# Coronavirus COVID-19 (SARS-CoV-2)

Paul G. Auwaerter, M.D.

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# MICROBIOLOGY

- Coronaviruses
  - Positive sense, single-strand enveloped RNA virus belonging to the family *Coronaviridae*.
  - Coronavirus name derived from the Latin *corona*, meaning crown. Viral envelope under electron microscopy appears crown-like due to small bulbar projections formed by the viral spike (S) peplomers.
- This topic covers the novel coronavirus 2019 (2019-nCoV) now referred to as SARS-CoV-2.
- For discussion of other coronaviruses, see individual highlighted modules:
  - Coronavirus for common human respiratory coronavirus infections.
  - SARS for the SARS-CoV virus, not known to circulate since 2002-2003.
  - MERS for the MERS-CoV virus, causing sporadic infections, mostly in the Arabian peninsula since 2012.
  - Coronaviruses also commonly infect birds and mammals causing gastroenteritis and respiratory infections.
- SARS-CoV-2 appears to have been a zoonotic infection that has adapted to humans.
  - Origin is uncertain although bats implicated.
  - Genetic analysis shows a great similarity to bat SARS-like coronavirus (genus *Betacoronavirus*, subgenus *Sarbecovirus*).

# CLINICAL

- **COVID-19** (novel coronavirus disease-2019) is the disease, **SARS-CoV-2** is the virus.

### Epidemiology

- COVID-19 Cases
  - Reported in most countries performing testing and all continents except Antarctica.
    - Declared a pandemic by the WHO.
  - Real-time global reports available through Coronavirus COVID-19 Global Cases Dashboard by Johns Hopkins CSSE.
- Risk groups
  - Older age, especially > 65 yrs and people with comorbidities appear more likely to develop an infection and severe symptoms and be at risk for death.
  - Younger adults are also being hospitalized in the U.S.

        - Adults 20–44 account for 20% of hospitalizations, 12% of ICU admissions.
    - Children appear less symptomatic with infection and less prone to severe illness.
- Seasonality
    - Although typical respiratory coronaviruses are seen mostly in winter in the Northern Hemisphere, in some countries, such as Thailand, they circulate year-round.
        - Unclear if SARS-CoV-2 will follow the traditional respiratory season with a decrease in the late spring and summer.
        - MERS-CoV is now seen sporadically year-round but more so during wintertime.

**Transmission**

- By respiratory droplets and by fomite. Virus found in respiratory secretions and saliva.
- Viral shedding by asymptomatic people may represent 25–50% of total infections.
    - VIral shedding may antedate symptoms by 1–2 days.
    - Viral titers are highest in the earliest phases of infection.
- Why widespread and rapid transmission occurs is not completely certain, and is provoking changes in public health recommendations as well as anxieties.
    - Asymptomatically infected people who shed and spread is a likely explanation.
        - People who are not ill, will not as carefully take measures to avoid spread.
        - This is in large part the rationale behind universal mask use.
    - Aerosol spread could occur, thought to be mostly in hospital settings
        - Airborne transmission frequency is debated.
        - Some widely publicized evidence is based on experimental aerosolization rather than human studies.
        - To date, there has not been a well document case of aerosol transmission (e.g., through HVAC ventilatory systems or airplanes).
- Stool shedding also described later in disease, but uncertain what role, if any, that plays.

**Incubation period**

- Mean of 6.4 days, range 2–12.
- For people quarantined, 14d observation recommended to exclude infection, though 24d asymptomatic time from exposure described.
- Viral shedding occurs following recovery, but unclear what role this plays in transmission.
- Children and intrafamilial spread appear to be a growing means of transmission.
- Some suggest that high viral load may equate with disease severity, but studies to date have not standardized.

**Symptoms**

- Fever (44%–98%)
    - Range may be lower at initial hospital presentation or in the outpatient setting

- Cough (46–82%, usually dry)
- Shortness of breath at onset (31%)
- Myalgia or fatigue (11–44%)
- Loss of taste or smell
    - Potential sign in early infection, but not unique to COVID-19 as may be seen with other viral infections.
- Less common symptoms:
    - Pharyngitis
    - Headache
    - Productive cough
    - GI symptoms
        - Have been described as a presenting symptom, and potentially heralding more severe illness.
    - Hemoptysis

**Disease spectrum**

- ~80% of infections are not severe and some may be asymptomatic.
- Illnesses caused by the virus can be either upper and lower respiratory tract infections.
- For hospitalized patients with pneumonia, limited studies suggest the disease course (Wuhan experience and others):
    - ~50% develop hypoxemia by day 8
        - Severe illness and cytokine release syndrome appear to develop mostly within 5–10d after symptom onset in susceptible patients.
        - Markers of severe infection include regular high fevers (>39°C), RR > 30, worsening oxygen requirements (4–6L nasal canula), also elevated IL-6 levels (> 40–100), CRP (>10x normal), ferritin (> 1000), d-dimer (>1).
    - ARDS develops in 17–29%
    - Patients in the ICU require:
        - Non-invasive ventilation (42%)
        - Mechanical ventilation (47%)
        - High-flow $O_2$ (11%)
        - ECMO (2-5%)
- Critical Illness experience (Washington State)[7]
    - Small patient series (n = 21)
        - Age: 70 (mean)
        - Comorbidities: in 86%
        - Duration of symptoms: 3.5d (mean)
            - Admission to ICU within 24h of hospitalization: 81%
        - Nearly all had radiographic abnormalities at presentation.
            - Leukopenia: in 67%
        - Mechanical ventilation: in 71%
            - ARDS in 100% of those who required mechanical ventilation, most developed within 72h.
        - Most patients were not in shock, but 67% received vasopressors.
        - Cardiomyopathy: developed in 33%

        - Unclear if direct viral effect v. critical illness stress
    - Mortality: 67% (as of publication date)

**Viral kinetics/immunopathogenesis:** three scenarios described[15]

- Paucisymptom patient: nasopharyngeal high viral titer (and virus in feces)
- Symptoms then decompensation (~day 10, respiratory decompensation): low viral titer compared to earlier in nasopharyngeal samples
- Progression/death: high viral titers in upper and lower respiratory samples plus persisting viremia.

**Differential diagnosis**

- Cannot easily distinguish from other causes of viral respiratory infection such as influenza or community-acquired pneumonia based only on clinical grounds,

**COVID-19 testing**

- With limited testing capacities in many locations, clinicians should use their judgment to determine if a patient has signs and symptoms compatible with COVID-19 and whether the patient should be tested.
- The most common symptoms include fever (subjective or confirmed) and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing) or initial nausea/vomiting/diarrhea.
- Other considerations that may guide testing are epidemiologic factors such as the occurrence of local community transmission of COVID-19 infections in a jurisdiction.

**Priorities for Testing Patients with Suspected COVID-19 Infection (CDC)**†

**Priority 1**

Ensures optimal care options for all hospitalized patients, lessen the risk of healthcare-associated infections, and maintain the integrity of the U.S. healthcare system.

- Hospitalized patients
- Healthcare facility workers with symptoms

**Priority 2**

Ensures those at highest risk of complications of infection are rapidly identified and appropriately triaged.

- Patients in long-term care facilities with symptoms
- Patients 65 years of age and older with symptoms
- Patients with underlying conditions with symptoms

- First responders with symptoms

**Priority 3**

As resources allow, test individuals in the surrounding community of rapidly increasing hospital cases to decrease community spread, and ensure the health of essential workers.

- Critical infrastructure workers with symptoms
- Individuals who do not meet any of the above categories with symptoms
- Healthcare facility workers and first responders
- Individuals with mild symptoms in communities experiencing high numbers of COVID-19 hospitalizations

**Non-priority**

- Individuals without symptoms

†*Source*: U.S. Centers for Disease Control and Prevention. Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19) Revised March 24, 2020.

**Other Diagnostic Testing**

- **In COVID-19 pneumonia**
  - Leukopenia in ~70% of hospitalized patients.
  - LDH may be modestly elevated.
  - LFTs elevated more commonly than in typical Community-Acquired Pneumonia cases.
  - Chest CT may show ground-glass opacities that may evolve into consolidation or ARDS.
    - Findings appear to peak at 10d of illness, resolution begins after day 14.
    - CT may show lung findings (such as ground-glass opacities) before the development of symptoms.
  - Among hospitalized patients, about one-third need to be in the ICU/intubated with an ARDS picture.
    - Elevations in IL-6 (> 40–100), CRP (> 10x normal), ferritin (> 1000) suggested correlating with a cytokine release syndrome-like picture and impending ARDS.
- **Confirmatory tests, molecular (PCR)**
  - Initially, all testing only done at CDC, but in U.S. local health departments and other approved labs able to test once assays validated, per FDA.
    - FDA has announced that they are allowing labs and hospitals around the U.S. to conduct testing.
      - The availability of testing growing, but capacity remains limited in many parts of the U.S.

            - Quest and LabCorp offer PCR testing (3–4d turnaround), specimens must be performed in a medical office/institution, not at a laboratory site.
            - Rapid molecular tests now offered (GeneXpert Cepheid < 45 min, ID NOW COVID-19 Abbot < 15 min).
            - List of molecular tests approved under emergency use authorization (EUA) by the FDA.
        - PCR sensitivity not known accurately
            - Likely < 90% depending on the assay used, sample procurement methods and stage of illness.
            - Second and third NP swabs described as needed in some patients; lower respiratory specimens (e.g., BAL) may offer superior yields.
    - Testing expanded for all people with respiratory symptoms and fever to be considered, significantly increasing the number of potentially tested patients.
        - Prior CDC Person Under Investigation (PUI) criteria that require close contact with a confirmed case, travel to Hubei province or travel to mainland China or country with a large number of cases (e.g., Iran, Italy).
        - As testing is limited, there are practical issues that are controversial:
            - Testing all who have respiratory tract symptoms would be helpful to limit the spread and free people from concern if not infected, but there is not currently sufficient testing capacity.
            - Putting all patients with undiagnosed pneumonia in airborne isolation not likely possible given resource limitations.
- **Serological testing**
    - In the U.S., since FDA has allowed bypass of federal approval, more assays will become available soon including point-of-care testing.
        - List of serological tests approved under emergency use authorization (EUA) by the FDA.
    - However, reservations remain about the utility of available antibody tests and how trustworthy they may be for clinical decision making.
        - Many currently offered tests may not have been sufficiently clinically validated.
        - FDA has warned not to use these tests yet to implicate authentic infection, protective immunity, or to rule out infection.
            - Cannot rule out infection except with molecular respiratory tests.
            - Positive results may be due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as coronavirus HKU1, NL63, OC43, or 229E.
    - Serologic response
        - One study found the serologic response to a recombinant SARS-CoV-2 nucleocapsid: IgM 85.4%, IgA 92.7% (median 5d after the onset of symptoms), and IgG 77.9% (14d after onset).[8]
        - Another study from China using IgM and IgG SARS-CoV-2 specific antibodies found < 40% seropositive if illness less than 7d, rising to ~100% 15d or more after onset.

        - The contribution of asymptomatic persons with SARS-CoV-2 to the transmission is not well characterized but will be much better understood when validated antibody testing available.
- **Viral culture**
    - Not recommended
- Currently commercially available respiratory multiplex molecular panels WILL NOT detect COVID-19.
- Additional details and specimen procurement can be found on the CDC website.
- See the Prevention section for screening recommendations.

**Mortality**

- Note that early data are from China; there appears to be great variability among countries with Italy appearing higher than others.
- The mortality rate from recent re-analysis of China experience [9th report, WHO Collaborating Center Imperial College, London, UK]
    - Wuhan case fatality rate: 1.38% (0.66% if asymptomatic cases are included)
    - The actual rate remains uncertain due to insufficient of serological testing as well as underreporting.
- The mortality rate is less than that commonly ascribed to severe community-acquired pneumonia (12–15%) but more than seasonal influenza (~0.1%) by 6–10x.
- Most deaths in patients with comorbidities and often elderly (> 60 considered a "risk factor"), although healthy younger patients also described.

COVID-19 Mortality by Age and Pre-Existing Condition*

| Age (yrs) | Case Fatality Rate (%) |
|---|---|
| 80 | 14.8 |
| 70-79 | 8.0 |
| 60-69 | 3.6 |
| 50-59 | 1.3 |
| 40-49 | 0.4 |
| 30-39 | 0.2 |
| 20-29 | 0.2 |
| 10-19 | 0.2 |
| 0-9 | None |

Case fatality rate for COVID-19 based on age and pre-existing conditions.

*Case Fatality Rate (%) = (number of deaths / number of COVID-19 cases) x 100 for each group

*Source*: Worldometers.info. Accessed 14 March 2020.

- Mortality rates in the US from early data (March 2020) compiled by the CDC:

Mortality rates for reported COVID–19 cases, by age group —United States[†]

| Age (yrs) | Mortality Rate |
|---|---|
| ≥85 | 10–27% |
| 65–84 | 3–11% |
| 55-64 | 1–3% |
| 20–54 | < 1% |
| ≤19 | 0% |

[†]Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep*. ePub: 18 March 2020.[11]

# SITES OF INFECTION

- Pulmonary
  - Co-infection with other viruses described.
- GI
  - Some patients have nausea, vomiting, or diarrhea at the onset.
    - May herald more serious disease.
  - The virus has been recovered from stool, but the significance is uncertain.

# TREATMENT

## General

- Supportive care, including oxygen, mechanical ventilation if needed.
  - Prone positioning appears helpful if worsening despite intubation and ventilation.
  - Johns Hopkins Medical Institution Guidance Document (PDF document) is available with frequent updates for a more complete discussion of risks/benefits for using off-label medications for COVID-19.
- Depending on the capabilities of local health systems, public health officials may recommend those with minor symptoms to stay home and not seek care in health clinics or hospitals.
  - Limit medical care to those who are short of breath, have severe symptoms, or require oxygen and supportive care that is only available in a hospital.
- **No proven efficacy of any drug for humans as of April 8, 2020**.

## Antivirals

**Caution is advised** as to whether any are effective or safe for COVID-19.

- A large number of antivirals and immunomodulators are being investigated for treatment or prophylaxis.
    - If a clinical trial available, consider enrolling patients rather than prescribing off-label drug use to assist in understanding whether intervention is efficacious for COVID-19.
    - If considering off-label use of available medication, consider data known, risks of drug therapy. Many limit considerations only to patients at high risk for serious COVID-19 disease.
- Many types of drugs under investigation include antivirals (protease inhibitors, influenza drugs, nucleoside analogs) anti-inflammatories, surface protein antagonists such as lecithins.[25]
- Much like with influenza, antiviral drugs if effective, likely need to be started early in infection course, or used as a preventative.

**Candidate therapies**: only widely discussed drugs listed below.

- Lopinavir/ritonavir (LPV/RTV) widely used in China and elsewhere; however, COVID-19 RCT in hospitalized patients who also received other medications yielded no benefit but was given relatively late in the disease course.[6]
- **Chloroquine**(CQ) or hydroxychloroquine (HCQ)
    - Reported to have some efficacy *in vitro* and in limited, very low-quality evidence for COVID-19 pneumonia, the mechanism may be by interfering with cellular acidification in the phagolysosome.[18],[19]
        - Much hype and preliminary reports of efficacy are from press releases or small studies.
    - Gautret et al. suggest decreased SARS-CoV-2 shedding in non-RCT of 36 patients; 6 patients in a post-hoc analysis who received HCQ combined with azithromycin had further viral carriage reduction.[10]
        - Original journal accepting this paper has withdrawn it from consideration due to the paper not being of the characteristics and standards for the journal.
        - Small sample size, lack of clinical outcomes, exclusion of patients who died or went to ICU, lack of paired stepwise statistical comparison means clinicians ought to not base decisions on these limited results, despite the widely interpreted lay conclusion that that HCQ + AZ is an effective combination.
    - Chen et al in an unpublished RCT of 30 patients did not find HCQ provided benefit.[31]
        - The study suggests that if HCQ has an impact, it is likely small.
    - Chloroquine is not generally available in the U.S., many reporting shortages of hydroxychloroquine.
    - HCQ may cause prolonged QT, and caution should be used in critically ill COVID-19 patients who may have cardiac dysfunction or if combined with other drugs that cause QT prolongation.

- **Remdesivir** (Gilead; used to treat Ebola)
  - Currently, in trials in Wuhan and U.S.; activity is seen *in vitro* with SARS-2-CoV, MERS-CoV (also including MERS-CoV primate studies).
  - Likely the most promising drug.
  - The drug has been used in the U.S. under compassionate use now limited only to pregnancy and children < 18 yrs.
- **Oseltamivir**
  - Frequently prescribed because of concern of influenza, which is clinically similar to COVID-19. No known effectiveness against SARS-CoV-2.
- **Baloxivir**
  - No known activity.
- **Favipiravir** (aka T-705, Avigan, or favilavir)
  - Anti-influenza drug available in China and Japan; in clinical trials.
- **Ribavirin**
  - Often proposed along with an interferon product to treat RNA viruses, in clinical trials.

# Immunomodulators

- Many agents under consideration in clinical trials or proposed roles.
- Most initial interest regards anti-IL6 agents, to interrupt hyperinflammatory responses that resemble cytokine release syndromes and cause lung injury.
- RCTs in progress to examine the impact on both early and late use of such drugs.
- **Tocilizumab**: an FDA-approved anti-IL6R agent for CAR-T cell cytokine release syndrome. Limited supplies in the U.S.
  - Unpublished study from China[32]
    - 21 total patients, 17 "severe" COVID-19, 4 critical illness
    - Lower $O_2$ requirements in 1 week and better CT findings
    - All survived
  - Anecdotal reports from large centers with experience suggesting some with rapid improvement with improved oxygenation often within 24–48 hrs of administration.
  - Some suggest it may be more effective earlier in the disease course (worsening pulmonary status, peri-intubation) than ARDS (many days on the ventilator) with lung and organ injury more advanced.
  - Dosing typically 8 mg/kg x single dose.
- Other potential drugs under discussion or study; some use anecdotally reported.
  - Sarilumab (anti-IL6R)
  - Siltuximab (anti-IL6)
    - 11 mg/kg IV x single dose
  - Anakinra (anti-IL1)
  - anti-GM-CSF
- Monoclonal antibodies, specific to SARS-CoV-2, in development.

# Convalescent plasma or serum; or IVIG

**Convalescent plasma or serum-containing neutralizing antibodies** against SARS-CoV-2

- Proposed as a useful treatment.
- RCTs for prophylaxis, early and late COVID-19 treatment are in progress.

- Plausibility based on successful historical use:
    - Bacterial diseases including toxin-based diphtheria, pneumococcal pneumonia)
    - Viral diseases in animal models.
    - Post-exposure prophylaxis for hepatitis A and B, mumps, polio, measles and rabies.
- Prior treatment studies
    - Suggest an impact on influenza, SARS, and Middle East Respiratory Syndrome (MERS).
    - In largest treatment study against SARS, 80 patients in Hong Kong who were treated prior to d14 had a shorter length of stay defined as discharge before d22.[28]
- Studies in COVID-19
    - An uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS showed improvements in clinical status after convalescent plasma containing neutralizing antibodies was administered.[9]
    - Other clinical trials with convalescent plasma are underway.
- Risks
    - Pathogen transmission (~1 per 2 million transfusions for HIV/HBV/HCV)
    - Allergic transfusion reactions
    - Transfusion-associated circulatory overload (TACO)
    - Transfusion-related acute lung injury (TRALI)
        - Risk < 1 per 5,000, potentially higher in COVID-19 due to pulmonary epithelial injury
        - Risk lower if routine donor screening includes HLA antibody screening of female donors with a history of pregnancy.
- Use under Emergency Investigational New Drug (eIND)
    - FDA has authorized an eIND for expanded access for convalescent serum
    - A licensed physician must request, but FDA does not provide the serum, rather the requestor must procure from a blood bank.
    - Eligible patients for use under expanded access provisions:
        - Must have laboratory-confirmed COVID-19
        - Must have severe or immediately life-threatening COVID-19
            - Severe disease is defined as:
                - Dyspnea,
                - Respiratory frequency ≥ 30/min,
                - Blood oxygen saturation ≤ 93%,
                - Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
                - Lung infiltrates > 50% within 24 to 48 hours
            - Life-threatening disease is defined as:
                - Respiratory failure,

        - Septic shock, and/or
        - Multiple organ dysfunction or failure
    - Must provide informed consent

**Intravenous immunoglobulin (IVIG)**

- Proposed as an intervention in the setting of viral-induced lung injury/ARDS that appears to be due to disordered regulatory T cells with a hyperimmune response.
- Better characterized in influenza-related ARDS, but COVID-19 appears similar.
- Pooled IVIG reduces immune responses through multiple mechanisms including lessening interrupting complement cascade, lessening activated CD4+ and cytotoxic CD8+ T cells.
- No clinical trial data to back use.

**Monoclonal antibodies** specific to SARS-CoV-2

- May become an alternative to convalescent plasma or serum when available.

# Prevention

- No vaccine is currently available.
    - Multiple candidate vaccines are in development.
    - Convalescent plasma or serum has been proposed; studies are underway.
- As a newly described virus, much remains to be learned.
    - Travel restrictions, quarantines, school/work closings, social distancing helpful to lower $R_o$ (contagiousness of infection) but whether to loosen or lift a considerable debate among public health officials and politicians.[3]
    - Difficulty sorting other causes of respiratory illness from the novel coronavirus, especially during influenza season.
- Healthcare workers and health systems in the U.S.
    - Recommend following CDC Guidance for Risk Assessment and Public Health Management of SARS-CoV-2 (2019-nCoV).[30]
    - Debate exists whether standard contact and respiratory droplet precautions are sufficient (as with SARS, MERS) versus aerosol/airborne precautions.
        - Current CDC recommendations are for aerosol (e.g., use of negative pressure isolation), but if resources strained, then pivot to droplet and standard precautions.
- General measures recommended:
    - Avoid sick individuals.
    - Wash hands with soap and water x 20 seconds before eating, after cough/sneezing or bathroom visits.
    - Social distancing maneuvers include keeping spacing >6 feet from other people.
    - Masks now universally recommended when in public.
    - Don’t touch the face, eyes, etc.
    - Stay home if ill.
    - Cover your sneeze.

    - Disinfect frequently touched household objects.
    - Current CDC recommendations do not suggest using a facemask for protection, though this is debated as a routine for all or special populations such as HCWs when interacting with all patients.

# Complications

- Heme: anecdotal reports of substantial rates of DVT and PE in critically ill patients. Some centers using low molecular weight heparin for prevention.
- CNS: Encephalitis or encephalopathy
- Secondary infection
    - Limited data on incidence because many COVID-19 patients are treated empirically with antibacterials for pneumonia.
    - Appears particularly in critically ill patients and those with prolonged hospitalizations.
    - Wuhan experience suggested a 10–20% incidence of bacterial and fungal infections, with a higher percentage in patients who died.
    - Anecdotal experiences growing regarding concern for the development of pulmonary aspergillosis.

# FOLLOW UP

- Early Wuhan experience suggested a case fatality rate as high as 4.3%, but likely 2% elsewhere in China.
    - Preliminary evidence suggests two strains of SARS-2-CoV circulating: one associated with milder illness (~30%), the other with severe illness (70%). Additional sequencing studies may help define if further mutations may lessen virulence and also help trace spread.
- Case fatality rates in other countries (as of March 2020) appear lower, but are higher in elderly, sick populations (e.g., Evergreen Health, Seattle, WA; Northern Italy).
- Preliminary evidence in humans and SARS-CoV-2 infected rhesus macaques suggest that reinfection does not occur.
- Most but not all patients recovered from COVID-19 producing neutralizing antibodies that are likely sufficiently protective against infection.
    - Coronaviruses immunity may not be long-lasting (e.g., 1 to 3 years) based on work with routine coronaviruses, SARS and MERS.
- Advice for COVID-19 (+) patients and self-isolation/quarantine:
    - Healthcare settings: current requirement is 2 sequential negative COVID-19 RT-PCR tests before airborne precautions can be lifted
    - Outpatients:
        - CDC
            - Three days without any fever or respiratory symptoms (not using cough suppressants, etc) and no less than 7d after symptom onset.
            - Patients who have impaired ability to make antibodies (e.g., immunosuppressed patients) are likely to shed virus longer.

    - WHO: 2 weeks, symptom-free

# OTHER INFORMATION

- Recommendations to consider testing for all respiratory symptomatic patients will be limited by the availability of SARS-CoV-2 testing.
- Severe illness is likely to strike the same populations at high risk for complications of seasonal influenza (e.g., elderly, immunosuppressed, and comorbidities).
- The case fatality rate is probably higher than seasonal influenza (≤0.1%) but may be lower than initially reported (~ 2-4%) but limited testing and lack of careful epidemiology survey makes this difficult to define but may be different in some countries as social distancing interventions and other factors differ.
    - Current estimates suggest COVID-19 is ~6-10x worse than seasonal influenza but has a steep age gradient.
    - Serological testing of larger populations will give a clearer picture of infectious impact.

# See also

- Coronavirus COVID-19 | Hopkins Guides Webinar (Video)

# References


1. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. *Travel Med Infect Dis*. 2020. [PMID:32145386]

   **Comment:** This parenteral agent appears to be the most promising agent from in vitro and animal data (from MERS-CoV). We await RCT information from China, hopefully, available in April 2020.

2. Colson P, Rolain JM, Lagier JC, et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020. [PMID:32145363]

   **Comment:** Raoult knows these drugs well from Q fever and Whipple's disease studies. Caution though is that preliminary in vitro data rarely translates into effectiveness in human infection, hence a plea to only trial drugs within an RCT. How this drug may work is alkalinizing the phagolysosome within cells and may have had some effectiveness in SARS. Early study in China of the in vitro activity of chloroquine against SARS-CoV-2, discovered during culture tests on Vero E6 cells with 50% and 90% effective concentrations (EC50 and EC90 values) of 1.13 μM and 6.90 μM, respectively (antiviral activity being observed when addition of this drug was carried out before or after viral infection of the cells)

3. Chinazzi M, Davis JT, Ajelli M, et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science*. 2020. [PMID:32144116]

**Comment:** Although extraordinary measures may have slowed or stopped COVID-19 in China, questions remain whether this is durable and at what cost to society? It may buy time but effective drugs or vaccines remain in the far future it seems. Authors suggest "the travel quarantine of Wuhan delayed the overall epidemic progression by only 3 to 5 days in Mainland China, but has a more marked effect at the international scale, where case importations were reduced by nearly 80% until mid-February. Modeling results also indicate that sustained 90% travel restrictions to and from Mainland China only modestly affect the epidemic trajectory unless combined with a 50% or higher reduction of transmission in the community."

4. Mizumoto K, Chowell G. Estimating Risk for Death from 2019 Novel Coronavirus Disease, China, January-February 2020. *Emerg Infect Dis*. 2020;26(6). [PMID:32168464]

   **Comment:** An early report and these typically have higher rates of infection due to concentrated, very ill patients than later in epidemics. Authors estimate of the risk for death in Wuhan reached values as high as 12% in the epicenter of the epidemic and ≈1% in other, more mildly affected areas. The elevated death risk estimates are probably associated with a breakdown of the healthcare system.

5. Liu W, Zhang Q, Chen J, et al. Detection of Covid-19 in Children in Early January 2020 in Wuhan, China. *N Engl J Med*. 2020. [PMID:32163697]

   **Comment:** A retrospective look at 366 children hospitalized for respiratory illness. SARS-CoV-2 detected only in 6 (1.6) of patients. Only 1 of the COVID children required ICU care. Of the COVID patients, fever and cough were common and four had pneumonia.

6. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020. [PMID:32187464]

   **Comment:** This trial did not yield benefits when given in hospitalized patients with c19. Whether the drug would work if administered earlier is unclear, but has low in vitro activity against this virus compared to HIV.

7. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA*. 2020. [PMID:32191259]

   **Comment:** Most notable finding is the high rate of cardiac complications that is unclear whether directly viral or related to critical illness. As this is a small series, further reports are needed to confirm.

8. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clin Infect Dis*. 2020. [PMID:32198501]

**Comment:** Authors used a nucleocapsid-based antibody for the detection of antibodies against SARS-CoV-2. IgM and IgA antibodies were found 5 days (IQR 3-6) after symptom onset, while IgG was detected on 14 days (IQR 10-18). Positive responses overall were seen as IgM 85.4%, IgA 92.7% and IgG 77.9% respectively. Considering both confirmed and probable cases, the positive rates of IgM antibodies were 75.6% and 93.1%, respectively. The detection efficiency by IgM ELISA is higher than that of qPCR method after 5.5 days of symptom onset. The positive detection rate is significantly increased (98.6%) when combined IgM ELISA assay with PCR for each patient compare with a single qPCR test (51.9%).

9. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*. 2020. [PMID:32219428]

   **Comment:** A small study of 5 patients who required mechanical ventilation who appeared to benefit from convalescent plasma containing neutralizing antibodies, though also received methylprednisolone and putative antiviral therapies directed against SARS-CoV-2 infection. Authors suggest that many parameters improved including in the 4 ARDS patients.

10. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020. [PMID:32205204]

    **Comment:** In this observational, non-randomized very small study (n=36) patients with SARS-CoV2 infection (6 patients were asymptomatic, 22 had URTI, 8 had LRTI) who received hydroxychloroquine 200 mg q8h for 10 days (n=20) were compared to controls (n=16, patients who did not receive hydroxychloroquine). On day 6, 70% of patients in hydroxychloroquine group clearance of virus compared to 12.5% in control group (p=0.001). Study excluded form analysis patients who were lost to follow up (e.g. escalation of care, death, incomplete treatment). No clinical outcomes were reported. Six patients in this study also received azithromycin along with hydroxychloroquine. Authors concluded that combination therapy was more effective in clearing virus, however this was not statistically significant and groups were not well balanced at baseline (e.g. more patients in monotherapy had lower CT values).

11. CDC COVID-19 Response Team. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(12):343-346. [PMID:32214079]

    **Comment:** US experience to date differs from China's experience in that a higher proportion of hospitalizations are among the not elderly.

12. Bourouiba L. Turbulent Gas Clouds and Respiratory Pathogen Emissions: Potential Implications for Reducing Transmission of COVID-19. *JAMA*. 2020. [PMID:32215590]

**Comment:** Wading into the aerosol v. droplet debate, the suggestion that forceful uncovered sneezes may cause infectious droplets to go beyond the 6 ft range currently advised by the CDC. This concern has prompted universal mask wear for HCWs, but also for the general public. There may be people who are not ill and therefore sneeze or cough, asymptomatic shedding and dispersing virus.

13. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020. [PMID:32213556]

    **Comment:** Paper suggests that some patients presented with GI symptoms as part of COVID-19, 11.4% of 651 in this study from Zheijiang University in Hangzhou. A caveat is their definition of GI included nausea only in addition to diarrhea and vomiting as they only needed one of the three to qualify for GI symptoms. They also suggested that patients who had GI had more severe COVID infection.

14. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. 2020. [PMID:32215618]

    **Comment:** Authors report on patients in earlier phases of COVID-19 infection, 20 (33.9%) reported at least one taste or olfactory disorder and 11 (18.6%) both. This is not unique though as other viral respiratory infections may also cause these symptoms.

15. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis*. 2020. [PMID:32224310]

    **Comment:** Series of only five patients from France; however, the descriptions of three potential phenotypes may offer insights into different viral- and Immuno-pathogenesis. 1. Paucisymptom patient: nasopharyngeal high viral titer (and virus in feces), 2. Symptoms then decompensation (~day 10, respiratory decompensation): low viral titer compared to earlier in nasopharyngeal samples and 3. Clinical progression/death: high viral titers in upper and lower respiratory samples plus persisting viremia.

16. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020. [PMID:31978945]

    **Comment:** An early report includes electron microscopy photomicrographs as well as sequence analysis of what is now termed COVID-19 disease and SARS-2-CoV virus.

17. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020. [PMID:32015507]

    **Comment:** Authors have sequenced what is now termed SARS-2-CoV. Its genome 79.5% sequence identify to SARS-CoV. Furthermore, it was found that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus.

18. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020. [PMID:32074550]

**Comment:** An early report that suggests the antimalarial chloroquine has shown efficacy against COVID-19 infection in Chinese trials. Of note, this drug has been tried for CHKV and others without good virological effect.

19. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020. [PMID:32020029]

**Comment:** Summary of earlier in vitro studies suggesting drugs that may work against COVID-19. Remdesivir is currently under investigation in the Wuhan epidemic. This drug has also shown activity in a rhesus macque module of MERS-CoV.

20. Bajema KL, Oster AM, McGovern OL, et al. Persons Evaluated for 2019 Novel Coronavirus - United States, January 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(6):166-170. [PMID:32053579]

**Comment:** People evaluated as per this report in the US mostly were those with a history of travel/contacts from Wuhan City, China which is the apparent epicenter of this epidemic. Of 210 people, 148 (70%) had travel-related risk only, 42 (20%) had close contact with an ill laboratory-confirmed 2019-nCoV patient or PUI, and 18 (9%) had both travel- and contact-related risks. Eleven of these persons had a laboratory-confirmed 2019-nCoV infection. Given reports now around the globe, it is unclear if testing only those with potential links to China is prudent, but the current availability of test kits from the CDC likely precludes wider testing until either FDA-approved or EUA approval is given to current commercially available respiratory panels to include COVID-19.

21. Benvenuto D, Giovanetti M, Salemi M, et al. The global spread of 2019-nCoV: a molecular evolutionary analysis. *Pathog Glob Health*. 2020. [PMID:32048560]

**Comment:** Strain analysis to date of COVID-19 suggests that they are very similar to bat SAR-like coronavirus.

22. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020. [PMID:32031570]

**Comment:** One of the initial major reports of the Wuhan COVID-19 epidemic. In this series, the median age was 56 and slightly more men (54%) affected. Predominant symptoms include fever, fatigue and dry cough. Leukopenia was seen in ~70%. Thirty-six patients (26.1%) were transferred to the intensive care unit (ICU) because of complications, including acute respiratory distress syndrome (22 [61.1%]), arrhythmia (16 [44.4%]), and shock (11 [30.6%]).

23. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology*. 2020. [PMID:32101510]

**Comment:** Chest CT shows early ground-glass infiltrates which may offer speedier "diagnosis" than PCR studies in an epidemic setting as a first finding if molecular assays not readily available.

24. Kam KQ, Yung CF, Cui L, et al. A Well Infant with Coronavirus Disease 2019 (COVID-19) with High Viral Load. *Clin Infect Dis*. 2020. [PMID:32112082]

**Comment:** No surprise, here an infant sheds high levels of the virus but is without symptoms. Children are well known "vectors" of viral infection often without significant disease is well known for regular coronavirus infections, influenza and others.

25. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol*. 2020. [PMID:32205870]

**Comment:** A look at the clinicaltrials.gov and Chinese clinical trial web sites that have registered trials.

26. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020. [PMID:32235945]

**Comment:** A small but well-conducted study looking at 9 cases with most patients on day 1 having mild or prodromal symptoms. Key findings include finding virus in upper respiratory tissues with no difference between nasopharyngeal and oropharyngeal speeding which was very high during the first week of illness, but not in stool. Viral RNA remained in sputum beyond the resolution of symptoms. Seroconversion occurred by day 7 in 50% of patients but by day 14 in 100%. Despite the knowledge gained about viral kinetics, this paper offers proof that illness may also present as a routine upper respiratory tract infection without pneumonia or lower tract symptoms.

27. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. [PMID:32217556]

**Comment:** Patients in this Chinese retrospective study were older (median 68 yrs), male (73%) and had cardiovascular disease, including hypertension. While ARDS was common, acute cardiac injury and heart failure were also felt to contribute to high mortality.

28. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-6. [PMID:15616839]

**Comment:** SARS paper that may inform COVID-19 infection. Benefit from convalescent plasma for treatment suggested by earlier discharge.


29. Interim Infection Prevention and Control Recommendations for Patients with Confirmed Coronavirus Disease 2019 (COVID-19) or Persons Under Investigation for COVID-19 in Healthcare Settings. *U.S. Centers for Disease Control and Prevention*. [https://www.cdc.gov…]
30. Interim U.S. Guidance for Risk Assessment and Public Health Management of Healthcare Personnel with Potential Exposure in a Healthcare Setting to Patients with Coronavirus Disease 2019 (COVID-19). *U.S. Centers for Disease Control and Prevention*. [https://www.cdc.gov…
31. Chen J, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19) PREPRINT, JOURNAL OF ZHEJIANG UNIVERSITY March 2020 [http://subject.med.wanfangdata.com.cn…]

    **Comment:** An unpublished study of 30 patients but in an RCT did not show a demonstrable effect with HCQ. This study while negative given its small size, does mean that if HCQ has an effect it is likely small, so a much larger study would be needed to show effect.

32. Xu X et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. Unpublished study. 2020 [http://chinaxiv.org…]

    **Comment:** Unpublished, a not yet peer-reviewed report from China on 21 patients in China hospitalized with COVID-19 and received tocilizumab. Most patients had a marked improvement in oxygen needs within 24h of IL6R mab administration. This suggests that interruption of a key cytokine might reverse the "storm" that appears to cause ARDS and further organ injury in a subset of patients.

33. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support, https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1 (accessed 4/5/20)

    **Comment:** Unpublished preprint, using an anti-IL6 mab, in 21 patients with advanced COVID-19 pneumonia or ARDS. Following administration, 33% (7/21) improved, 43% (9/21) stabilized without identifiable change, and 24% (5/21) worsened. This uncontrolled study suggests that if such a drug is helpful for cytokine release syndrome from COVID-19, it may be more difficult to improve the sickest, i.e., ill the longest and with most lung damage.


# Cross Links


- Baseline & routine testing
- Coronavirus COVID-19 | Hopkins Guides Webinar (Video)
- Hypertension Management
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- Coronavirus COVID-19 | Hopkins Guides Webinar (Video)
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