
Coronavirus COVID-19 (SARS-2-CoV)

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MICROBIOLOGY

- Coronaviruses are 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:
 - [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-2-CoV appears to have been a zoonotic infection that has adapted to humans.
 - Origin is uncertain although bats and pangolins currently implicated.
 - Preliminary genetic analysis shows a great similarity to bat [SARS-like coronavirus](#) (genus *Betacoronavirus*, subgenus *Sarbecovirus*).

CLINICAL

- COVID-19 is the disease, SARS-2-CoV is the virus.
- Transmission
 - Respiratory and likely by fomite. Virus found in respiratory secretions and saliva.
 - Stool shedding also described, 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.
- Cause of upper respiratory tract disease and pneumonia.
 - The most common symptoms include fever, fatigue, and dry cough.
 - Fever (83-98%)
 - Cough (46-82%, usually dry)
 - Myalgia or fatigue (11-44%)
 - Shortness of breath at onset (31%)

- Less common symptoms:
 - Pharyngitis
 - Headache
 - Productive cough
 - GI symptoms
 - Hemoptysis
 - Estimates are ~80% of infections non-severe, including asymptomatic infection likely.
 - The mortality rate is thought to be $\leq 2\%$, but precise numbers uncertain due to a lack of available serological testing.
 - The mortality rate is less than that commonly ascribed to severe [community-acquired pneumonia](#) (12-15%) but more than [seasonal influenza](#) (~0.1%).
 - Most deaths in patients with comorbidities and often elderly (> 60 considered a "risk factor"), although healthy younger patients also described.
 - Epidemiology
 - China remains with most reported cases, but as of March 2020, upswing in many countries including especially S Korea, Italy, US (California, Washington state).
 - COVID-19 cases described in many countries, and all continents except Antarctica.
 - Real-time global reports available through [Coronavirus COVID-19 Global Cases Dashboard by Johns Hopkins CSSE](#)
 - Average age appears to be in the mid- to late 50s with slight male predisposition among early series from Wuhan City.
 - In hospitalized patients, limited studies suggest the disease course (Wuhan experience):
 - ~50% develop hypoxemia by d8
 - ARDS 17-29%
 - For all ICU patients
 - Non-invasive ventilation 42%
 - Mechanical ventilation 47%
 - High-flow O₂ 11%
 - ECMO 2-5%
 - **Persons Under Investigation (PUI)** definition
 - CDC PUI criteria for COVID-19 was revised on February 27, 2020:

Criteria to Guide Evaluation of PUI for COVID-19†		
Clinical Features	&	Epidemiologic Risk
Fever ¹ or signs/symptoms of lower respiratory illness (e.g.,	AND	<ul style="list-style-type: none"> • Expanded definition (3.4.2020) to symptomatic patients with respiratory symptoms <p>--Clinicians should use their judgment to determine if a patient has signs and symptoms compatible with COVID-</p>

Criteria to Guide Evaluation of PUI for COVID-19[†]

Clinical Features	&	Epidemiologic Risk
cough or shortness of breath)		<p>19 and whether the patient should be tested. Decisions on which patients receive testing should be based on the local epidemiology of COVID-19, as well as the clinical course of illness. Clinicians are strongly encouraged to test for other causes of respiratory illness, including infections such as influenza.</p> <ul style="list-style-type: none"> Any person, including healthcare workers², who has had close contact³ with a laboratory-confirmed⁴ COVID-19 patient within 14 days of symptom onset
Fever ¹ and signs/symptoms of a lower respiratory illness (e.g., cough or shortness of breath) requiring hospitalization	AND	A history of travel from affected geographic areas ⁵ (see below) within 14 days of symptom onset
Fever ¹ with severe acute lower respiratory illness (e.g., pneumonia, ARDS) requiring hospitalization and without an alternative explanatory diagnosis (e.g., influenza) ⁶	AND	No source of exposure has been identified

[†]Source: U.S. Centers for Disease Control. [Evaluating and Reporting Persons Under Investigation \(PUI\)](#). Revised March 4, 2020.

¹Fever may be subjective or confirmed

²For healthcare personnel, testing may be considered if there has been exposure to a person with suspected COVID-19 without laboratory confirmation. Because of their often extensive and close contact with vulnerable patients in healthcare

Criteria to Guide Evaluation of PUI for COVID-19†

Clinical Features	&	Epidemiologic Risk
<p>settings, even mild signs and symptoms (e.g., sore throat) of COVID-19 should be evaluated among potentially exposed healthcare personnel. Additional information is available from CDC.[15]</p> <p>³Close contact is defined as—</p> <p>a) being within approximately 6 feet (2 meters) of a COVID-19 case for a prolonged period of time; close contact can occur while caring for, living with, visiting, or sharing a healthcare waiting area or room with a COVID-19 case</p> <p>– or –</p> <p>b) having direct contact with infectious secretions of a COVID-19 case (e.g., being coughed on)</p> <p>If such contact occurs while not wearing recommended personal protective equipment or PPE (e.g., gowns, gloves, NIOSH-certified disposable N95 respirator, eye protection), criteria for PUI consideration are met.</p> <p>Additional information is available from CDC.[13]</p> <p>Data to inform the definition of close contact are limited. Considerations when assessing close contact include the duration of exposure (e.g., longer exposure time likely increases exposure risk) and the clinical symptoms of the person with COVID-19 (e.g., coughing likely increases exposure risk as does exposure to a severely ill patient). Special consideration should be given to healthcare personnel exposed in healthcare settings as described by CDC.[15]</p> <p>⁴Documentation of laboratory-confirmation of COVID-19 may not be possible for travelers or persons caring for COVID-19 patients in other countries.</p> <p>⁵Affected areas are defined as geographic regions where sustained community transmission has been identified. Relevant affected areas will be defined as a country with <u>at least</u> a CDC Level 2 Travel Health Notice. See all COVID-19 Travel Health Notices.</p> <p>⁶Category includes single or clusters of patients with severe acute lower respiratory illness (e.g., pneumonia, ARDS) of unknown etiology in which COVID-19 is being considered.</p>		

Diagnostic testing

- See the Prevention section below for screening recommendations.
- For those with COVID-19 pneumonia
 - Leukopenia in ~70% of hospitalized patients. LDH may be modestly elevated.
 - 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.
 - Among hospitalized patients, about one-third need to be in the ICU/intubated with an ARDS picture.
- Confirmatory tests, molecular (PCR)
 - Initially, all testing only done at CDC, but for US local health departments and other approved labs able to test once assays validated, per FDA.
 - FDA has announced that they are letting labs and hospitals around the U.S. to conduct testing.
 - Availability of testing locally not widely available as of 3/9/2020.

- Quest and LabCorp offer PCR testing (3-4d turnaround), specimens must be performed in a medical office/institution, not at a laboratory site.
- Testing expanded for all people with respiratory symptoms and fever to be considered, significantly increasing the number of potentially tested patients.
 - Prior CDC 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 RTI 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 severe pneumonia in aerosol isolation not likely possible given resource limitation.
- Serological testing in development.
 - 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](#).

SITES OF INFECTION

- Pulmonary

TREATMENT

General

- Supportive care, including oxygen, mechanical ventilation if needed.
- If epidemic widespread, 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 who require oxygen and supportive care only available in a hospital.
- **Antivirals**
 - None currently (March 2020) with proven efficacy in humans.
 - A large number of antivirals and immunomodulators are being investigated. Caution is advised as to whether any are effective or safe for COVID-19. Much like with influenza, any antiviral drug is likely to be most effective as a preventative or with administration early after the onset of symptoms.
 - Remdesivir (Gilead; used to treat [Ebola](#)) currently under study in a trial in Wuhan; activity is seen in vitro with SARS-2-CoV, MERS-CoV (also including MERS-CoV primate studies).
 - [Chloroquine](#) has been reported to have some efficacy in vivo and in COVID-19 pneumonia, the mechanism may be by interfering with cellular acidification.[\[6\],\[7\]](#)
 - List of medications currently under investigation[\[14\]](#):
 - ASC09/ritonavir, [lopinavir/ritonavir](#), with or without umifenovir
 - ASC09/oseltamivir, ritonavir/oseltamivir, [oseltamivir](#)
 - Azvudine

- Baloxavir marboxil/favipiravir and [lopinavir/ritonavir](#) in combination(s)
- Camostat mesylate
- Darunavir/cobicistat alone or with [lopinavir/ritonavir](#) and thymosin α 1 in combination(s)
- Remdesivir
- [Chloroquine](#) or hydroxychloroquine
- Interferon alfa-2b alone or in combination with [lopinavir/ritonavir](#) and [ribavirin](#)
- Methylprednisolone
- Camrelizumab and thymosin
- Tocilizumab

Prevention

- As a newly described virus, much remains to be learned.
 - Travel restrictions, quarantines, school closings, mass social distancing of uncertain long-term benefits with this viral infection and remain a source of considerable debate about effectiveness and costs among public health officials and politicians[3].
- Screening for illness/fever instituted in U.S.
 - Travel quarantine instituted in some cities within China (including Wuhan City) and Italy.
 - School closures, limiting mass events are strategies taken by some countries.
 - Difficulty sorting other causes of respiratory illness from the novel coronavirus, especially during influenza season.
 - Interim Guidance from the CDC regarding evaluating persons under investigation (PUI):
 - See the [clinical section](#) above.
- 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).[15]
 - Likely that standard contact and respiratory droplet precautions are sufficient (as with [SARS](#), [MERS](#)) which is the WHO recommendation; however, some debate using negative pressure rooms for extra safety but then this may divert from known needs such as TB or measles.
 - 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.
 - 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.
- No vaccine is available.

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%).
- 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).

OTHER INFORMATION

- Recommendations to consider testing for all respiratory symptomatic patients will be limited by availability of SARS-2-CoV testing.
- Severe illness is likely to strike the same populations at high risk for complications of seasonal influenza (e.g., elderly, immunosuppressed, and those with comorbidities).
 - Those with comorbidities appear to have mortality rates similar to [community-acquired pneumonia](#), ~10-15%.
- The case fatality rate is probably higher than seasonal influenza ($\leq 0.1\%$) but lower than initially reported (~ 2-4%). Serological testing of larger populations will give a clearer picture of infectious impact.

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. 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.

5. 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.

6. 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.

7. 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 macaque model of MERS-CoV.

8. 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.

9. 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.

10. 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%]).

11. 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.

12. 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.

13. 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...>]
14. Harrison, C. Coronavirus puts drug repurposing on the fast track. *Nature* Feb 27, 2020 (<https://www.nature.com/articles/d41587-020-00003-1> , accessed 3/3/20)

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

15. 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...>]

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* Article titles in AMA citation format should be in sentence-case

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