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Keck School of Medicine of USC
COVID-19 Evidence-Based Summary
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Section 1: What’s new this week?

- **COVID-19 in California:** In follow-up to the recent LAC+USC study reporting that 5.3% of patients with mild flu-like illness in mid-March were positive for COVID-19 -- long before community spread in California had been recognized -- a new Stanford study will estimate the proportion of Californias with COVID-19 antibodies. If a substantial proportion have antibodies, it may indicate that herd immunity may partially explain why the state has thus far been relatively spared vs. other regions of the U.S.

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

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

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

- **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.

- **COVID-19 and the Elderly/Chronically Ill:** COVID-19 may cause complications among those of any age, but a new CDC report found that “COVID-19–associated hospitalizations in the United States are highest among older adults, and nearly 90% of persons hospitalized have one or more underlying medical conditions [underscoring] the importance of preventive measures … to protect older adults and persons with underlying medical conditions.” Another analysis concluded “people <65 years old have very small risks of COVID-19 death even in the hotbeds of the pandemic and deaths for people <65 years without underlying predisposing conditions are remarkably uncommon.” Another study found that in Italy “the case fatality rate for 70-79-year-olds is 13 times the rate for 50-59 year-olds, the corresponding rate for 80+ is 20 times that.” Still, another study found that “many adults with comorbid conditions lacked critical knowledge about COVID-19 and, despite concern, were not changing routines or plans.”

- **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.”

- **SARS-CoV-2 detected in blood donations in China:** A new research letter found that blood donations from asymptomatic donors was positive for the SARS-CoV-2 virus, suggesting the potential need for screening of the blood supply.

- **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.
Section 2: Epidemiology, Incubation and Transmission

Infection Burden

- L.A. County: [Current L.A County Numbers](#) and [interactive city and community level map](#)
  - As of April 9: L.A. County has 7,955 cases and 223 deaths, with 1,894 hospitalizations.
  - Characteristics of 7,543 cases: 1% in ages 0-17 yrs, 33% in ages 18-40 yrs, 45% in ages 41-65, 21% in ages >65 yrs, median age is 50. 52% of cases are male.
  - Cases are doubling every 6.8 days in Los Angeles County.
  - Infection has been detected in 65 institutional settings (Rehab, Nursing homes) in Los Angeles County as of April 5, including the jail and a homeless shelter.
  - Case-fatality rates increase with age, at 0.2% in 10-19 yrs, 3.6% in 60-69 yrs, 8% in 70-79 yrs, and 14.8% in those 80 yrs and older, based on data from China.
  - As of March April 9, New York is showing case-fatality rates in people with underlying conditions by age: <1% in 0-17 yrs, 1% case-fatality rates in those 18-44 yrs, 3% in 45-64 yrs, 8% in 65-74 yrs, and 15% in those 75 yrs and older. In people without underlying conditions, case-fatality rates were <1% among all age groups.
  - Underlying conditions associated with a higher risk cardiovascular disease, obesity, hypertension, diabetes, chronic respiratory disease and cancer.
  - Although older age is a stronger risk factor for severity and death, poor outcomes are also seen in younger patients, especially those with underlying conditions.
  - The Los Angeles County Department of Public Health released data on the distribution of COVID-19 deaths by race/ethnicity for 93 patients: Latinos (28%), non-Latino whites (27%), Asians (19%), Blacks (17%), and Other (9%). Blacks are overrepresented and Latinos underrepresented relative to their population distribution, however, because these data were not adjusted for confounding factors of age and sex, interpretation is limited.

- California: As of 04/08/20: 18,309 cases and 492 deaths: [CDPH](#)
- U.S.: As of 04/09/20: 427,460 cases & 14,696 deaths: [CDC](#)
- Worldwide: As of 04/10/20: 1,650,210 cases & 100,376 deaths: [JHU Map](#)
Incubation

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

Transmission

- **Person-to-person transmission** occurs mainly via respiratory droplets, similar to influenza, and thus droplet precautions are recommended.
- **Facemask use by the general public:** After considerable debate, the CDC has begun recommending voluntary use of cloth face coverings by the public, particularly in areas where there is substantial community spread. There is mechanistic evidence to support this recommendation, as well as some experimental evidence from the SARS epidemic.
- **Airborne spread:** Though some experts have suggested that there may be airborne transmission of COVID-19 via aerosolized particles, guidelines from the CDC and WHO suggest that the disease predominantly spreads via respiratory droplets within 6 feet, except during certain high risk aerosolizing procedures such as intubation.
- COVID-19 can live on surfaces for up to 72 hours (plastics, stainless steel). NEJM paper suggests the virus can remain viable and infectious in aerosols for hours.
- **Fecal-oral transmission.** Some studies suggest that fecal-oral transmission doesn’t appear significant, however others suggest it may occur.
- Studies report secondary spread rates of 1-5% and 0.45%.
- A case study suggests that COVID-19 is transmitted even in hot and humid conditions.
- **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).
  - MMWR (March 27) on asymptomatic transmission in a Seattle nursing home:
    - After one positive case, 23 residents tested positive (30%); 10 were symptomatic at the time of initial testing and 13 were asymptomatic.
    - Seven days later, 10/13 initially asymptomatic patients had developed symptoms. Nursing home recommendations need to account for asymptomatic spread.
- **New CDC Guidance for Essential Workers Who Have Been Exposed:** New CDC guidelines indicate that “to ensure continuity of operations of essential functions, CDC advises that critical infrastructure workers may be permitted to continue work following potential exposure to COVID-19, provided they remain asymptomatic and additional precautions are implemented to protect them and the community.”
- **SARS-CoV-2 detected in blood donations in China:** A new research letter found that blood donations from asymptomatic donors was positive for the SARS-CoV-2 virus, suggesting the potential need for screening of the blood supply.
Section 3: Clinical Care

Clinical Presentation

- COVID-19 presents similarly to many other viral respiratory infections.
- In a study of 138 hospitalized patients in Wuhan, initial symptoms were as follows:
  - Fever in 99% (In another study, however, fever was present in only 44% of patients on admission, though 89% experienced fever during the hospitalization).
  - Fatigue in 70%
  - Dry cough in 59%
  - Anorexia in 40%
  - Myalgias in 35%
  - Dyspnea in 31%
  - Sputum production in 27%
- **GI symptoms and COVID-19:** Contrary to earlier reports, digestive symptoms including diarrhea may be a symptom in up to 50% of cases; patients presenting with GI symptoms may have worse outcomes. Recent evidence suggests that digestive symptoms -- including anorexia -- may be a common presenting symptom of COVID-19. There is also growing concern that fecal-oral transmission may occur, though this remains uncertain.
- **Anosmia and COVID-19:** A study from Italy reports at least one taste or olfactory disorder in 33% of patients with SARS-CoV-2 infection. Olfactory and taste disorders (OTDs) are more frequent in patients and these symptoms may precede the onset of clinical disease. Patients may also experience runny nose and sore throat as well as a loss of smell. The American Academy of Otolaryngology Head and Neck Surgery has suggested that anosmia be included in testing and self-isolation criteria.

Diagnostic Testing

- Testing for COVID-19 involves the reverse transcriptase-PCR.
- FDA approved an Abbott Labs point-of-care COVID-19 test, offering results within several minutes.
- **Antibody Test Approved.** The FDA authorized the first COVID-19 antibody test. The package insert indicates that this serology test is specific for the novel coronavirus, and it turns positive even in those with asymptomatic infections. There is growing interest in antibody screening tests to identify immune individuals who can drive the return to work.
- According to one analysis from China, 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 …”
- Actual sensitivities and specificities are not yet available.
● Nasopharyngeal testing for COVID-19 may have limited sensitivity. In 1,050 samples from 205 patients with confirmed COVID-19, samples were positive in only 72% sputum specimens and 32% pharyngeal swabs while 29% had positive feces. New analyses continue to raise concerns about whether negative NP swabs are sufficient to clear patients. However, these analyses were conducted in China during an earlier phase of the epidemic and testing methods may now be better. According to one paper, “It is likely that lower respiratory samples (e.g., minibranchial alveolar lavage) are more sensitive than a nasopharyngeal swab … it is important to emphasize that, depending on the clinical presentation, a negative RT-PCR result does not exclude COVID-19.”

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

Treatment

● For the vast majority of COVID-19 cases, treatment includes supportive care.
● See interim guidance on COVID-19 management from American Thoracics Society.
● ACEi/ARBs/NSAIDs: SARS-CoV-2 utilizes ACE2 for binding, which raises a potential role for ACEi/ARBs/NSAIDs, all of which impact ACE2.
  ○ 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.
  ○ Because of their effects on ACE2, some have hypothesized that ACEi/ARBs may be harmful. However the ACC/AHA released a statement advocating for the continuation of these agents and other medical experts have cautioned against the discontinuation of proven therapies due to hypothetical concerns.
  ○ Some research suggests ACEi/ARBs are safe while others have suggested ARBs may be a therapeutic option. In fact, a clinical trial has been proposed to evaluate their use in treating COVID-19.

● Hydroxychloroquine/Chloroquine: Though rigorous clinical trial data are not yet available, in vitro data suggest a potential benefit for hydroxychloroquine/chloroquine in treating COVID-19. Based on these medications’ cellular interaction with the virus, investigators advocate further research into the therapeutic potential of hydroxychloroquine/chloroquine.
  ○ In a non-randomized study, patients with COVID-19 pneumonia benefited from Hydroxychloroquine. This led investigators to advocate for its continual study.
  ○ With limited evidence but lack of alternative proven therapy, the CDC suggested the use of Hydroxychloroquine, while acknowledging its risk of use. The FDA has now enacted its emergency use. These decisions have led to much controversy.
  ○ As the debate continues, two small non-peer reviewed randomized studies have shown seemingly contradictory results. In one study, hydroxychloroquine made no difference in regards to fever improvement and negative PCR. In another study, hydroxychloroquine showed significant improvement in symptoms and pneumonia (by CT scan).
Given the lack of clear evidence to support hydroxychloroquine, medical experts have asked clinicians to exercise caution and to consider the risk of the medication--notably the potential cardiac complications. Because the data is still unclear, there are several ongoing trials of hydroxychloroquine.

- **Hydroxychloroquine and Azithromycin**: A small non-randomized study -- which subsequent to publication received an expression of concern from the sponsoring society -- has suggested a benefit of combining hydroxychloroquine with azithromycin for treating COVID-19. Larger studies are needed to further evaluate the safety of combining these meds, as the combination of the two can potentiate cardiac complications.

- **Convalescent serum**: In response to new encouraging but small and uncontrolled studies, the FDA has approved convalescent serum for COVID-19 treatment under an emergency Investigational New Drug (IND) application.

- **HIV protease inhibitors**: Lopinavir-Ritonavir (Keletra) is being investigated, but in the most recent study it failed to show improvement over standard of care.

- **Remdesivir**: The nucleoside analog Remdesivir was theorized to be effective in MERS and has been advocated for its use in COVID-19. Due to an overwhelming demand of Remdesivir for compassionate use, the medication is now restricted for two trials looking at its use in moderate and severe disease. The makers of Remdesivir are attempting to make it more available via an expanded access program.

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

- **Immunomodulators**: Because a cytokine storm may be the catalyst for severe disease, clinicians are investigating immunosuppressants which target IL-6. Early indication shows Tocilizumab (Actemra) to be effective in severe cases and its use has been advocated. Two major studies are now underway. Similarly, Sarilumab (Kevzara) is under investigation.

- **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.

### Intensive Care Unit (ICU)

- The ICU lies on a continuum of care (community, outpatient, inpatient ward/telemetry/ICU, discharge or death). Prevention and treatment in one part of the continuum have effects throughout the continuum with implications for resource availability.

- Useful overviews in: JAMA; Internet Book of Critical Care; Cochrane review.

- Common complications include:
  - Acute Respiratory Distress Syndrome (ARDS) diffuse alveolar damage, pneumocytes with viral cytopathic effect implying direct viral damage.
  - 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.

- Clinical markers include: elevated C-reactive protein and ferritin
● **Current management** largely involves supportive care
  ○ Early invasive ventilation/Personal Protective Equipment
  ○ ARDSnet lung protective ventilation protocol
  ○ Conservative fluid resuscitation, Early vasoactive support.

● **Prone Positioning and ARDS**- A recent small study has shown the potential benefit of prone positioning for ventilated COVID-19 patients with ARDS.

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

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

● Published resources include:
  ○ 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

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

● 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)

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**Prognosis and Outcomes**

● **Prognostic factors**: 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. Elevated LDH, CRP and D-dimer, and reduced platelet and lymphocyte counts were associated with severe disease.

● **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).

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

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

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

**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.”
- There does seem to be immunity in other primates.

**Pediatric Populations**
- CDC data from Feb 12–April 2, 2020 reported 2,572 (1.7%) of 149,760 lab confirmed COVID-19 cases in US were aged <18 (median age 11) but had limited data on clinical course confirmed it was generally mild (https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6914e4-H.pdf)
- Among 2,143 Chinese children with likely COVID-19, few developed severe infection:
  - 55% asymptomatic-mild (4% asymptomatic), 39% moderate (pneumonia, dry cough, fever, lung lesions), 5% severe (fever, cough, GI symptoms, shortness of breath, decreased oxygen saturation), and 0.6% critical (respiratory failure, heart failure, multi-organ dysfunction)
  - Infants (<1 year) are more likely to have severe infection (10.6%).
- Children were mostly infected by household and child-to-child transmission.
- Fecal-oral transmission may be possible based on studies in children.
- Recommendations for COVID-19 in children address differences by severity of disease.
- CDC resources regarding children and COVID-19
- American Academy of Pediatrics (https://downloads.aap.org/AAP/PDF/COVID%2019%20Initial%20Newborn%20Guidance.pdf) has issued recommendations for the care of infants delivered by COVID-19 positive or suspect mothers including bath after birth, protective clothing for health care workers

**Pregnant Women and Breastfeeding**
- Limited data but pregnant women (third trimester) with COVID-19 had a similar clinical course to that of non-pregnant adults.
- Preterm delivery in ~50% of pregnant women (n=32) hospitalized with COVID-19.
- Among 6 babies delivered by C-section to women with COVID-19, all had anti-COVID antibodies (IgG) and two had IgM (which does not usually cross the placenta), raising concern about transplacental infection.
- Studies of similar coronavirus infections (MERS, SARS) found increased fetal loss for first term infection and also observed increased preterm birth for later infection.
Recommendations for the care of pregnant women with a flowchart of steps in care.

CDC recommendations for care of pregnant women and breastfeeding: A mother with COVID-19 may continue breastfeeding since the virus does not appear to be present in breast milk but should “wash her hands before touching the infant and wear a face mask, if possible, while feeding at the breast.”

The Elderly

- Risks increase with increasing age and comorbidities.
- **Comorbid cardiovascular disease increases risk of death** (acute coronary syndrome due to inflammation, depressed myocardial function, arrhythmias)
  - In >400 hospitalized patients in Wuhan, 20% had cardiac injury with elevated cardiac biomarkers (e.g., HStroponin), older in age (mean 74 years vs 60 years), and amongst those with cardiac injury, 50% died.
- **US:**
  - CDC resources for and about elderly
  - Nursing home near Seattle: 167 cases in 101 residents, 50 health care personnel, and 16 visitors. The case fatality rate for residents was 33.7%.
- **China:**
  - Mortality for persons >59 in Wuhan was 5.1 times that of persons 30-59 years
  - 191 hospitalized adults, in 54 decedents, mean age 69 years while in 52 discharged survivors, mean age 52. Adjusted odds of death increased by 10% per year of age (p=0.004).
- **Italy:**
  - As of March 17: **7.2% case fatality rate** (1,625 deaths)
  - Of those who died, mean age 81+ y; 2/3 had diabetes, cardiovascular disease, cancer, or smokers.
  - Men more likely to die than women and younger at death
  - Limited ventilator supply restricts use to younger patients

Palliative Care and Ethical Considerations

- During pandemics, a triage plan should include palliative care.
- **WHO** and **CDC** developed ethical guidance for pandemic influenza.
- A discussion paper from the National Academy of Medicine aims to assist in healthcare planning and application of Crisis Standards of Care for COVID-19.
- The Hastings Center suggests an ethical framework for healthcare institutions during the novel coronavirus pandemic by managing uncertainty with planning, safeguarding communities, and guiding practice.
- Italy’s SIAARTI’s Ethics Section Recommendations: intensive care treatments to aid in provider moral distress, transparency, and allocation of scarce resources.
● In Italy, ethical concerns have arisen regarding patients dying alone in hospitals without family or palliative care. In the unusual case of limited ventilator resources, an article in the NEJM calls for a volunteer committee of respected clinicians and leaders to assist in decision-making regarding withdrawing ventilator support, communicating with families, and empowering an expert palliative care team to intervene in order to buffer clinicians from disabling distress, providing symptom management and family support.

● A NEJM article provided 6 recommendations regarding allocation of resources during pandemic to include maximizing benefits of resources; prioritizing care for front-line healthcare workers; not to allocate based on a first-come, first-serve basis; respond quickly to evidence; recognize research participation; and applying same principles to COVID and non-COVID patients.

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

● Care for vulnerable populations: A Hastings Center report highlights that providing high quality care for vulnerable patients globally is both ethical and necessary to ensure Americans’ health.

● Ethical considerations surrounding masks: In the setting of mask shortages, experts have highlighted the role of government officials in discouraging hoarding in order to protect the safety of frontline healthcare workers.
Section 4: Preventing Spread in Healthcare Settings

Personal Protective Equipment

- Updated infection prevention advice from CDC specific for COVID
- Nature paper on aerosolization suggests face masks may be useful in preventing spread from asymptomatic individuals and BMJ analysis favoring masks for general public
- General infection precaution advice from the CDC for healthcare providers Personal protective equipment recommendations for close patient interaction include:
  - N95 respirator mask if available, medical facemask if not.
  - N95 strongly preferred when performing aerosol-generating procedures.
  - Eye protection: goggles or disposable face shield that covers front/sides of face.
  - Gloves
  - Gown use is preferable but can be prioritized for aerosol-generating procedures, anticipated splashes and sprays, high-contact activities.
- Before/After Work: coming home from work guide on how to stay safe American College of Emergency Physicians
- CDC infographic on donning and doffing PPEs.
- HCW need to be prioritized for testing and care else healthcare systems risk absenteeism
- Equipment Supplies: CDC suggested strategies to optimize facemasks supply, including use of homemade masks; FDA issued guidance on preserving gloves and ventilators.
- Reuse of N95 Masks Duke has begun a novel initiative to decontaminate N95 masks and allow for their reuse, which they are currently evaluating. A website is collating data about different decontamination practises for N95 masks.

Hospital Precautions

- With appropriate adherence to evidence-based infection control practices, in-hospital COVID-19 transmission among patients and healthcare workers appears to be low.
- Nevertheless, there are reports out of Italy, Spain and China strongly suggesting in-hospital transmission, perhaps due in part to suboptimal adherence to infection control practices.
- Limit visitors and traffic.
- Patients with known or suspected COVID-19 should be placed in a single room with a door closed and a dedicated bathroom, and should wear a facemask.
- Airborne infection isolation rooms should be reserved for patients who will be undergoing aerosol-generating procedures.
- Caution when considering high-flow nasal oxygen or noninvasive ventilation as increased risk of dispersion of aerosolized virus.
- Facilities could consider designating entire units within the facility, with dedicated HCP, to care for known or suspected COVID-19 patients.
- Some Asian countries cohorted healthcare workers and patients, though rigorous evidence that these measures were effective are lacking:
  - Singapore’s Ministry of Health limited doctors to a single facility. Singapore also limited movement of patients and healthcare staff between facilities.
○ Many Asia countries developed dedicated hospitals and units exclusively for treating patients with COVID-19.
○ There are not rigorous studies evaluating the extent to which cohorting – rather than other measures – explains the success of other Asian countries in containing COVID-19.

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

Airway Management and Intubation

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

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

Managing Exposures in Healthcare Settings

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

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

The Four S’s of Disaster Relief Planning:

**Staff**
- Interim CDC guideline for healthcare facilities emphasizes preparation for potential personal protective equipment supply and staff shortages.
- **Surge planning** includes anticipating absenteeism in response to contagion and planning for staff shortages, while supporting staff to prevent this
  - Create registries of volunteers, plans for emergency or rapid credentialing.
  - Coordination with military medical 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

**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

**Space/Structure**
- Increasing hospital capacity is the most commonly cited factor.
- 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

**Systems**
- 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.

### 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 COVID era.

● Practices can consider proactively identifying patients with long term health conditions and elderly to avoid interruptions in care.

● Professional societies have suggested limiting elective medical care

● **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 COVID era.

### Surgery

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

### Supplemental Resources:

● 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

- Covid-19 is caused by the SARS-CoV-2 virus, which is a coronavirus.
- 7 coronaviruses infect humans: 4 cause colds, plus SARS, MERS and COVID-19. Many more (100s) in animals, and closest relatives so far found to SARS-CoV-2 are in bats.
- Spike protein on the outside of the virus binds to ACE2 and helps determine tropism (alveolar epithelial type II cells, upper respiratory tract). Soluble recombinant ACE2 inhibits the virus in vitro and is a potential therapy.
- Entry also requires a low pH step (endosome) which chloroquine blocks, hence suggested drug.
- Other antiviral drugs are being evaluated for cross-reactivity against coronavirus proteins. These include HIV drugs and influenza drugs.
- SARS-CoV-2 is an RNA virus, so RNA replication is also a drug target. This is the basis of the nucleoside analog inhibitor remdesivir.
- Other candidate drugs such as EID-2801 act by increasing the virus’ mutation rate to a point of ‘lethal mutagenesis’.
- Study has identified human cell partners of 26 of the 29 unique coronavirus proteins, and lists 69 potential drugs that could target those interactions.
- RNA viruses can mutate rapidly, however so far SARS-CoV-2 shows limited mutation. Early reports of strains evolving to have greater virulence have been disputed.
- Differences in circulating strains can identify origins of outbreaks. For example New York was seeded mostly by European introductions.

Vaccine Development

- Both traditional and newer technologies are being deployed in a race to make an effective safe and scalable vaccine.
- First vaccine trial is Moderna’s mRNA vaccine (mRNA-1273). mRNA is injected and makes the spike protein inside the body. Using mRNA is much faster to develop than traditional recombinant or viral vector vaccines. Trial in Seattle started 16 March 2020.
- Vaccine challenges:
  - Efficacy - will it make the right type of immunity, with an effective combination of either neutralizing antibodies or T cell responses?
  - Safety - some vaccines can make infections worse through eg antibody-dependent enhancement of entry into cells.
  - Time - even fast-tracked vaccines take time to demonstrate safety and efficacy.
- J&J announced intent to partner with US DHHS, to start clinical trials by September 2020, deliver first vaccine for emergency use in early 2021, and supply one billion vaccines worldwide for emergency pandemic use.
• Tobacco plants are being evaluated to make a vaccine, using a rapid and large-scale technology that was previously effective for an Ebola vaccine.
• The anti-TB vaccine, BCG, has been suggested to confer some protection and vaccination is being tested in Australia and the Netherlands as a way to boost immunity against Covid-19.
Section 7: Public Health Considerations

Simulations

- Without interventions, mortality in the U.S. would peak in mid-June with ~55,000 deaths per day and culminate with 2.2 million fatalities.
- A model developed at USC accounting for underlying conditions and age projects 5,500 hospitalizations in the Service Planning Area covering Metropolitan Los Angeles, our main catchment area, by 100 days with a reproductive number of 2.2 and by 250 days with a reproductive number of 1.5.
- Two scenarios reflecting various combinations of interventions:
  - **Mitigation strategy**: Goal is to reduce the health impact and not to interrupt transmission completely. Strategy includes closure of schools and universities, case isolation and household quarantine, social distancing of those aged over 70. Duration: 3 months.
  - Contact tracing: Testing, contact tracing and isolation of contacts strategies have the best chance of breaking the chain of transmission, as was accomplished in China and is being accomplished in South Korea.
  - **Suppression strategy**: Goal is to reduce the average number of secondary cases each case generates. Strategy includes closure of schools and universities, case isolation, population-wide social distancing, and household quarantine. Duration: 5 months.
    - With close monitoring of disease trends, possibly relax measures temporarily as things progress but will need to be maintained until a vaccine becomes available (18 months).
    - A **suppression strategy** could reduce deaths by about 49% and peak ICU beds needed by about 67%.
- The U.S. needs approximately 295,000 ICU beds under the worst case scenario.
  - Currently, there are 96,596 critical care beds where two-thirds are likely occupied by other non COVID-19 patients.
  - Tsai et al. estimated assuming a 40% population infection rate, if transmission occurs over six months, the need for hospital beds will be at 274% of capacity, and the ICU need will be 508% of capacity.
- Another simulation model from the Institute of Health Metrics and Evaluation projects that with current social distancing policies in place, peak resource need will occur in the second week of April.
  - Peak demand for ICU beds is expected to exceed capacity by about 25%, and the U.S. will need about 16,500 ventilators.
  - In California, the peak is expected to be much lower than other parts of the country, and is not expected to cause shortages of ICU beds, hospital beds, or ventilators.
○ Total number of deaths in the U.S. attributable to COVID-19 is expected to be 60,000 [~18 deaths per 100,000], with approximately 1,600 in California [~4 deaths per 100,000]

Approaches to Easing Social Distancing Restrictions

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

- **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.

- **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.
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