Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Novel Coronavirus Outbreak: What We Know and What We Don't

When, Where, and How?

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A severe respiratory disease emerged in the city of Wuhan, Hubei province, China, in December 2019. As of early February 2020, at least 28,088 diagnosed and 24,702 suspected cases have been reported, including at least 564 deaths. Unfortunately, the disease has spread globally. The etiologic agent, a novel coronavirus, now called SARS-CoV-2, was immediately identified and characterized in China. Although we know the presence of unprecedented genetic diversity of viruses in nature, this outbreak further indicates that there is considerable uncertainty in predicting when, where, and how novel disease-causing pathogens emerge.

Phylogenetic analyses reveal that SARS-CoV-2 is closely related to a group of SARS-like coronaviruses. However, it remains unclear where the virus comes from and how it was transmitted to humans in the first place. Unlike with other zoonotic agents such as hantavirus and arenavirus, thus far we haven't found a SARS virus in animals that is the same as that in humans. Fortunately, SARS virus has not appeared in humans since 2004. In contrast, this new virus seems to have stronger transmission capabilities among people. Compared to the primary virus in humans, we still know less about whether, what, and how the virus has changed and the effect of the changes for their epidemics in humans. Control and prevention of the disease is especially difficult in China and elsewhere if there are infected individuals with no clinical signs.

Sandbags for Disease X

Marion Koopmans
Erasmus MC

Whether it will be contained or not, this outbreak is rapidly becoming the first true pandemic challenge that fits the disease X category, listed to the WHO's priority list of diseases for which we need to prepare in our current globalized society. Initial resemblances with the SARS outbreak in terms of its origin, the disease associated with infection, and the ability to spread are clear. But since 2003, global air travel has increased more than 10-fold, and the efforts needed to try to contain the epidemic are daunting. There have been great advances since 2003, with the coordinated efforts of WHO and funders focusing on the priority threats. But unfortunately, as in past outbreaks, key knowledge gaps and medical countermeasures need to be assessed on the fly, and scientists and public health experts alike are wasting precious time writing grant applications to do what we long know needs to be done but which is not part of routine investment in science and (global) public health preparedness. In my birth town, we used to watch the rivers flood inevitably every winter, with some people losing their homes because "that is what a happens." Now, there are modern flood barriers built to channel the river, based on forward-looking investments in the past decades. Our ways of dealing with outbreaks is a mixture of modern floodwalls in some parts of the world while relying on sandbags in others. Needless to say where the weakest links will be. Time will tell whether the consolidated efforts of the Chinese authorities and the international public health and research community will succeed. But we also need to understand how we make this model of preparedness future-proof.

Comparisons to SARS

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Many SARS-related coronaviruses are widely prevalent in bats. It has been suspected that one such bat coronavirus had jumped into civet or other mammals and adapted to cause the 2003 SARS epidemic. Thus, we again suspect that this time, too, wild animals should be the source, though the exact animal host has not yet been identified. Many speculate that this is another SARS epidemic, but epidemiologically and clinically, this outbreak appears different from the 2003-SARS in terms of higher transmissibility with efficient intra-familial spread and a lower crude mortality. The key question is to find the molecular determinant that allows transmission from animal to human and then human to human. It is notable that the nucleotide identity of SARS-CoV-2 genome, especially at the external ectodomain of the receptor binding domain (RBD) of spike protein, is quite different from that of the SARS coronavirus. Knowing the exact biophysical mode of proteolytic activation of this novel spike protein and the interaction between this RBD with the host receptor ACE2 at physiological and endosomal pH would reveal how this virus overcame the species barrier between animals and humans. Such information would enable us to understand pathogenesis, to design effective antivirals, and to develop safe vaccines.

Sequencing and Beyond

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Science has moved with blazing speed during this epidemic. Within weeks of authorities recognizing a novel outbreak, the virus had been identified, isolated, and sequenced. Public sharing of data rapidly allowed for the creation of diagnostic tests and validation of ACE2 as the receptor for the virus.

Sequencing of this coronavirus has especially moved at a rapid pace, with currently more than 50 sequences shared openly. This sequencing information has allowed us to learn critical features of the virus and epidemic, including (1) guiding design of diagnostics, drugs, and vaccines; (2) identifying bats as the likely reservoir; (3) showing that the epidemic was the result of a single spillover event; (4) that the epidemic is sustained by human-to-human transmission, which has been ongoing since the beginning; and (5) that the beginning of the epidemic was likely in mid-November to mid-December of 2019.

As the epidemic expands, it is important that virus sequencing and open data sharing continues. Critical questions that sequencing will help to address include an understanding of how effective intervention strategies are, whether we are missing transmission chains, how locations of virus transmission are connected, and what environmental and human factors may contribute to spread. In addition, we also need to understand how easily the virus spreads between people, including the level of asymptomatic spread and transmission during the incubation period. While development of new vaccines and therapeutics is unlikely to affect the trajectory of this epidemic, repurposing of preexisting drugs could offer new opportunities for treating people infected with SARS-CoV-2.

Understanding the Virus

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The SARS-CoV-2 epidemic that began in Wuhan, China, and has spread to several countries throughout the world has led to intensive efforts by healthcare, public health, and governmental authorities. The epidemic has had enormous impacts economically and socially in China, and while first efforts must be to control the epidemic, limit virus spread, and provide appropriate patient care, several questions need to be addressed. First, why is this virus more transmissible than other CoV that cause severe respiratory disease (SARS-CoV and MERS-CoV)? Does this virus replicate more readily in the upper airway than these other viruses and more similarly to HCoV-NL63, which causes croup and the common cold (but not pneumonia)? Is virus spread primarily by droplet, as was true for SARS-CoV and MERS-CoV? How much transmission occurs when patients exhibit the earliest signs of disease or even have subclinical disease? Second, is the virus mutating to better infect humans, like SARS-CoV, but not MERS-CoV, did? How well does the virus bind to its putative cellular receptor (angiotensin converting enzyme-2), and if the binding is not strong, is the virus adapting to bind better? Third, what is the zoonotic source for the virus? Bats may be the ultimate source, but is an intermediate host involved? Finally, what are the unique molecular attributes of the virus that contribute to its pathogenicity?

Basic and Public Health Questions

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The recent emergence of SARS-CoV-2 and its rapid, continuing spread across China and movement around the world raise many scientific and public health questions and challenges.

From the basic science view, we must be forward looking to address questions about the interplay between coronaviruses and their hosts. SARS-CoV-2 is the third recently emerged zoonotic coronavirus. Genomic sequences support that these viruses are closely related to bat coronaviruses. Given the large number of novel coronaviruses identified in bat populations, we likely will continue to have spillover to humans. What factors drive this? Are there genomic signatures in bat viruses that may help predict which viruses will eventually emerge? Do the emerging viruses need to route through an intermediate host prior to infecting humans? What accounts for the spectrum of disease outcomes when this happens, and what drives human-to-human spread? Are there viral and/or host genetic factors involved in disease outcome?

From the public health perspective, the development of effective vaccine and antiviral therapeutics and how rapidly these can be available are pressing. Previous work with pathogenic severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) coronaviruses provides insight and platforms that can help expedite the process, but none has moved beyond phase 1 trials. The rapid availability of genomic sequences of SARS-CoV-2 isolates might move things along quickly, possibly on a faster-than-normal track for vaccine development. The availability of the virus and animal models will also help. This will become a more critical priority if the SARS-CoV-2 continues to spread and becomes embedded in the respiratory virus disease landscape. Much remains to be learned about the SARS-CoV-2 and its interplay with its human host and what will constitute the most effective, safe vaccine strategy.

The Need for Diagnostics

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In the age of metagenomics with almost endless possibilities for rapid pathogen identification, diagnosing a new viral disease seems like an easy task. For SARS-CoV-2, the first genome was released on January 10, the first diagnostic PCR assay on January 15. Never before did we have the means to diagnose a new virus almost immediately after its appearance.

Widely available reagents and commercial kits now allow high-income countries to test suspected cases and screen returning travelers. However, a well-equipped molecular diagnostic laboratory with trained staff and a functional supply chain is required for this task. In resource-limited areas such as sub-Saharan Africa, testing capacities are often limited to reference laboratories, if existing at all. A realistic chance of importation of SARS-CoV-2 exists there, due to close economic relations with China and intensive air traffic between regions.

With scarce screening opportunities in low-income areas, the containment of a new virus, especially one that presents with mild symptoms, is nearly impossible to achieve. Despite immense technological development in molecular diagnostics, up to today no robust, reliable, and easy-to-implement diagnostic point of care tool is widely available that can be rapidly adapted for situations like the current outbreak of SARS-CoV-2.

The lack of such diagnostics puts already vulnerable countries at an even higher risk and further strains weak health systems during epi- and pandemics. Investment in smart diagnostics that can be rapidly applied to emerging pathogens on a large scale is needed and needs to be prioritized by stakeholders.