3 reasons the coronavirus outbreak has been so severe

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February 27, 2020 -- WASHINGTON, DC - Why has the current outbreak of coronavirus been so severe compared with past epidemics of viral respiratory diseases? It has to do with unique characteristics of the coronavirus itself, according to a speaker at a February 26 congressional briefing.

Viral outbreaks are not new in the 21st century, according to Ralph Baric, PhD, from the University of North Carolina at Chapel Hill. Baric provided an update on the state of the coronavirus, including how the current outbreak began and what's being done to combat the spread of the disease, at a briefing held by the Congressional Biomedical Research Caucus.

Baric noted that four major respiratory viruses have emerged in the last 17 years:

- The first outbreak of severe acute respiratory syndrome (SARS) in 2003: SARS originated in China and led to over 700 deaths in the six months of the outbreak
- Influenza A (H1N1)pdm09, which in 2009 triggered the 2009 global flu pandemic and resulted in infection of an estimated 11% to 21% of the population and over 12,000 deaths in the U.S.
- Middle East respiratory syndrome (MERS), a coronavirus that caused over 700 deaths in 2012, with an astounding 37% mortality rate in 2012
- The novel coronavirus SARS-CoV-2, or "SARS 2.0" as Baric refers to it, that is causing the disease known as COVID-19

Baric believes that SARS-CoV-2 could surpass the three previous outbreaks to be the largest outbreak of the 21st century to date.

Why SARS 2.0 will be more difficult to control

To understand how to prevent further outbreak of SARS-CoV-2, it is crucial that scientists learn how molecular drivers influenced the evolution of the virus and characteristics that make it a high-risk strain.

Coronaviruses can traffic easily between species. These viruses can easily change their genetic material to adapt to different natural environments. However, recently we have seen accelerated cross-species movement of coronaviruses. Using regulated fidelity, a function whereby polymerase can fix replication errors, a coronavirus can protect its large RNA genome from error catastrophe and viral death. Moreover, coronaviruses can tolerate high rates of mutations, which makes them resilient in nature.

There are several preepidemic coronavirus strains. Coronaviruses "are quite clever," according to Baric. They use RNA recombination to produce chimeric strains that are genetically diverse. This modular evolution allows critical virulence genes to be shuffled and drives outbreaks and pandemics.

The viruses have evolved as generalists that can live and replicate in a number of animal reservoirs. They can also utilize both animal and human angiotensin-converting enzyme 2 (ACE2) receptors for viral entry.

These high-risk features indicate that coronaviruses are often primed to cause epidemics. Because they already have the ability to bind to both human and animal receptors, they may not require an intermediate host or mutation to cause infection.

Another high-risk feature of coronaviruses is that they cause acute respiratory distress syndrome (ARDS), the cause of death for SARS 2.0.

SARS 2.0 spreads asymptomatically. Lastly, SARS 2.0 will be exceedingly difficult to control due to the asymptomatic spread of the disease, Baric said. This means that you can be infected with the virus and not know it, and that makes it difficult to control, he said. Here, there are paths of transmission that cannot be tracked. He suggests that this more efficient form of transmission may occur from replication in the upper respiratory tract, although currently the cause is unknown. This feature never occurred in previous respiratory viral outbreaks.

It is because of asymptomatic spread that epidemiological models predict that the virus will inevitably spread to the U.S. and Europe.

Countermeasures in development

From extensive genomic profiling of many coronaviruses, researchers have identified 14 residues on the spike protein of SARS-CoV-2 that match with ACE2 receptor in humans. While many coronaviruses can use the receptor, the current strain is a particularly good fit. These mutations impact virus tropism (where the virus replicates in the respiratory tract), virulence, and transmission frequency -- all features that have caused the deadly spread of the virus.

Unfortunately, the spike protein of SARS-CoV-2 is 22% different than earlier SARS-CoVs. This means that drugs, antibodies, and vaccines developed in 2003 to target SARS do not apply to this SARS-CoV-2.

Currently, two types of therapies are being developed to combat SARS-CoV-2: antiviral drugs and vaccines. Vaccines are difficult to develop because they are not efficacious in aged patients who are most at risk for SARS 2.0, and the potential for immune pathology caused by vaccination (Th2 response).

Vaccines will be crucial to eliminating the new coronavirus, Baric said, which is why his team is working on developing vaccines that protect not only against known strains of coronaviruses but also viruses that may occur in the future. However, at least in the U.S., vaccines must undergo extensive animal testing and human clinical trials. So although vaccine development is underway, they will not be available to the public for another four to six months.

Alternatively, drug repurposing efforts have led researchers to use broad-spectrum antiviral drugs as potential therapies. These small molecules can be used under compassionate care laws, meaning they can rapidly enter the clinic (within one month).

Currently, Remdesivir, a broad-spectrum antiviral drug initially developed for the treatment of Ebola, is undergoing phase I clinical trials in Nebraska. The maker of the drug, Gilead Sciences, is interested in increasing the bioavailability of the product so it can be administered as a tablet instead of intravenous therapy.

As the world struggles to grapple with the coronavirus outbreak, one thing is for sure: The economic cost will be significant.

"The economic consequences of SARS 2.0 have far exceeded any viral outbreak in the history of the planet as we know it," Baric concluded.

The Congressional Biomedical Research Caucus was established in 1989 to broaden the support and knowledge of basic and clinical biomedical research issues throughout the U.S. Congress in a bipartisan manner. The caucus membership is comprised of 75 members of the House of Representatives and eight members of the Senate with Reps. Steve Stivers (R-OH), Jackie Speier (D-CA), Steve Cohen (D-TN), and John Curtis (R-UT) serving as co-chairs.

The Coalition for the Life Sciences (CLS) is an alliance of professional organizations working together to foster public policies that advance basic biological research and its applications in medicine and other fields. The issues addressed by the CLS include science education, professional training, and the funding, management, and oversight of scientific work, especially by the federal government.