutions [not all research](#) has been favorable. In fact, a recent [Cochrane review](#) of 8 studies shows uncertainty as to whether plasma is effective with current available studies being at risk for bias. The [FDA currently allows](#) use of convalescent plasma [based on strict criteria](#).
- **Immunomodulators:** Because a [cytokine storm](#) may be the catalyst for severe disease, clinicians are investigating immunosuppressants.
 - **Tocilizumab** (Actemra) targets IL-6 and its [potential use](#) has been [advocated](#) with two [major studies](#) now [underway](#).
 - Non-randomized studies support the use of Tocilizumab in severe COVID-19 cases. In a [small retrospective study](#), patients were found to have improved clinical manifestations, lung imaging, and lab markers, with all patients discharged on average 15 days after administration of the medication. The authors suggest the medication is effective to reduce mortality and improve clinical outcome. In another [small retrospective analysis](#), it was again found that Tocilizumab improved lung imaging and inflammatory markers. Authors noted the medication also reduced the requirement for ventilatory support.
 - [Preliminary results](#) of a randomized trial showed patients with moderate or severe COVID-19 pneumonia had significantly reduced number of deaths or life support interventions when treated with Tocilizumab compared to a control group. More research is needed to validate these findings and explore the medication's potential side effects.
 - In a [non-randomized study](#), researchers compared 78 intubated patients who received tocilizumab with 76 who did not receive the medication. They found a 45% reduction in hazard of death and improved status, despite higher risk of superinfection occurrence. This study is not yet peer-reviewed.

- **Sarilumab** (Kevzara) also targets IL-6 and is currently involved in a [large clinical trial](#). Preliminary results, however, [are not promising](#).
- [News broke recently](#) that Tocilizumab did not help patients with early stage COVID-19 pneumonia, however [a large retrospective study](#) showed reduced risk of invasive mechanical ventilation or death in patients receiving tocilizumab vs. standard care. A [large randomized placebo controlled trial](#) and a study [combining the medication with Remdesivir](#) is in the works.
- **Dexamethasone for Severe Disease:** The UK is in the midst of a large randomized trial involving 11,500 patients called the [RECOVERY Trial](#), investigating the use of Hydroxychloroquine, Lopinavir-Ritonavir, Convalescent Plasma, Tocilizumab, and Dexamethasone. The study has shown that [Dexamethasone reduces mortality](#) in patients with severe disease. The study, which has now been peer-reviewed and published in the [NEJM](#), showed a one third reduction in mortality for those requiring mechanical ventilation with a number needed to treat of 8. There is also a statistically significant improvement in mortality for those requiring supplemental oxygen with a NNT of 25. There is [cause for caution](#), however, as there was a trend toward worsened mortality for those not requiring oxygen and there are unknown outcomes for approximately. Nevertheless, hospitals are now seeing a [shortage of Dexamethasone](#).
- **Blood purification device:** Despite limited data, the [FDA issued an emergency use authorization](#) for a blood purification device that filters inflammatory mediators.
- **Adjunct Care:** A number of existing medications have been suggested to be repurposed for the management of COVID-19.
 - **Statins:** Due to its anti-inflammatory properties, [statins](#) have been suggested for respiratory illness. Early observational data suggested a trend toward better outcomes for those with [Pneumonia](#) and [Influenza](#). As such, statins were suggested for [MERs](#). Because statins increase ACE2 receptors, [its therapeutic potential](#) in COVID-19 has been [proposed](#). Despite no clinical evidence to suggest its use, [many institutions](#) are utilizing statins. Cardiologists have weighed in, suggesting the continuation of statins for those with atherosclerotic cardiac disease or diabetes and consideration of initiating if COVID-19 patients have cardiac injury. If patients are not on a statin as an outpatient, then it is unclear if there is a role in initiating the medication, but [some have suggested](#) initiating if at increased risk for clinical atherosclerotic cardiovascular disease.
 - **Famotidine:** An epidemiologic [study](#), not yet peer reviewed, found that famotidine use was associated with a hazard ratio of death of 0.29. However, a randomized trial will be needed to evaluate the potential role of famotidine for treatment. [Observational studies](#) for hospitalized patients not initially in an intensive care setting showed that the heartburn drug famotidine was associated with a two-fold reduction in clinical deterioration leading to intubation or death.
 - **Zinc:** Over the years Zinc has been reported to have antiviral effects. Animal studies with the [Avian Influenza](#) showed promise and in vitro studies showed an ability to [reduce viral replication](#) in SARS. Refined research [has been mixed](#) on the [use of Zinc](#) in treating patients with respiratory illnesses. To date there is no research on the use of Zinc with COVID-19. Despite weak clinical evidence, Zinc

[has been suggested](#) as an [adjunct in the management](#) of COVID-19. A [clinical trial](#) combining Zinc with Hydroxychloroquine is currently being investigated.

- **Vitamin D:** There is some [suggestion](#) that vitamin D repletion may reduce complication rates. According to a new [analysis](#), “based on retrospective data and indirect evidence [there is] a possible role of Vit D in reducing complications attributed to unregulated inflammation and cytokine storm.” Another [review](#) found that: “Vitamin D supplementation was safe and reduced risk of ARI, despite evidence of significant heterogeneity across trials ... protection was associated with administration of daily doses of 400-1000 IU vitamin D for up to 12 months.” However, a randomized trial is needed to evaluate this hypothesis.

Expert Recommendations on Treatment

- **ATS Guidelines:** ATS recognizes the lack of empirical evidence to guide COVID-19 management. In light of ongoing daily new cases, [ATS offers guidance](#) based on scarce direct evidence, indirect evidence, and clinical observations. Their main points are:
 - Hydroxychloroquine: Reserved for hospitalized patients with evidence of pneumonia, on a case-by-case basis, with shared decision making with the patient.
 - Lopinavir/ritonavir- For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.
 - Remdesivir- For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.
 - Tocilizumab- For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.
 - Systemic corticosteroids: For hospitalized patients with evidence of pneumonia, no suggestion either for or against treatment.
- **Updated IDSA Treatment Guidelines:** The [updated guidelines](#) recommend glucocorticoids for patients admitted to the hospital with severe COVID-19 and hypoxemia; and remdesivir for hospitalized patients with severe disease. The guidelines also emphasized the importance of recruiting patients into clinical trials to better determine safety and efficacy of available treatments:
 - HQ/chloroquine +/- azithromycin may be considered in context of a clinical trial
 - Lopinavir/ritonavir may be considered in context of a clinical trial
 - Recommends tocilizumab for admitted patients only in context of a trial
 - Recommends convalescent plasma in context of clinical trial
- **NIH Treatment Guidelines:** The NIH has released [COVID-19 treatment guidelines](#). The guidelines do not recommend any specific antiviral or immunomodulatory drug treatment for COVID-19 disease outside of a research setting, nor for pre- or post-exposure prophylaxis; the group recommends against systemic steroids for patients who are mechanically ventilated who don't have ARDS; the guidelines do recommend low-dose steroids for patients with refractory shock.

Management Guidelines

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

[systematic review](#) has found that chest CT is sensitive but not specific for COVID-19 pneumonia.

- **Prone positioning for nonintubated patients:** A new [cohort study](#) suggests a benefit of prone position among patients with COVID-19 in improving oxygenation and preventing intubation, however the findings will require confirmation in a randomized trial.
- **Venous Thromboembolism Prevention:** Literature continues to emerge highlighting the VTE risk in COVID-19 patients. In one Chinese study, the [incidence of VTE was high in ICU patients](#) and potentially related to poor prognosis. In a retrospective French study, a high incidence of VTE in ICU led to suggestions of [systematic screening of VTE](#) and therapeutic anticoagulation in severe cases. Studies like these have led many to advocate for [close attention to VTE risk](#) in COVID-19 patients. The [American Society of Hematology](#) has attempted to issue some guidance and some institutions have created their own [management algorithms](#) for VTE prevention and treatment.
- **Lupus anticoagulant:** COVID-19 may be associated with [lupus anticoagulant positivity](#), which may explain with the observed hypercoagulability and thromboembolic disease.
- **Management recommendations for MI amidst COVID:** [Recommendations](#) highlight special considerations to ensure infection control for patients and staff.
- **NSAIDs:** Because NSAIDs may upregulate [ACE2](#), some have [questioned their safety](#) in patients with COVID-19. While some [organizations](#) are calling for further evaluation, the [WHO doesn't recommend avoiding NSAIDs](#).
- **ACEIs/ARBs:** Early in the pandemic, [concerns were raised about ACEIs/ARBs](#), which prompted the ACC/AHA and other medical experts to [advocate for continuation of these agents](#) and to [caution against discontinuation](#) of proven therapies.
 - A retrospective, single-center case series evaluated 1178 COVID-19 hospitalized patients, focusing on the 362 patients with hypertension and [found no difference between those taking ACEIs/ARBs and those who did not](#) in regards to severity of disease and risk of death.
 - A retrospective, multi-center study looked at 1128 patients with hypertension and COVID-19, finding those on [ACEIs/ARBs actually had a lower mortality rate](#) than those not on the medications.
 - A [large observational study](#) spanning multiple countries and including 8910 patients showed no association between ACEIs/ARBs with mortality.
 - Another population-based case-control study of 6272 patients [showed no evidence](#) that ACEIs/ARBs affect the risk of COVID-19.
 - A [systematic review](#) showed ACEIs/ARBs not associated with more severe COVID-19 disease.
 - Another large epidemiologic [analysis](#) has failed to identify an association.
 - A [systematic review and meta-analysis](#) found that “ACEI/ARBs use for COVID-19 patients does not lead to harmful outcomes and may even provide a beneficial role and decrease mortality from COVID-19. Clinicians should not discontinue ACEI/ARBs for patients diagnosed with COVID-19 if they are already on these agents.”
 - [Clinical trials](#) are further investigating [ACEIs/ARBs](#) and their role in COVID-19.

Intensive Care Unit (ICU)

- **ICU survival improvement:** A new [meta analysis](#) shows ICU survival rates have improved since the start of the pandemic around the world.
- The ICU lies on a continuum of care (community, outpatient, inpatient ward/telemetry/ICU, discharge or death). Prevention and treatment in one part of the continuum have effects throughout [with implications for resource availability](#).
- Useful overviews in: [NEJM](#); [JAMA](#); [Internet Book of Critical Care](#); [Cochrane review](#).
- **Risks factors for hospitalization and critical illness:** An [analysis](#) from New York reports that “age and comorbidities are powerful predictors of hospitalization; however, admission of oxygen impairment and markers of inflammation are most strongly associated with critical illness.”
- **Association with Aspergillosis:** A [study](#) has shown that high incidence of pulmonary aspergillosis among critically ill COVID-19 patients and that its occurrence seems to change the natural history of disease.
- **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](#). It seems to particularly be a [risk factor](#) among younger adults.
- 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](#).
 - The [incidence of venous thromboembolism \(VTE\)](#) amongst COVID-19 patients with severe pneumonia is 25%; another [study](#) highlights the need for early surveillance and screening for VTE in hospitalized patients.
 - [Cytokine storm](#) syndrome which is a dysregulated hyperinflammatory response to the viral pathogen.
 - [Cardiomyopathy and arrhythmias](#) which can occur late, may be [multifactorial in etiology](#).
 - [Neurologic complications](#) may include encephalopathy, delirium, and corticospinal tract signs, as well as [other neurological manifestations](#).
- [Clinical markers](#) include: elevated C-reactive protein, LDH and ferritin
- [Current management](#) largely involves supportive care:
 - [Invasive Ventilation/Personal Protective Equipment](#)
 - ARDSnet lung protective ventilation [protocol](#)
 - Conservative fluid resuscitation, Early vasoactive support.
 - Prone Positioning
 - A [small study](#) has shown the potential benefit of prone positioning for ventilated COVID-19 patients with ARDS.
 - [Prone positioning in non-ventilated patients](#) with moderate ARDS (non COVID in a recent paper) supported by [high flow O2](#) or NIV reduced need for intubation
 - [Increasing use of prone positioning in the non-ventilated patient - management guidelines](#) including useful flow chart
- [Considerations](#) for extracorporeal membrane oxygenation (ECMO)
- [Resources from European ICU](#) including papers and blogs from Italian ICUs

- Published resources:
 - [Critical Care Medicine paper \(5/26/20\) from Atlanta](#): ICU and ventilator mortality
 - [ATS paper \(4/29/20\) from Boston](#): respiratory pathophysiology of mechanically ventilated patients
 - [JAMA paper \(4/20/2020\) from New York](#): characteristics and outcomes
 - [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 (ESICM) and Derek Angus - Critical Care Update: [JAMA interview](#) (6/8/2020)
 - Derek Angus - Update on Critical Care management: [JAMA interview](#) (4/1/2020)
 - Maurizio Cecconi (ESICM) from Italian centers: practice PPE before you need to do it in real life and ICU management - [JAMA interview](#) (3/16/2020)
- Framework for [assessing rehabilitation needs](#) after ICU from UK intensive care society

Prognosis and Outcomes

- **Prognostic indicators:** [Models are being developed](#) to assist in predicting disease severity and mortality.
 - **Elderly Age and Comorbidities:** A [review article](#) of 53,000 patients found that the strongest predictors of disease severity were age ≥ 50 , smoking, and co-morbidities, particularly CKD, COPD, and cerebrovascular disease. Age >60 , CVA, HTN, and DM were found to be independent prognostic factors for death. Another review article, [found elderly male patients](#) were more likely to develop into critically ill patients. In a single-center, cross-sectional analysis, [elderly age \(age \$>65\$ \) and heart failure](#) were strong risk factors for hospitalization.
 - **Obesity as a risk factor:** A retrospective study looking at a single center E.D. experience found [BMI to be an independent risk factor](#) in individuals younger than 60 years. A single center retrospective cohort study found obesity to be a [risk factor in disease severity](#). A single center large retrospective study of 3400 patients found [obesity to be independently associated with mortality](#) in patients younger than age 50. Another [analysis](#) among hospitalized patients with diabetes showed that “BMI, but not long-term glucose control, was positively and independently associated with tracheal intubation and/or death.” CDC now lists [severe obesity as a risk factor](#).
- **COVID has Higher Mortality than the Flu:** A cohort [study](#) from Denmark reports that inpatients positive for COVID-19 experienced about 3-fold increased 30-day mortality rate vs. influenza; for outpatients, there was a 5.5 to 6.9-fold increased mortality rate compared to influenza.

- **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).
- **ICU Patients:** Many [will require](#) mechanical ventilation. [Outcomes](#) of those requiring mechanical ventilation are poor.
- **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

- **Decay of SARS-CoV-2 Antibodies:** A study from the UK has shown that antibodies in the plasma of recovered COVID-19 patients [decrease over time](#), with steep decreases 3 months after infection. Another [analysis](#) suggested even faster declines among those with mild/no symptoms: Among those with mild COVID-19 symptoms, the half-life of antibodies was just [36 days](#). [Another](#) found that not all patients have SARS-CoV-2 specific antibodies, though all who recovered from severe infections had detectable neutralizing antibodies.
- **Neutralizing Antibodies:** An [analysis](#) has found that “the vast majority of infected individuals with mild-to-moderate COVID-19 experience robust IgG antibody responses against the viral spike protein ... titers are stable for at least a period approximating three months, and that anti-spike binding titers significantly correlate with neutralization of authentic SARS-CoV-2. Our data suggests that more than 90% of seroconverters make

detectable neutralizing antibody responses and that these titers are stable for at least the near-term future.”

- **Seroconversion Doesn't Always Occur:** A [study](#) has found that “several antibody tests conducted six weeks after an outbreak of SARS-CoV-2 did not detect all previously PCR-positive tested individuals.”
- **T Cell Immunity:** Another [study](#) suggests that many individuals have specific T-cell immunity against SARS-CoV-2, perhaps from prior infections with other coronaviruses.
- A new [study](#) has found that “forty percent of asymptomatic individuals became seronegative and 12.9% of the symptomatic group became negative for IgG in the early convalescent phase.” It is not known how well IgG levels correlated with immunity.
- It is not clear whether those who have previously been infected can be reinfected. “Other coronaviruses demonstrate [evidence of reinfection](#) [but] this usually does not happen for many months or years.
- A WHO [scientific brief](#) has concluded that “there is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection ... there is not enough evidence ... to guarantee the accuracy of an ‘immunity passport’ or ‘risk-free certificate.’” In a [clarifying tweet](#), the WHO explained: “We expect that most people who are infected ... will develop an antibody response that will provide some level of protection.”
- A [JAMA viewpoint](#) concludes that: “existing limited data on antibody responses to SARS-CoV-2 and related coronaviruses, as well as one small animal model study, suggest that recovery from COVID-19 might confer immunity against reinfection, at least temporarily. However, the immune response to COVID-19 is not yet fully understood and definitive data on post infection immunity are lacking.” Another [JAMA viewpoint](#) highlights that there is not currently sufficient evidence to support “immunity certification” programs, but this may change as further data emerge.
- **Update on the South Korean Patients Reported to Have been 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.
- There does seem to be [immunity in other primates](#) according to multiple [studies](#).

Pediatric Populations

- Prevalence and Clinical Course
 - Among 95 cases of multisystem inflammatory syndrome in [children \(MIS-C\) in NY](#), 31% 0 to 5 yo, 42% 6-12, and 26% 13-20. All had fever or chills; 97% tachycardia, 80% GI sx, 60% rash, 27% mucosal sx. All had elevated CRP and most high D-dimer, and troponin; 80% in ICU and 2 died.

- Among 570 reported cases of MIS-C in the US, all tested were SARS CoV2+, 203 (35.6%) had typical sx (i.e., shock, cardiac dysfunction, abdominal pain, and very high inflammatory markers) and 367 (64.4%) with less severe disease had sx typical of acute COVID-19 or Kawasaki,^{2/3} required ICU care but only 10 died. <https://docs.google.com/document/d/1aNIOG36RLiK0YvyiqE4-Wm37QK5h8zEbF5BZn6K8a10/edit>
- The [WHO](#) preliminary case definition for MIS-C in COVID-19 + children with features of toxic shock and atypical Kawasaki disease. CDC has issued a [health advisory](#) on MIS-C.
- [CDC data from Feb 12–April 2, 2020](#) reported only 2,572 (1.7%) of 149,760 lab confirmed COVID-19 cases in the U.S. were aged <18 years (median 11 years) limited data on clinical course but generally mild.
- A study of [582 hospitalized children](#) with COVID-19 from 25 European countries finds that 25% of those in ICU had comorbidities and other risks for ICU were: age<1 mo, males, and lower resp sx at admission. By end of the study, 4 had died and 25 still symptomatic
- 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.
- [Clinical course](#) described in 35 children in Southern California: most symptomatic, association of viral load and disease severity in children <5 years.
- In a Swiss study of 53 children (<16) and 352 adults with SARS CoV2 and no sx, viral loads were similar ([SARS-CoV-2 viral load in the upper respiratory tract of children and adults with early acute COVID-19](#))
- [50 hospitalized children in NYC](#), 80% lung sx or fever; obese children aged 2+ more likely to need respiratory support; 1 child died but no severe disease in infants or immunocomprised children
- Transmission
 - [School closures](#) were associated with a 62% decline in the incidence of COVID-19/week (265% per week before closures). The absolute reduction in COVID-19 incidence associated with school closures was estimated at 424 cases per 100,000 people during days 17–42 after closures. It is not clear whether the school closures vs. other factors were responsible for this association.
 - [A modeling study](#) suggests that screening every 2 days using a rapid, inexpensive, and even poorly sensitive (>70%) test, with strict behavioral interventions to keep $R_t < 2.5$, is estimated to keep the number of COVID-19 infections down to promote safer return to residential university/college campus.
 - [Children aged 10-19](#) may be more likely to transmit than adults or younger children in a study from S Korea - ages 10-19: 19% of household contacts infected versus: ages 30–49: 12% infected and 0–9 years: 5% infected.
 - Another [analysis](#) found “children aged under 10y have significantly lower susceptibility to SARS-CoV-2 ... Opening of primary schools and daycare facilities is expected to have limited effect on community spread, particularly under smaller class sizes and in the presence of mitigation measures ... [however] there is evidence of robust SARS-CoV-2 spread in schools for older children, and opening middle/high schools should be undertaken with caution.”

- In contrast to other studies, an [analysis](#) of 145 people with mild/moderate COVID-19 found that children younger than 5 had high amounts of SARS-CoV-2 viral RNA in their nasopharynx compared with older children and adults.
- A new CDC [report](#) has found that “SARS-CoV-2 spread efficiently ... in all age groups (6+), despite efforts by camp officials to implement most recommended strategies to prevent transmission. Asymptomatic infection was common and potentially contributed to undetected transmission ... Measures not implemented were cloth masks for campers and opening windows and doors for increased ventilation in buildings.”
- 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.
- A [study](#) of household contacts of 40 Swiss children <16 infected with SARS-CoV-2 showed that 79% had at least one adult family member with suspected/confirmed COVID-19 before the child’s symptoms began, suggesting that adults are more likely to transmit to children rather than vice versa. A seroprevalence [study](#) at a school that recently experienced an outbreak found that overall seroprevalence was 9.9% for students and 16.6% for staff, and among students antibody positivity was associated with younger age, lower grade level and contact with confirmed cases.
- [Fecal-oral transmission](#) may be possible based on studies in children and [fecal shedding may persist weeks after respiratory infection has resolved](#) - concern for school-based transmission.
- Teens
 - A [survey of 770 teens](#) reported that 68% were not social distancing but a greater understanding of the severity was associated with distancing
- Recommendations
 - **Schools:** New CDC [recommendations](#) call for “concurrently implementing multiple strategies to prevent the spread of COVID-19 (e.g., social distancing, cloth face coverings, hand hygiene, and cohorting).” National Academies of Medicine [recommendations](#) for school reopening.
 - [Recommendations](#) for care of 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
 - CDC study of 8,207 pregnant women in the US finds COVID-19 affects especially [Hispanic pregnant women](#). Pregnant women are more likely to be hospitalized and develop severe disease but not to die.
 - A [systematic review](#) finds that women with COVID-19 are less symptomatic than the general population but adverse birth outcomes are higher.

- [Comparison](#) of 28 pregnant and 54 reproductive age women had a similar clinical course: severity of disease, virus clearance time - None of 23 neonates infected.
- [Summary of international guidelines](#) for care of pregnant women: [flowchart](#) of steps in care.
- In areas of high COVID-19 prevalence such as New York City, [universal screening of women](#) admitted for delivery is recommended due to frequent asymptomatic infection. However, in WA state, there was [low prevalence](#) in 188 pregnant/postpartum women (2.7%).
- Birth outcomes
 - [Preterm delivery](#) in ~50% of women (n=32) hospitalized with COVID-19.
 - Increased Stillbirths During COVID: A UK [study](#) has found an increase in stillbirths, though a direct link to SARS-CoV-2 infection is uncertain.
 - A [systematic review](#) reported that, among 666 neonates of COVID-19 mothers, 28 were infected and usually asymptomatic, and the risk was similar regardless of type of delivery or breast/bottle-fed.
- Maternal-child transmission
 - A [systematic review](#) of 18 studies with 157 mothers and 160 neonates, reported that 5 (6%) had a positive test for SARS-CoV-2 but they concluded that they were unlikely to reflect maternal child transmission.
 - However, [a report](#) of a neonate born to a mother infected in the last trimester and presenting with neurological symptoms offers strong evidence of transplacental infection.
 - Among [82 neonates delivered by infected women](#) in NYC, none infected despite nearly all roomed with mothers and were breastfed - using safety procedures
 - Among 6 C-section deliveries to women with COVID-19, all had anti-COVID antibodies (IgG) and two had IgM (which does not usually cross the placenta), [raising concern about transplacental infection](#).
- Environmental risks for infection
 - In NYC, odds of [infection were higher among women with lower SES](#): residing in neighborhoods with high unemployment rates (interdecile OR=2.13 [95% CI= 1.18-3.83]), large household membership (interdecile OR=3.16 [95% CI= 1.58-6.37]), and greater household crowding (interdecile OR=2.27 [95% CI= 1.12-4.61]).
- Testing and Management
 - In NYC, 15% of 155 [asymptomatic maternity patients](#) tested positive for SARS-CoV-2 despite having screened negative on a telephone screening tool.
 - [American Academy of Pediatrics](#) has issued recommendations for the care of infants of COVID-19 positive or suspect mothers--bath after birth, protective clothing for health care workers.
- Breastfeeding and Pregnancy
 - [CDC recommendations](#): CDC concurs that pregnant women have a similar disease course to nonpregnant women. Women with or suspected to have COVID-19 -- express milk and someone who is healthy feed the infant.
 - [WHO recommendations](#): Breastfeeding with precautions (hand washing, masking) but not to breastfeed if severely ill.

The Elderly

- Case fatality rates rise with increasing age, especially over 60 years. Comorbidities further increase risk of death.
- General resources:
 - [CDC resources for and about elderly](#)
 - [CDC guidance for retirement communities](#)
 - [CDC guidance for testing in nursing homes](#)
- Mortality rate by age
 - Among [5,700 patients hospitalized with COVID-19 in New York](#), 553 (9.7%) died (of these 75.8% ≥ 65); 2,081 (36.5%) discharged alive (32.5% ≥ 65); 3,066 (53.8%) still hospitalized (48.5% ≥ 65).
 - [Mortality](#) for persons >59 yrs in Wuhan was 5.1 times that of persons 30-59 years
 - Among [1,625 deaths in Italy](#): mean age 81+ years and 2/3 had diabetes, cardiovascular disease, cancer, or smokers. The case fatality rate for persons <60 was 1% or less versus 8% for 70-79 and 20% for 80+ years.
 - Among [388 inpatients with COVID-19 in Italy](#) (median 66 years) odds of mortality increased by 10%/year of age.
- Comorbidities and complications
 - In [CDC study of 7,162 COVID-19 cases](#) 71% of 1,037 hospitalized and 78% of 378 in ICU had 1+ comorbidity (e.g. diabetes, cardiovascular, chronic lung disease) vs 27% of 5,143 not hospitalized
 - [Confusion](#) can be the presenting symptom in elderly with prior cognitive impairment.
 - [Comorbid cardiovascular disease increases risk of death](#) (acute coronary syndrome due to inflammation, depressed myocardial function, arrhythmias)
 - [Neuropathological findings](#) from autopsies of 18 patients with COVID-19 aged 53 to 75 showed no encephalitis or changes indicating direct viral infection.
 - 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.
 - Disparities [in Atlanta adults](#) with COVID-19 increased risk for hospitalization (all AORs ≥ 1.9) age ≥ 65 , black race, male, diabetes, obesity, uninsured, smoking.
- Predictors of mortality
 - A [nomogram to predict inpatient mortality](#) based on 1,590 patients with COVID-19: age 75 or older (hazard ratio [HR]: 7.86, 95% CI: 2.44 to 25.35), age 65 - 74 (HR: 3.43, 95% CI: 1.24 to 9.5), coronary heart disease (HR: 4.28, 95% CI: 1.14 to 16.13), cerebrovascular disease (HR: 3.1, 95% CI: 1.07 to 8.94) dyspnea (HR: 3.96, 95%CI:1.42-11), and laboratory measures.
- Challenges in specific settings
 - Among [147 encounters with calls for emergency medical care](#) (mean age 75) only half had fever and/or hypoxia, most did not need advanced care at that time but 52% ultimately died.

- [Long-term care facilities](#) have been an epicenter of COVID-19 infection, morbidity, and mortality.
- In a [skilled nursing facility](#), surveillance found more than half testing positive were asymptomatic initially, contributing to transmission.
- [167 confirmed cases](#) in Washington State nursing homes: 101 residents (mean age 83; 34 [33.7%] died), 50 health care personnel (no deaths), 16 visitors (mean age 62.5; 1 [6.2%] died).
- Poor outcomes from ICU care: Among 1,689 patients (median age 64 years) admitted to the ICU with an outcome reported, 51% died after an average of 6 days ([ICNARC report](#), 10 April 2020).
- [Acute kidney disease with COVID-19](#) is placing demands on limited dialysis units and dialysis units are at risk for spread of infection.
- COVID-19 in [1,128 surgical patients](#) resulted in 51% pulmonary complications and, of these, 38% died; highest mortality in men aged 70+.
- Social issues
 - [Social isolation of elderly in nursing homes](#) is increasing dementia and other adverse mental health outcomes. These can be managed with pharmacotherapy, however alternatives to isolation are needed.
 - Despite the increased risks among the elderly, another [study](#) found that “many adults with comorbid conditions lacked critical knowledge about COVID-19 and, despite concern, were not changing routines or plans.”

Palliative Care and Ethical Considerations

Ethical Concerns:

- **Duty to Plan:** From pandemics of the past, [WHO](#) and [CDC](#) developed ethical guidance for Pandemic Influenza, Society of Critical Care Medicine’s [Ethics of Outbreaks](#) Position Statements, [AMA’s Code of Medical Ethics](#): Guidance in a Pandemic
- **Proposed [ethical framework](#) for healthcare institutions**
- **Fair resource allocation:** [a volunteer committee of respected clinicians and leaders](#) can assist in decision-making, [6 recommendations](#) for allocation, Italy’s SIAARTI’s Ethics Section: [Recommendations](#) for intensive care, a [guide statewide allocation](#) of ventilators, [experts have](#) highlighted that government must discourage hoarding, [AMA’s recommendations](#), [ACS’s ethical framework](#) recommending mortality prediction tools, [AGS’s position](#), [maximizing](#) use of available resources, general public vaccine rationing should [prioritize groups](#) structurally and historically disadvantaged, despite overall lower life years gained.
- **Physical distancing**, [civil liberties](#) and [economic](#) hardship
- **Right to Health:** Shelter-at-home orders are further [impoverishing](#) vulnerable communities, [widening health inequities](#), requiring a coordinated human-rights based response. A [report](#) highlights that [access](#) to high quality care for [vulnerable patients](#) globally is both [ethical and necessary](#), including [older adults](#), [low-SES minorities](#), [LGBTQ+](#) populations, the [incarcerated](#) and the [homeless](#). **Ensuring access to technology** for marginalized populations during [social isolation](#).
- Ethics of universal masking and [herd immunity](#)

- **Research considerations:** Pressures of a crisis, may lead to [reliance on anecdotes](#) over evidence-based approaches. [Ethical commencement](#) of a controlled trial requires “[no treatment preference.](#)” Recommendations that studies on COVID be considered [highly sensitive](#) and protect the wellbeing of participants. [Ethical framework](#) for SARS-CoV-2 [human challenge studies](#). ‘Natural’ or ‘unplanned’ experiments during a pandemic have high power but [require responsibility](#). Concerns when pausing current research includes [human cost and needs to divert talent](#).
- **Right to Try:** outside of a clinical trial.
- Privacy infringement via [mobile phone applications](#) for [contact tracing](#)
- [Duty to Treat](#) despite personal & [family risk](#), noting [moral professional, legal obligations](#)
- [Immunity passports](#)
- [Shared ventilation](#)
- [Consenting](#) patients during periods of limited resources
- **AMA guidance** [Students graduating early](#), [Providing remote care](#), [obligations to protect healthcare professionals](#), use of [public registries](#), and [physicians in the media](#)

Palliative Preparedness:

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

Prognostication:

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

Advance Care Planning:

- Importance of advance care planning and a [framework](#) for informed assent.
- [ACC’s recommendation](#) for ACP and management in heart disease
- [GEDC recommends](#) ED physicians understand patient's goals, nursing home capabilities

- High risk older adults who received [GOC discussion in the ED](#) with PC response team declined CPR/mechanical ventilation opting for comfort care.
- In primary care, [group visits](#) improve ACP documentation
- In nursing homes, ensure [updated and appropriate](#) ACP and Advance Directives.
- [Communication](#) Tools: [Toolkits](#) include [VitalTalk](#): COVID-Ready Communication Skills, Respecting Choices [Guide for proactive care planning for COVID-19](#), Serious-Illness [Conversation Guide](#) for Inpatient and Outpatient Care, [Best case/Worst Case](#): ICU conversations
- POLST: [complete](#) for COVID when appropriate, POLST in [Crisis Standards or Care](#)

Symptom Management:

- Nonpharmacologic [dyspnea](#) management, [Pharmacologic](#) management of [psychological](#) distress, management of [nursing home](#) symptomatology
- Delirium may be caused by pain, hunger, fear, frustration, boredom, hallucinations, overstimulation, environment/routine changes, unfamiliarity with PPE
 - Alzheimer's Association recommends a HIPPA-compliant [personal information form and strategies to respond](#) to the behaviors
 - [Change](#) to usual guidelines proposed
 - Recommendations for [communication with mask](#)

Section 4: Preventing Spread in Healthcare Settings

Infection Prevention and Personal Protective Equipment

- **IDSA Guidelines:** IDSA [recommendations](#) for protecting healthcare workers include:
 - health care personnel caring for patients with suspected or known COVID-19 use either a surgical mask or N95
 - no recommendation for the use of double gloves versus single gloves
 - no recommendation for the use of shoe covers versus no shoe covers
 - health care personnel involved with aerosol-generating procedures on suspected or known COVID-19 patients use an N95
- **Factors Associated with Healthcare Transmission:** A new [study](#) has found that “universal masking, reinforcement of hand hygiene, and PPE with medical masks ... allowed protection of HCW and containment of the outbreak. Residual transmissions were related to persistent exposures with undiagnosed patients or colleagues and not to contacts with children attending out-of-home care facilities.”
- **Exposure and healthcare workers:** A [review paper in Annals](#) shows use of PPE and infection control training are associated with decreased infection risk and certain exposures such as intubation are associated with increased risk.
- **Simple Measures Effective in Protecting Healthcare Workers:** A new [analysis](#) has found that “multimodal infection control and prevention interventions are highly effective in mitigating SARS–CoV–2 infections of healthcare professionals.”
- **Meta-Analysis of Preventive Measures:** A [meta-analysis](#) of observational studies found the following odds ratios for various preventive measures: OR 0.18 for physical distancing of at least 1 meter; OR 0.15 for face mask use; and OR 0.22 for eye protection.
- **Aerosolization:** [JAMA paper](#), a [pre-print](#), and related [op-ed](#)
- **Mask Fit for protection:** [Paper emphasizing importance of fit for N95 protection](#), dome shaped N95s better than duck-bill shaped, with extended use fit should be re-evaluated
- **Updated infection prevention for facilities:** [CDC \(as of May 18th\)](#)
- **Transmission of COVID:** [Updated advice from CDC \(as of May 21st\)](#)
- [A small simulation study of intubation in ED](#) found particles on necks of team members suggesting body suits may be necessary, supported by a [research letter in JAMA](#)
- [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 in ICUs - health care workers should clean their shoes, half of the ICU staff shoes tested positive.
- **Face masks prevent spread:** [Nature paper](#) suggests face masks may prevent spread from asymptomatic individuals; [BMJ analysis](#) on general public’s mask use; [report on infection in health care workers](#) supporting masks for all.
- General [infection precaution advice](#) from the CDC for healthcare providers. PPE 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
- **Donning and doffing PPEs:** [CDC infographic](#)
- 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 for reuse, which they are [currently evaluating](#); others are developing [decontamination protocols](#) as well. A [website](#) is collating data about different decontamination practises for N95 masks. [Microwaving N95s](#) using household props - glass container, elastic band, mesh produce bag and appears to be effective in decontamination.
- **Extended N95 Associated with Reduced Efficacy:** Per new [JAMA research letter](#).

Hospital Precautions

- [The CDC has updated their guidance](#) on strategies to optimize PPE during shortages
- [Studies of contamination in a Wuhan COVID hospital](#) found no virus in the air in high risk areas, but significant contamination in areas of high touch surfaces, beepers (50%), 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 from a patient with an unrecognized infection to 3 healthcare workers, and [another](#) reports on the characteristics of infected healthcare workers.
- There are also reports out of Italy, [Spain](#) and China strongly suggesting in-hospital transmission, perhaps due to suboptimal adherence to infection control practices.
- **Blood Supply:** Case [study](#) suggests potential need to screen blood supply.
- 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](#), with limited movement of patients and healthcare staff between facilities.

- Many Asian countries developed dedicated hospitals and units exclusively for treating patients with COVID-19.
- There are no 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 [experimental evidence](#) suggests the potential value.

Airway Management and Intubation

- [A review of evidence and summary of learning](#) for anesthesiologists on minimizing infection risks and effective use of PPE
- [Guidelines from major UK societies on managing intubation](#) including systems to prevent infection for health-care workers
- Practical guidance for precautions and preventive measures to be taken in very high-risk exposure situations such as patient intubation are linked below:
 - [American Society of Anesthesiologists](#)
 - [UK Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists](#)
 - Papers in a [special edition](#) of Anesthesiology
 - Very [practical blog with images from an ED intensivist](#)
- [ASA guidelines on purchase and wearing of PPE](#) for anesthesiologists and other anaesthesia professionals.

Managing Exposures in Healthcare Settings

- [Guidance](#) on what to do if potential exposure occurs to a healthcare professional:
 - Covers potential risk of different types of exposures, what action should be taken, and what monitoring of the health care provider should occur.

Section 5: Health System Best Practices

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

The Four S's of Disaster Relief Planning

Staff

- One [proposal](#) argues for rotating staff schedule of a 4 days on, 10 days quarantine off to help minimize spread of the virus in the absence of extended testing
- Interim CDC [guideline for healthcare facilities](#) emphasizes preparation for potential personal protective equipment supply and staff shortages.
- [Surge planning](#) includes anticipating absenteeism in response to contagion and planning for staff shortages, while supporting staff to prevent this
 - Create registries of volunteers, plans for emergency or rapid credentialing.
 - Coordination with military medical corp is an option to expand staffing
- Clinician and staff psychosocial needs/distress must be addressed
 - [Increased need](#) for emotional/psychological support for staff [and patients](#).
- Consider alternate housing and childcare for workers with families at risk
- Malpractice/liability for good samaritans as enacted in the [State of New York](#)
- [UCSF Healthforce](#) recommendations describe staff scale up during surges
- George Washington University has a [model](#) to predict staff attrition
- A recent [NEJM article](#) cited advocacy in key workforce areas: “top of license” and expanded practice for allied health professionals, malpractice and indemnity reform to protect providers working outside their typical scope of practice, COVID work credit to senior medical and nursing students, focus on comprehensive social needs for patients/providers, streamlined hospital accreditation practices, recruitment of non-practicing providers (e.g. 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.
- In NYC, implementation of universal COVID screening for patients admitted for non-COVID illnesses reported 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.
- A University of Pittsburgh [case study](#) reports on 3,000 ambulatory patients with COVID-19. The team found that “83% of patients were managed by the automated program without escalating to human care.”
- **Medicare Promotes Home-Based Care for Medicare Recipients:** A new [Medicare emergency policy waiver](#) will allow hospital outpatient departments to relocate services to off-campus sites, including beneficiaries’ homes. These services will be reimbursed at the higher outpatient prospective payment system rates rather than the typical physician fee schedule rates -- an increase of approximately 40% for similar outpatient services.
- One degree has developed an [online toolkit for LA County](#) connecting COVID patients to social and financial resources that can be applied for online.
- Practices can consider proactively identifying patients with [long term health conditions](#) and elderly to avoid interruptions in care.
- Virtual chatbots, direct to patient channels, and remote patient monitoring are other [tools](#)
- **Scheduling redesign:** The AAP has suggested [separating well vs. sick](#) patients to separate times and spaces (ie., well visits in AM, sick visits after).
- There are [calls for urgent changes to quality monitoring](#) in the COVID era.
- **Reduced ED Utilization During the Pandemic:** A CDC [report](#) has found that “in the 10 weeks following declaration of the COVID-19 national emergency, ED visits declined 23% for heart attack, 20% for stroke, and 10% for hyperglycemic crisis.” Another [study](#) showed similar results in Marin County.

Surgery and Procedures

- A [study](#) from the Netherlands reported a decrease in cancer diagnosis since the COVID-19 guidelines were instituted, especially for skin cancer, with the implication that COVID-19 may be leading to delays in cancer diagnoses.
- **Reduction in Myocardial Infarction:** Since the pandemic began, there has been a [reduction in the incidence of myocardial infarction](#). The explanation for this is uncertain.
- **Cardiac Death Rates Stable:** A [new report](#) found that despite the reduction in hospital admissions for MI during the pandemic, overall cardiac death rates have not changed.
- **Cardiac Outcomes:** A [study](#) has found that myocardial infarction “case rates began to decrease on February 23, 2020, followed by a modest recovery after 5 weeks. Although no statistically significant difference in treatment approaches was found, the risk-adjusted mortality rate among patients with ST-segment elevation myocardial infarction increased substantially.”

- 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.
- **Pre-Procedural COVID Testing:** Like many health systems, [Virginia Mason](#) has conducted pre-procedural COVID testing. Yield from these efforts has been low.

Reopening Health Systems

- As of April 22, Governor Newsom (CA) allowed [partial re-opening of hospitals](#) for procedures “foundational to people’s health” (cancer surgeries, colonoscopies, heart valve surgeries, and surgeries related to diabetes). Purely cosmetic procedures are prohibited.
- The [White House](#) and 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](#).
- **Hospital Screening:** Based on a [study](#) in a French children’s hospital, “symptom-based SARS-CoV-2 testing strategy failed to identify 45% of hospitalized children infected ...”
- **Kaiser Permanente’s Plans to Combat COVID:** In a [NEJM Catalyst piece](#), Kaiser leaders describe key measures to suppress infection rates: 1) Increasing testing capacity; 2) contact tracing; 3) community healthcare (rather than just providing care for assigned patients); 4) promoting innovations in home-based care; 5) developing surge capacity; 6) safely reopening healthcare facilities based on public health priorities; 7) supporting research efforts; and 8) public education through communication.

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](#) also suggests direct transmission from horseshoe bats to humans. Moreover, other bat coronaviruses have the predicted necessary characteristics to suggest additional future transmissions from bats to humans are likely. Possibility that SARS-CoV-2 was a [lab accidental release](#) is considered extremely unlikely.
- **RNA replication and mutation rates:** SARS-CoV-2 is a large RNA virus of 30,000 nucleotides. As is common with RNA viruses, it is [mutating](#) over time and can undergo recombination.
- Differences in circulating virus strains can identify origins of outbreaks. For example [New York](#) was seeded mostly through European introductions.
- RNA replication is a drug target, inhibited by the nucleoside analog [remdesivir](#), or the target of other candidate drugs such as [EID-2801](#) that act by increasing the mutation rate of the virus to a point of ‘lethal mutagenesis’
- **Spike (S) protein and entry:** S protein on the outside of the virus binds ACE2 which helps determine tropism (alveolar epithelial type II cells, upper respiratory tract). [Soluble recombinant ACE2](#) inhibits the virus in vitro and is a potential therapy.
- Spike protein is activated by cleavage by TMPRSS2, which is also a [drug target](#). TMPRSS2 expression is increased by androgens, which could explain why men are more susceptible and why [androgen-deprivation therapy](#) in prostate cancer is associated with reduced susceptibility and severity of COVID-19.
- Entry also requires low pH (endosome) which hydroxychloroquine blocks, so [proposed as a drug](#).
- Spike protein acquires a [mutation D614G](#) over time in multiple populations, leading to speculation that this change [makes the virus more transmissible, for example, by creating a better functioning Spike protein](#), or by conferring an immunological advantage. Lab studies show that the G614 variant is [more infectious](#) in vitro, though another [study](#) suggests the mutation has not made the virus more virulent.
- **Main viral protease:** The main protease (Mpro or 3CLpro) cleaves the viral polyprotein, deubiquitinates viral and cellular proteins, and antagonizes the interferon (IFN) response (data from SARS). Structure of Mpro is being used to suggest [drugs](#) that could inhibit it.
- A [trial](#) is underway to test if heartburn drug famotidine could inhibit Mpro following observations from Chinese COVID patients taking the drug, and computational modeling. In [observational studies](#) for hospitalized patients not initially in an ICU, famotidine was associated with a 2-fold reduction in clinical deterioration leading to intubation or death.

- **Other drug targets:** [Antiviral drugs](#) used against other viruses are being evaluated for cross-reactivity against SARS-CoV-2 including [HIV](#) drugs and [influenza](#) drugs.
- A [study](#) identified human cell partners of 26 of the 29 unique coronavirus proteins, and lists 69 potential drugs that could target those interactions.
- Proteomics studies of SARS-CoV-2 infected cells showed that viral infection [alters phosphorylation of host proteins](#), resulting in production of cytokines, cell cycle arrest and induction of cell protrusions containing viral particles. Eighty-seven FDA-approved drugs were identified that could block these events including Silmitasertib, which is being evaluated as an anti-COVID therapy.

Vaccine Development

- **Types of vaccines:** Both [traditional and newer technologies](#) are being used to make vaccines. mRNA and DNA vaccines that encode one or more viral proteins (typically the Spike protein) are expected to be faster to produce than more traditional vaccines based on killed virus particles, attenuated virus strains, recombinant viral proteins (Spike protein) or viral vector vaccines such as adenovirus expressing one or more viral proteins. The WHO maintains a [list of vaccines](#) in clinical trials and under development. The NY Times has a useful [coronavirus vaccine tracker](#).
- **Vaccine development challenges:**
 - Efficacy- will it induce the right type of immunity, with an effective combination of either neutralizing antibodies or T cell responses?
 - Longevity- evidence that [antibodies in COVID patients](#) wane over time
 - Safety- concern it could make coronavirus infections worse through [antibody-dependent enhancement](#) (ADE) of entry into cells.
 - Time and scalability- ease of manufacture varies for different vaccine technologies.
 - How to select the candidate vaccines [to test](#).
- **Vaccines progress:** The [WHO](#) keeps a list of vaccines in human clinical trials, including trials in the US (Moderna, Pfizer, Inovio and Novavax), China and Europe (Oxford University), and candidates in pre-clinical trial stages.
- The Coalition for Epidemic Preparedness Innovations ([CEPI](#)) is funding several trials.
- The Gates Foundation planning how to [scale production](#) capacity.
- The US [Operation Warp Speed](#) plan has selected [5 vaccine candidates](#) to champion.
- **Type of vaccines:**
- **RNA vaccines expressing Spike:** Moderna's first-in-human [trial](#) (mRNA-1273), started 3/16/20 in Seattle. Injected mRNA makes the spike protein inside the body. This Phase I trial enrolled [45 participants](#) who received 2 injections of different doses and produced neutralizing antibodies at levels equivalent to those found in COVID-19 recovered patients. Side effects included headache, muscle ache and injection site pain. A phase 2 trial is ongoing.
- Pfizer and BioNTech started a Phase 1/2 [clinical trial](#) in Germany of a mRNA vaccine (BNT162) and will start in the U.S. soon. If successful, expect to supply millions of vaccine doses by the end of 2020, and hundreds of millions in 2021.
- **Killed virus:** injection with killed virus vaccine ([PiCoVacc](#)) protected macaques from challenge. Human trials began April 16.

- **Adenovirus vectors expressing Spike:** are being developed by several companies. The University of Oxford in collaboration with AstraZeneca is using one based on chimpanzee virus ChAdOX1. A [Phase I trial](#) with 508 test vaccinees showed the vaccine to be immunogenic and tolerated: neutralizing antibodies developed in 90% of vaccinees after one dose and in 100% of 10 volunteers receiving 2 doses. T cell responses were also detected. Side effects were mild. A combined Phase II/III trial started in May.
- An adenovirus vaccine based on human adenovirus Ad5 and expressing Spike was developed by Wuhan biotech company CanSino Biologics. [Phase I results](#) in 382 vaccinees showed both antibodies and T cell responses, including in people older than 55. However pre-existing anti-Ad5 antibodies blunted antibody responses.
- J&J are also developing an adenovirus vector and [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.
- Russia is producing an adenovirus vaccine and plans [mass vaccinations](#) by October.
- **DNA vaccines expressing Spike** given to 25 macaques induced both [antibody and cellular responses](#) and cellular responses, including neutralizing antibody titers comparable to those found in COVID patients. Eight vaccinated animals had no detectable virus following challenge, and the others had only low levels of virus.
- **Passive immunization with monoclonal antibodies:** Screens are being carried out to identify [neutralizing antibodies](#) in patients that could then be synthesized and used as a therapy. [Tobacco plants](#) are being evaluated to make this type of vaccine, using a rapid and large-scale technology that was previously effective for a monoclonal antibody-based Ebola vaccine. [Eli Lilly](#) has started a trial of antibody LY-CoV555 while Regeneron has [initiated a phase 3 trial](#) of another antibody.
- **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](#).

Section 7: Public Health Considerations

Simulation Modeling

- [More than a dozen simulation models](#) forecast the number of short-term and long-term COVID cases and fatalities, relying on various techniques including traditional epidemiological SEIR models, machine learning, and statistical curve fitting. In general, the models predict about 5,500 to 6,500 deaths per day in late June and July, relatively steady after a decline from 9,000 to 13,000 deaths per week mid May. The models project that by Mid August, the US will have recorded between 150,000 to 160,000 total deaths.
- Without interventions, deaths would have been much higher
 - An early and highly influential model from Imperial College London suggested that without interventions, mortality in the U.S. would peak in mid-June with ~55,000 deaths per day and culminate with [2.2 million fatalities](#).
- [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_t :** [Experts](#) are increasingly suggesting the need for regular tracking and public reporting of R_t -- the number of secondary infections per primary infection -- in different communities as a metric to assess how well social distancing is working.
- **Physical 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, as does a new [Health Affairs study](#), a BMJ [analysis](#), a study in [Texas](#), and another yet-to-be peer-reviewed [analysis](#).
- **The Protests and SARS-CoV-2 Spread:** A [study](#) concludes there was “a significant increase in COVID-19 case counts in counties that experienced a protest [highlighting the value of] social distancing as an intervention to minimize the spread of SARS-CoV-2.”
- **The Benefits of Early and Aggressive Physical Distancing:** A Columbia University [model](#) suggests that if distancing regulations had been implemented 1-2 weeks earlier, the U.S. COVID-19 death toll may have been substantially lower.
- **Effects of extreme social distancing, testing and quarantine in Wuhan, China:** Before the mitigation, the reproductive number was 3.0 before January 26; after these measures were implemented these decreased to below less than 0.3 after March 1.
- **Effect of Travel Restrictions:** An [analysis](#) of travel restrictions in China found that: “travel quarantine of Wuhan delayed the overall epidemic progression by only 3 to 5 days in mainland China but had a more marked effect on the international scale, where case importants were reduced by nearly 80% until mid-February.”
- **U.S. domestic travel more important than international travel in disease spread:** A [genetic analysis](#) (not yet peer reviewed) showed that U.S. domestic travel was responsible for more spread than international travel.
- **Suppression in Vo, Italy:** A [case study](#) of a 14-day lockdown in Vo, Italy found that the prevalence of COVID-19 in the community decreased from 2.6% before the lockdown to 1.2% afterwards.
- **Crowding and Risk:** [Modelling studies](#), which have not yet been published in peer-reviewed journals, strongly highlight the role of crowding/population density in viral spread both at the community level and within institutions.

- **Mental Health Consequences of Social Distancing:** This [perspective piece](#) highlights some of the potential mental health consequences of social distancing.
- **Projections on duration of social distancing:** Absent a vaccine, a [new projection](#) suggests that physical distancing may be required until 2022 or beyond.

Policy Approaches to Easing Physical Distancing Restrictions/Reopening the Economy

- **American Academy of Pediatrics Advocates for School Reopening in the Fall:** The [guidance](#) highlights the value of in-person education for the health of children and the well-being of society, and recommends measures to minimize risk. New [data](#) from Europe also suggests that schools can be safely reopened as long as rates of community spread are modest and appropriate safety-measures are in place.
- **Mass Testing:** CDC report has demonstrated the value of repeated facility-wide surveillance testing in [skilled nursing facilities](#) and [jails](#), and [models](#) suggest a benefit in Universities, however the CDC does not recommend universal testing in most other settings including [Universities](#). When conducting mass testing, it appears that [testing frequency and speed of results](#) may be more important than test sensitivity.
- **Mask Mandates:** A study in [Health Affairs](#) suggested that state policies that required the use of masks in public were associated with significant reductions in case growth.
- **Report on “Return to Work” Policies:** A [NEJM report](#) recommends a number of policies to ensure safety of the workplace, including masks, hygiene practices, symptom checklists and physical distancing protocols.
- **Plans to Reopen the Economy:** Comprehensive plans to reopen the economy from the [Center for American Progress](#) and [American Enterprise Institute](#) focus on criteria needed to reopen and state responsibilities including increasing testing, case isolation, contact tracing, travel restrictions, disease surveillance, increasing availability of PPE in healthcare settings, and use of nonmedical cloth face coverings in the general public. The [Harvard Center for Ethics](#) and [Paul Romer](#) have additional plans that focus only on testing capacity. The [White House](#) has also released a plan.
- **Easing of Social Distancing Measures:** As COVID-19 rates peak in the U.S., experts have begun suggesting validated approaches -- such as “[suppress and lift](#)” policies (supported by this [analysis](#)), [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.
- **Swedish Policy:** An [analysis](#) found that the Swedish policy of “mild mandates overlaid with voluntary measures can achieve results highly similar to late-onset stringent mandates. However, this policy causes more healthcare demand and mortality.”
- **Testing Capabilities for Reopening the Economy:** A [Harvard white paper](#) estimates that it will require millions of daily COVID-19 tests to safely reopen the economy; Economist [Paul Romer](#) similarly estimates that testing of the entire US population weekly or biweekly may be necessary, and is still effective to inform case isolation even with a high false negative rate.
 - [Testing could be ramped up](#) by significantly increasing federal reimbursement, and reinforcing the supply chain for intermediate supplies (swabs, reagents, etc.).

- [Pooled sample testing](#) could also be used whereby several samples are run on the same test, and if the pool is positive, individual tests are used to determine which individuals are positive.
- **Spring Break Outbreak:** A CDC [report](#) describes outbreak control during a college trip involving contact tracing of travelers, household and community contacts.
- **Serial Testing at a Skilled Nursing Facility:** A [case report](#) describes the successful use of serial COVID-19 testing to help control an outbreak at an LA SNF.
- **Mass Testing on College Campuses:** Initial results from [campus-wide testing at UCSD](#) identified zero positives among 1,300 students. Enrollment in the study was lower than expected “partly because it involved the discomfort of nasal swabbing ... [and because] many students skipped the test because they feared exposing themselves to the virus, or that they might lose their housing if they tested positive.”
- **Municipal Sewage as a Leading Indicator of Infection Rates:** A new [analysis](#) has found that “SARS-CoV-2 RNA concentrations [in sewage] were a seven-day leading indicator ahead of compiled COVID-19 testing data and led local hospital admissions data by three days.” Sewage sampling could be a strategy for guiding “decisions to implement or relax public health measures and restrictions.” Another [analysis](#) in Chile had similar findings.
- A [JAMA viewpoint](#) provides a concise update on the public health issues surrounding COVID-19: “For the foreseeable future, fundamental public health measures such as physical distancing, wearing a mask in public, frequent handwashing, and staying at home when symptoms occur, will remain the best tools to prevent COVID-19.”
- **Contact Tracing:** The U.S. may need as many as [100,000](#) 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. The GAO has released a [summary](#) of digital contact tracings Apps and there is another [summary](#) from Cornell.
- **Japanese Tracing App:** A [study](#) found that the App had “significant effects in reducing the reproduction number, however [the App alone] is insufficient to control an outbreak.
- **Viral Genome Sequencing to Track Spread:** Full [viral genome sequencing](#) may help assess transmission dynamics, an [approach the CDC plans to promote](#).
- **Preventive Measures:** An [analysis](#) found that “individual adoption of handwashing, mask-wearing, and social distancing, can ... mitigate and delay the epidemic.” [Another](#) found that “social distancing, lower population density, and temperate weather were associated with a decreased R_t for SARS-CoV-2 in counties across the United States.”

- **SARS-CoV-2 Genome Sequencing Aids Modeling:** An Australian [analysis](#) of real-time viral genome sequencing helped to clarify “the probable source of infection in cases where epidemiological links could not be determined, decreased the proportion of cases with contentious links ... and identified previously unsuspected links. Only a quarter of sequenced cases appeared to be locally acquired.”
- **Genome Sequencing to Help Track Hospital Outbreaks:** A [study](#) shows the potential value of genome sequencing for tracking hospital outbreaks. [Another](#) shows the potential to track infections among healthcare workers.
- **Genetics of New York Outbreak:** Genetic viral [analysis](#) suggests the New York outbreak most closely resembles the virus circulating in Europe.
- **Air Disinfection:** [Germicidal UV fixtures](#) have been suggested as a tool for air decontamination in high risk spaces, such as waiting rooms, emergency departments, ICUs, endoscopy and bronchoscopy suites; [UV light](#) from the sun may have modulated the epidemiology of the pandemic..
- **Preventing a Second Wave:** [In China](#), non-pharmacologic, public policy measures, including social distancing were able to reduce the reproduction number, R, below 1, which caused the number of cases to fall towards zero. However, new cases imported from other countries may require close monitoring to prevent a second transmission wave as these public policy interventions are relaxed.
- **The Public’s Willingness to Take a New Vaccine:** A Pew [survey](#) showed that 72% of Americans would get a SARS-Co-V-2 vaccine. The number was lower for African Americans, Evangelicals and Republicans.
- **Public Attitudes Toward Stay-at-Home Orders:** According to a new [CDC survey](#), “among adults in New York City and Los Angeles and broadly across the United States [there is] widespread support of stay-at-home orders and nonessential business closures and high degree of adherence to COVID-19 mitigation guidelines.”
- **Criteria for Lifting ‘Stay at Home’ Orders in LA County:** Los Angeles County has [announced](#) four criteria it will use to determine when to lift ‘stay at home’ orders: a) Ensuring hospitals have capacity to care for both COVID-19 and non-COVID-19 patients; b) Ensuring adequate protections are in place for the most vulnerable (e.g. homeless, elderly); c) Ensuring capacity to “test, isolate and quarantine” all who are ill and conduct surveillance; and d) Be prepared to provide clear guidance to businesses to ensure appropriate social distancing is maintained when the economy reopens.
- **California Releases Four-Phased Reopening Plan:** In the [plan](#), phase 1 involves ‘stay-at-home’ orders (current phase); phase 2 will involve lifting restrictions on low-risk workplaces; phase 3 will involve reopening higher risks businesses (e.g. gyms, in-person religious services); and phase 4 will involve higher risk activities (e.g. large in-person audiences) once a vaccine and/or an effective therapeutic is available.

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