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**OUTBREAK: CORONAVIRUS PRESENTS CHALLENGES, OPPORTUNITIES**

The 2018 “Outbreak” exhibit at the Smithsonian’s National Museum of Natural History could not have been more prescient: A life-threatening pathogen jumps from animals to humans in an Asian market with live animals, quickly spreads locally, and is transported worldwide before anyone comprehends what is happening. Within a few weeks after emergence of a previously unknown human coronavirus in Wuhan, China, the number of people diagnosed with infections and the number of associated deaths had far eclipsed those associated with the 2003 severe acute respiratory syndrome (SARS) and the 2012 Middle East respiratory syndrome (MERS).

The seriousness of the challenges of containing this new virus were soon evident, and the worldwide threat continues. The U.S. government responded with travel bans and the first quarantines in a half century. Public health officials and microbiologists created names for the disease (COVID-19) and the new virus (SARS-CoV-2).

With a panicked public focusing on the risk of COVID-19, the media effectively pivoted to pointing out the clear and present danger of influenza and other diseases and supporting the importance of preventive vaccinations in a connected world. In the meantime, researchers began looking for ways that drugs and vaccine/antibody platforms could be adapted for the new virus. Here’s a summary of what they are finding as SARS-CoV-2 continues its daily assault worldwide.

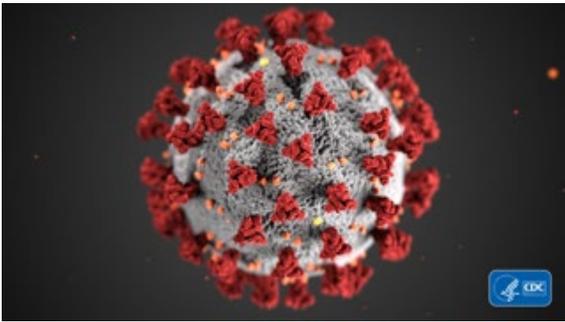
**VAGUE SYMPTOMS, MASS MIGRATION PRODUCE WIDESPREAD DISEASE**

The Coronaviridae family of viruses received its name because of spikes on the protein coat that resemble crowns, hence corona, Latin for crown (Figure 1). Coronaviruses are within the Nidovirales order, a group of positive-sense, single-stranded RNA viruses.

According to a description in the *Journal of the American Medical Association* of early patient cases of COVID-19, the new coronavirus spread quickly after being transmitted from an unknown animal reservoir to humans in the central Chinese city of Wuhan, presumably at a

seafood and live animal market (many of the people who presented initially were connected to the market, but not all were). The virus is easily transmitted among people in close contact with one another. Based on what is known about SARS and MERS, the new virus is likely transmitted primarily through airborne droplets following coughs and sneezes and on surfaces.

 **SARS-CoV-2** appears to be communicable during a relatively symptom-free incubation period of 2 days to 2 weeks. Once symptomatic with COVID-19, many people have mild symptoms that would not lead them to stop working or seek care, and this delay increases viral spread by keeping infected people in the community and sometimes carrying on with their daily lives.



**FIGURE 1.** Morphology of the Coronavirus. The spikes on the outer surface of the virus impart the look of a corona, or crown, giving the virus its name.

Source: U.S. Centers for Disease Control and Prevention.

**Chinese scientists** reported that about 80% of patients identified with the virus have mild disease and that the overall mortality rate based on identified deaths and cases is 2.3%. However, whether the denominator in this calculation is much larger remains unknown. In those younger than 40 years of age, the mortality rate has been 0.2%, while in those older than 70 years, 8% of patients with COVID-19 have died. The **worldwide movement of people** during Chinese Lunar New Year—considered the largest human migration each year—was the final element in this perfect storm. Before Wuhan and other parts of China were quarantined, many people began traveling, and this gave the virus quick passage around China, to other parts of the Pacific Rim, and across oceans and continents. By end of February, the virus had infected more than 82,000 people on six continents, with deaths exceeding 2,000 and some 10,000 patients critically ill. Researchers using **modeling programs** were estimating the number of COVID-19 cases would be at least 550,000 and perhaps as high as 4.4 million before being contained.

## RESPONDING TO THE SARS-COV-2 THREAT

In Washington, DC, officials in the U.S. Department of Health and Human Services (HHS) had quickly formed an interagency medical countermeasures task force. The group, aware of the lack of progress made in treating previously identified coronaviruses during the two outbreaks in just 16 years, formed working groups to focus on four areas: therapeutics, vaccines, diagnostics, and clinical trials.

 At a **February 13 session of the National Vaccine Advisory Committee (NVAC)**, coronavirus researchers described the spikes on viral protein coats as an obvious target for drugs and vaccines but perhaps not as good as the supporting stems. The spikes are not highly conserved, meaning they frequently mutate. This could enable the virus to develop resistance or sufficient antigenic drift such that vaccines might not be effective. The stems show less genetic variation.

## LOOKING FOR THERAPEUTIC TARGETS

Compared with other viruses, coronaviruses should be amenable to drug, biologic, or vaccine interventions. In fact, the Nidovirales are the only order of viruses that encode a proofreading exon, and this reduces the number of mutations, compared with other viruses. During replication, this exon checks for and removes incorrect nucleotides. This reduces genetic variation. However, the proofreading exon also makes an entire group of antiviral drugs—the nucleoside analogues—largely ineffective, as they recognize the errors introduced by these agents.

As people were hospitalized in Wuhan and other parts of China, **clinicians began using existing antiviral agents** based on what is known about the six human coronaviruses previously identified. These agents included oseltamivir (indicated for influenza), protease inhibitors (HIV), chloroquine (malaria), and an investigational agent being tested for use against Ebola virus, remdesivir.

 This last agent, a Gilead Sciences product, is particularly intriguing, **Mark Denison, MD, of Vanderbilt University**, said at the NVAC session. Remdesivir has performed well in animal models, potently inhibiting coronaviruses by terminating the RNA chain during replication. When resistance mutations have occurred, they make the virus weaker. In mouse and monkey models, remdesivir showed efficacy in prevention of infection by the 2003 SARS coronavirus. When infection occurs, the drug decreases disease severity and reduces viral titers. The agent, administered intravenously and safely in earlier clinical trials of patients with the Ebola virus, is being rushed into clinical trials to see if it is effective in people with COVID-19.

## SPEEDING WORK ON VACCINES

Despite the challenges of creating an effective vaccine within a timeframe useful for stopping SARS-CoV-2, researchers at the U.S. National Institutes of Health had identified promising targets on the coronavirus structure within hours after Chinese scientists had posted the genetic makeup of the pathogen. Finding partners willing and able to develop and test a vaccine, not to mention produce it in quantities needed to stop a pandemic, is a much harder step.

**Ralph S. Baric, PhD**, who specializes in coronaviruses in his work at the University of North Carolina, provided hopeful information at the February NVAC meeting: In addition to the spikes and stems mentioned earlier, a broadly cross-reactive vaccine could be effective against SARS-CoV-2 and other members of that group of coronaviruses, as might vaccines that target the globular head. There was also bad news, though. In prior tests of vaccines against human coronaviruses in this group, substantial heterogeneity has limited vaccine efficacy, and use of adjuvants has led to adverse effects after vaccination. The poorer responses of older adults to vaccines also limit their impact in a group particularly susceptible to the virus.



The U.S. government is working on a vaccine with Moderna, Inc., a biotechnology company whose efforts focus on messenger RNA therapeutics and vaccines. With funding from the [Coalition for Epidemic Preparedness Innovations](#), Moderna is collaborating with the [National Institute of Allergy and Infectious Diseases \(NIAID\)](#) to design and manufacture a vaccine against SARS-CoV-2. NIAID will conduct preclinical studies and a phase 1 clinical trial of the vaccine. [Sanofi Pasteur](#), Johnson & Johnson, and GSK later were reported to be joining the federal effort to develop a vaccine against SARS-CoV-2, adding important partners able to produce large amounts of vaccine.



**FIGURE 2.** End-to-End Development of Medical Countermeasures Targeting SARS-CoV-2 by the U.S. Government.

**Source:** Robert Johnson, Influenza and Emerging Infectious Diseases Division of Biomedical Advanced Research Development Authority, U.S. Department of Health and Human Services. Presentation to the National Vaccine Advisory Committee; February 13, 2020; Washington, DC.

The team working on a possible vaccine is well aware of the challenges posed by this virus, **Robert Johnson, PhD**, told the NVAC attendees. Director of the Influenza and Emerging Infectious Diseases Division of Biomedical Advanced Research Development Authority at HHS, Johnson pointed to the many steps between identification of candidate vaccines and large-scale production (Figure 2). Reflecting on the lack of progress against coronaviruses despite three outbreaks in two decades, Johnson asked the group, “How do we align our efforts across the U.S. government to try to overcome this barrier we have right now of no licensed vaccine and no licensed therapeutics...? What does that end-to-end solution look like? Who’s going to handle what? How are we making sure there’s not a gap? [If someone has a particular model] how do we make that happen so we have the capacity that is

needed as we move forward?”

## SOURCES AND RESOURCES

- Centers for Disease Control and Prevention. [Coronavirus Disease 2019 \(COVID-19\)—information and updates for health care, public health, and laboratory professionals..](#)
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