A New Coronavirus Emerges, This Time Causing a Pandemic

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Throughout recorded history, humans have been assaulted by severe epidemics of infectious disease. These epidemics have exacted a terrible toll, and some have changed the course of history. The successive waves of bubonic plague, the Black Death, killed 50% or more of European populations during the Middle Ages, and smallpox and other imported infectious diseases allowed the rapid European conquest of the Americas by virtually wiping out many native populations. Not all epidemics are restricted to specific geographical regions; those that spread worldwide are designated pandemics. And pandemics are not restricted to humans. Plant and animal virus pandemics have the potential to disrupt agriculture and the food supply. Two notable, widespread viral pandemics of the last century, the 1918 influenza and acquired immune deficiency syndrome (AIDS), had devastating consequences. Coming at the end of World War I, with millions of displaced persons, the absence of antibiotics to cure secondary bacterial infections, and insufficient healthcare resources, the 1918 influenza pandemic killed tens of millions of people. AIDS, caused by human immunodeficiency virus, was similarly lethal before being brought under relative control by highly effective antiretroviral drugs.

This year saw the emergence of a new pandemic, coronavirus disease 2019 (COVID-19), caused by a previously unknown virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although SARS-CoV-2 infection usually causes a relatively mild disease, COVID-19 can present with severe pneumonia, leading to respiratory collapse and death. At this writing, there are more than 2 million documented cases of COVID-19 worldwide and nearly 200,000 deaths. As many SARS-CoV-2 infections are only mildly symptomatic or entirely asymptomatic, the true prevalence of infection is undoubtedly much higher. Although COVID-19 has so far claimed far fewer lives than the worst historical pandemics, it is particularly terrifying because it arose so abruptly and spread explosively. It also has the dubious distinction of being the first pandemic followed by billions of people in real time through instantaneous communication and social media. In an attempt to control the spread of the virus, most of the world's population is under lockdown or

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subject to stringent physical distancing mandates, compounding the medical disaster with potential social and economic ruin.

What is the culprit? SARS-CoV-2 is a coronavirus, an enveloped virus with an approximately 30,000-base, single-stranded, positive-sense RNA genome. Coronaviruses are well known to virology. The first human coronavirus was described in 1964 by June Almeida in London. There are at least four known human coronaviruses that cause mild respiratory infections, including the common cold. Other animals can be infected with particular coronaviruses such as mouse hepatitis virus, infectious bronchitis virus of chickens, and transmissible gastroenteritis virus of swine. SARS-CoV-2 is a member of the class of coronaviruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), severe respiratory disease outbreaks that emerged in 2002 and 2012, respectively. SARS and MERS are similar diseases to COVID-19 but with higher case-fatality rates. Fortunately, these earlier coronavirus outbreaks affected only a few thousand people before subsiding. Like most emerging viruses, SARS-CoV-2 existed in an animal reservoir, probably bats, before it entered the human population. The proximate animal host of SARS-CoV-2 prior to humans is not clear, but a leading candidate is the pangolin, an amazing animal indigenous to Asia that looks like a cross between an anteater and an armadillo that was suddenly thrust into Western consciousness by the emergence of COVID-19.

When COVID-19 arrived in humans in late 2019, it landed not in a barren patch of land but on a field tilled for more than half a century by virologists. Fortunately, because of substantial prior knowledge of coronaviruses, including viruses closely related to SARS-CoV-2, the COVID-19 causative agent was rapidly isolated and identified as a coronavirus, and its genome was sequenced. SARS-CoV-2 sequences were widely disseminated to the research community, mobilizing an army of investigators to study this new agent. This intense, global scientific effort led to the rapid characterization of the SARS-CoV-2 attachment/fusion protein and identification of its cell-surface receptor (the human enzyme ACE2, which is the same receptor used by SARS-CoV, the cause of SARS). The viral attachment protein is of great interest because it could be an important component of future vaccines. Remarkably, the structure of this protein was determined at atomic-level resolution within a few months. Unfortunately, government leaders in much of the world did not display sufficient urgency to this new threat and were not adequately prepared, which delayed the recognition of a new pandemic and led to an ineffective public health response.

Although the SARS and MERS outbreaks certainly accelerated studies of this virus group, much coronavirus research predated these outbreaks, and coronavirus research continued after these diseases subsided. The insights gained from these studies highlight the importance of basic virus research with no obvious immediate medical or agricultural implications. This work revealed the basic features of the coronavirus replication strategy, which involves synthesis and packaging of the largest known viral RNA genome, production of a large polyprotein processed into at least 16 protein products, and an interesting and complex gene expression mechanism incorporating template jumping and nested messenger RNA molecules. This information will be vitally important for the development of effective antiviral therapeutics and vaccines against SARS-CoV-2. However, we should remember that SARS and MERS were brought under control not by medical, scientific, or technological advances but by public health measures long known to be effective against contagions: widespread testing, isolation of infected individuals, and contact tracing. The vast scope of the COVID-19 pandemic, which dwarfs SARS and MERS by many orders of magnitude, may limit the utility of these tried-and-true approaches, but these strategies are a good place to start and are, frankly, the only way forward we have at present.

The COVID-19 pandemic has taught us many important lessons. First and foremost, although we cannot predict when they will arrive or their severity, future pandemics are inevitable. Some may be more serious than COVID-19 if they are caused by pathogens with higher transmissibility between humans or higher case-fatality rates. Second, the importance of improved surveillance and transparency is paramount. It is essential to recognize potential pandemics early to allow prompt public health interventions when the population burden of disease is low. Third, governments must develop coordinated responses including stockpiling essential supplies and equipment and formulating plans to distribute them rapidly where they are most needed. Fourth, barriers to effective scientific exchange must be removed to allow information and reagents to be made widely available, avoiding duplication of effort and stoking rapid progress in confronting the disease. Fifth, physical distancing to limit transmission leads us to find new ways to remain productive and engage with each other remotely. These efforts are hard but essential, as we need each other now more than ever. Finally, research in basic virology, cell biology, immunology, biochemistry, and other relevant areas must proceed apace, even in interpandemic intervals. These studies provide the necessary head start to conquer new viruses before they overtake us and wreak havoc on our health system, economy, and society.