# SARS-CoV-2 (COVID-19)

## Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or COVID-19, has rapidly increased to pandemic scale since it first appeared in Wuhan, China, in December 2019 (1).

Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome (~29Kb) that likely originated in bats and adapted to non-bat variants as it crossed species to infect humans (2). In late December 2019, COVID-19 was identified in patients presenting with cough, fever, and dyspnea with acute respiratory distress syndrome in Wuhan, China. In the past two decades, coronaviruses have caused three pandemic diseases, namely COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) (3).

## Epidemiology

At present, 199 countries have reported cases of COVID-19. Globally, as of March 29, 2020, there are 712,995 reported cases, 33,599 deaths, and 150,881 recoveries, worldwide. In the United States, there are 136,785 confirmed reported cases, 2,413 deaths and 4,430 recoveries (4).

The virulence of COVID-19 can be assessed by A. transmission rate (Ro), which is defined as the number of newly-infected people from a single case, B. Case Fatality Rate (CFR), the percent of cases that result in death, C. Possible asymptomatic transmission. Preliminary studies estimated Ro between 1.5 to 3.5 (5) for comparison, the Ro for the common flu is 1.3 and 2.0 for SARS. The case fatality rate is estimated to be approximately 2% for comparison, the case fatality rate for SARS was 10%, and 34% for MERS (6). Symptoms of COVID-19 may appear in as few as 2 days or as long as 14. During this time, although the virus is contagious, the patient does not display any symptoms (asymptomatic transmission).

For comparison, every year, an estimated 300,000 to 650,000 people die worldwide from influenza viruses, which corresponds to 795 to 1,780 deaths per day. From November 2002 to July 2003, the SARS outbreak, which originated in China and spread to 29 countries, resulted in 8,096 infections and 774 deaths (fatality rate of 9.6%). MERS (2012) killed 858 people out of the 2,494 infected (fatality rate of 34.4%).

## Pathogenesis

Coronaviruses are named because they look like halos, known as coronas, when viewed under the electron microscope **(Figure 1)**. These viruses have the highest known frequency of recombination of any positive-strand RNA virus. In other words, these viruses mutate and change at a high rate, which can create havoc for both diagnostic detection, as well as therapeutic (and vaccination) regimens (7).

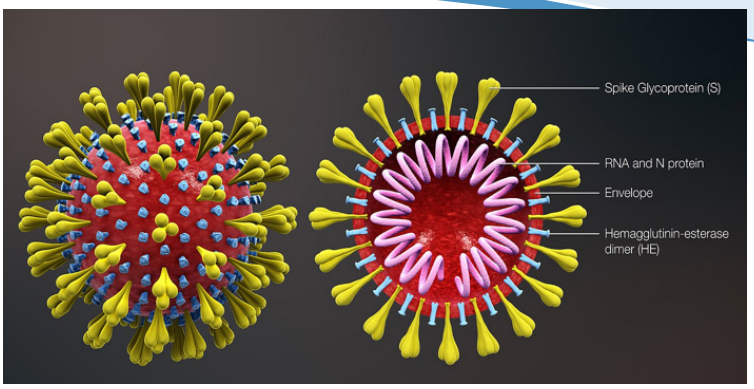


**Figure 1.** Diagram of coronavirus structure showing spikes that form a "crown" like the solar corona (http://commons.wikimedia.org/wiki/File:3D_medical_animation_corona_virus.jpg)

COVID-19 S-protein binds to the host cell angiotensin-converting enzyme 2 (ACE2) as its entry receptor **(Figure 2)**, while MERS-CoV binds to Dipeptidyl peptidase 4 (DPP4, also known as CD26) (8,9). After the virus enters the cells, the viral RNA genome is released into two polyproteins and structural proteins, after which the viral genome begins to replicate (10). Once the viral particles are incorporated and formed, they fuse with the plasma membrane to be released (3). When the virus enters the cells, its antigen is recognized by the antigen presentation cells (APC), which are a central part of the body's anti-viral immunity. Unfortunately, there is still a lack of any report about COVID-19 and antigen presentation.

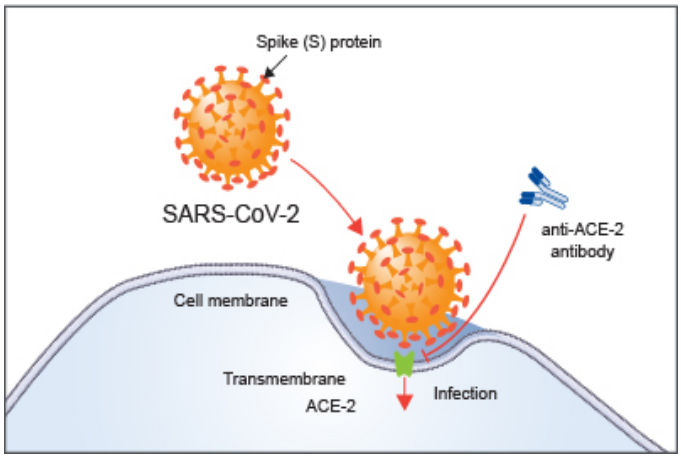


**Figure 2.** ACE-2 is the host cell receptor responsible for mediating infection by SARS-CoV-2, the novel coronavirus responsible for coronavirus disease 2019 (COVID-19). Treatment with anti-ACE-2 antibodies disrupts the interaction between virus and receptor (rndsystems.com).

Similar to common acute viral infection, the antibody profile against the SARS-CoV virus has a typical pattern of IgG and IgM production **(Figure 3)**. Although SARS-specific IgM antibodies disappear at the end of week 12, IgG antibodies can last for a long time, indicating that IgG antibodies may mainly play a protective role (11). Six years after SARS-CoV infection, specific T-cell memory responses to the SARS-CoV S-peptide library were still be identifiable in 14 of 23 recovered SARS patients (12).

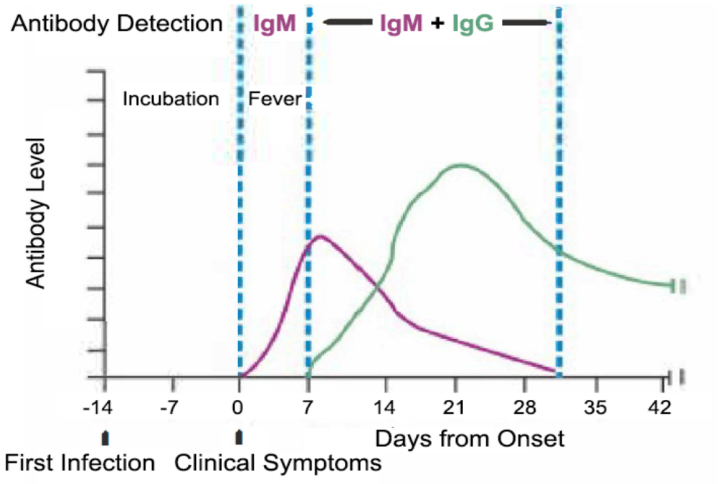


**Figure 3.** COVID-19 IgG/IgM development profile (aurorabiomed.com).

Acute Respiratory Distress Syndrome (ARDS) is the common immunopathological event for COVID-19, SARS-CoV, and MERS-CoV infections. The main mechanism for ARDS is facilitated by the "cytokine storm", a deadly, uncontrolled systemic inflammatory response resulting from the release of large quantities of pro-inflammatory cytokines (IFN-a, IFN-g, IL-b, IL-6, IL-12, IL-18, IL-33, TNF-a, and TGF-b) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10). The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS, multiple organ failure, and may lead to death in severe cases (13).

## Clinical Presentation

As a disease, COVID-19 shows considerable symptomatic variation. Individuals may have no symptoms at all, while some may present with a mild cough and fever, and an unlucky few may experience severe pneumonia and respiratory failure. COVID-19's most common symptoms strongly overlap with those presented by other co-circulating respiratory illnesses:

**Table 1**. Comparison of the typical symptoms of COVID-19 with the common cold, flu and allergy.

| Symptom | COVID-19 | Common Cold | Flu | Allergy |
|---|---|---|---|---|
| Fever | Common (99%) | Rare | Common | Occasional |
| Dry Cough | Common (59%) | Mild | Common | Occasional |
| Shortness of Breath | Common (31%) | No | No | Common |
| Headache | Occasional | Rare | Common | Occasional |
| Aches and Pains | Occasional (35%) | Common | Common | No |
| Sore Throat | Occasional | Common | Common | No |
| Fatigue | Common (70%) | Occasional | Common | Occasional |
| Diarrhea | Common | No | Occasional | No |
| Runny Nose | Rare | Common | Occasional | Common |
| Sneezing | No | Common | No | Common |

Because of this, diagnosing COVID-19 solely on the basis of clinical symptoms is highly inaccurate and must be confirmed by the use of highly specific diagnostic tests. (http://thenativeantigencompany.com).

One modeling study estimated that symptoms would develop in 2.5% of infected individuals within 2.2 days and in 97.5% of infected individuals within 11.5 days (14). The median incubation period in this study was 5.1 days. A study from the Chinese Center for Disease Control and Prevention, reported disease severity in approximately 44,500 confirmed infections as; 81% mild (no or mild pneumonia), 14% severe disease (with dyspnea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours), and 5% critical disease (with respiratory failure, shock, or multiple organ dysfunction). Most of the fatal cases occurred in patients with advanced age or underlying medical comorbidities (15).

The proportion of severe or fatal infections may vary by location. In Italy, 12% of all detected COVID-19 cases and 16% of all hospitalized patients were admitted to the intensive care unit. The estimated case fatality rate was 7.2% in mid-March (16, 17). However, in South Korea, the estimated case fatality rate in mid-March was 0.9% (18). This may be related to distinct demographics of infection. In Italy, the median age of patients with infection was 64 years, whereas in Korea the median age was in the 40s. In addition, in a subset of 355 patients who died with COVID-19 in Italy, the mean number of pre-existing comorbidities such as cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer, and chronic kidney disease was 2.7%, and only three patients had no underlying condition (17).

## Laboratory findings

In patients with COVID-19, the white blood cell count can vary. Leukopenia, leukocytosis, and lymphopenia have been reported, although lymphopenia appears most common (19). Elevated lactate dehydrogenase and ferritin levels are common.

## Imaging findings

Chest CT scan in patients with COVID-19 most commonly demonstrates ground-glass opacification, consistent with viral pneumonia (20). Case series have suggested that chest CT abnormalities are more likely to be bilateral, have a peripheral distribution, and involve the lower lobes. A study in Wuhan, China, evaluated 1,014 patients who underwent both reverse-transcription polymerase chain reaction (RT-PCR) testing and chest CT for evaluation of COVID-19. A "positive" chest CT for COVID-19, as determined by a consensus of two radiologists, had a sensitivity of 97 percent using the PCR tests as a reference; however, specificity was only 25 percent (21). The low specificity may be related to other etiologies causing similar CT findings.

## Diagnosis of COVID-19

Patients who meet the testing criteria described by the Centers for Disease Control and Prevention (CDC), should undergo testing for SARS-CoV-2 in addition to testing for other respiratory pathogens (e.g., influenza, respiratory syncytial virus). In the United States, the CDC recommends the collection of a nasopharyngeal swab specimen to test for SARS-CoV-2 (22). An oropharyngeal swab can be collected, but is not essential. If collected, it should be placed in the same container as the nasopharyngeal specimen. Oropharyngeal, nasal mid-turbinate, or nasal swabs are acceptable alternatives if nasopharyngeal swabs are unavailable.

The accuracy and predictive values of SARS-CoV-2 testing have not been systematically evaluated. The sensitivity of testing likely depends on the precise test as well as the type of specimen obtained. If initial testing is negative, but the suspicion for COVID-19 remains, the World Health Organization (WHO) recommends resampling and testing from multiple respiratory tract sites (23). Infection control precautions for COVID-19 should continue while performing repeat evaluations.

## Immunoassays

The biggest advantage of immunoassays is the ability to detect past infections. Once a patient has recovered from COVID-19 and virus is cleared from the body, viral RNA is no longer available for detection in the respiratory tract, leaving only a short window during the acute stage of infection in which SARS-CoV-2 is detectable. While this works well for the diagnosis of ongoing infections, it does not indicate whether a patient has had the infection historically, and whether they are immune to COVID-19 or still susceptible to infection.

Unlike RNA, antibodies are long-lasting and can persist in the bloodstream for many years after infection. As such, immunoassays enable us to identify patients that have had COVID-19, retrospectively. The type of antibody and its relative levels could also be used to indicate the stage of infection and estimate time since exposure for contact tracing.

Antibody tests have their limitations as well. As immunological data continues to emerge, it is becoming apparent that the body's antibody response to COVID-19 is slow – considerably slower than we might expect. While data at this point is still limited, it appears that the initial IgM antibody response doesn't peak until approximately nine days after initial infection and the IgG antibody response doesn't peak until approximately day 11 **(Figure 3)**. In comparison, most viruses elicit a primary IgM response within five days. Because of this, SARS-CoV-2 antibodies are unlikely to make useful markers of acute COVID-19 infection.

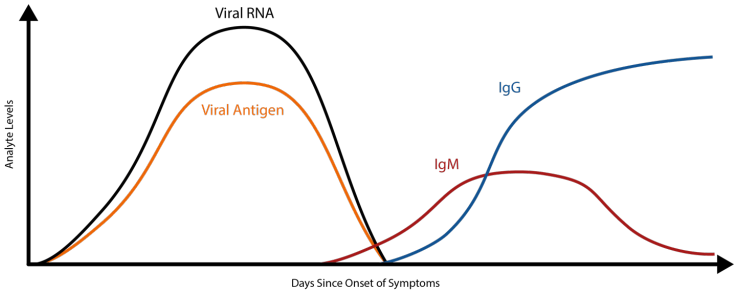


**Figure 4.** Kinetics of viral RNA (-), viral antigen (-), IgM (-), IgG (-).

While antibodies may not be appropriate for acute-phase diagnosis, they still show many valuable applications for COVID-19. Potentially the most valuable is the use of wide-scale antibody testing as a public health tool.

**Table 2**. Statistical Analysis of Various Outbreaks in United States.

| Outbreak Name | Reported Cases | Hospitalizations | Deaths |
|---|---|---|---|
| SARS virus, 2002-2003 | 8 | NA | 0 |
| Swine Flu, 2009-2010 | 60,800,000 | 274,000 | 12,469 |
| MERS, 2012-2014 | 2 | 2 | 0 |
| Ebola virus, 2014 | 2 | 2 | 0 |
| Zika virus, 2016 | 5,168 | NA | 0 |
| Common Flu, 2017-2018 | 44,800,000 | 808,100 | 61,000 |
| Common Flu, 2019-2020* | 36,000,000 | 370,000+ | 22,000+ |
| COVID-19, 2019-2020** | 160,417 | NA | 2,953 |

*CDC estimates covering October 1, 2019 through March 7, 2020

**www.worldmeters.info (through morning of March 30th, 2020)

**Table 3.** COVID-19 cases by state (To 10 states; as of March 30th, 2020)*

| State | Total Cases | Total Deaths | Active Cases |
|---|---|---|---|
| New York | 66,497 | 1,218 | 61,075 |
| New Jersey | 16,636 | 198 | 16,438 |
| California | 6,528 | 135 | 6,372 |
| Michigan | 6,498 | 184 | 6,309 |
| Massachusetts | 5,752 | 56 | 5,686 |
| Florida | 5,473 | 63 | 5,410 |
| Illinois | 5,056 | 72 | 4,982 |
| Washington | 4,896 | 202 | 4,274 |
| Pennsylvania | 4,087 | 48 | 4,039 |
| Louisiana | 4,025 | 185 | 3,840 |

*www.worldmeters.info

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