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Perspective

A Novel Coronavirus Emerging in China — Key Questions for Impact Assessment

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A novel coronavirus, designated as 2019-nCoV, emerged in Wuhan, China, at the end of 2019. As of January 24, 2020, at least 830 cases had been diagnosed in nine countries: China, Thailand, Japan, South Korea, Singapore, Vietnam, Taiwan, Nepal, and the United States. Twenty-six fatalities occurred, mainly in patients who had serious underlying illness.[1] Although many details of the emergence of this virus — such as its origin and its ability to spread among humans — remain unknown, an increasing number of cases appear to have resulted from human-to-human transmission. Given the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012,[2] 2019-nCoV is the third coronavirus to emerge in the human population in the past two decades — an emergence that has put global public health institutions on high alert.

China responded quickly by informing the World Health Organization (WHO) of the outbreak and sharing sequence information with the international community after discovery of the causative agent. The WHO responded rapidly by coordinating diagnostics development; issuing guidance on patient monitoring, specimen collection, and treatment; and providing up-to-date information on the outbreak.[3] Several countries in the region as well as the United States are screening travelers from Wuhan for fever, aiming to detect 2019-nCoV cases before the virus spreads further. Updates from China, Thailand, Korea, and Japan indicate that the disease associated with 2019-nCoV appears to be relatively mild as compared with SARS and MERS.

After initial reports of a SARS-like virus emerging in Wuhan, it appears that 2019-nCoV may be less pathogenic than MERS-CoV and SARS-CoV (see table). However, the virus's emergence raises an important question: What is the role of overall pathogenicity in our ability to contain emerging viruses, prevent large-scale spread, and prevent them from causing a pandemic or becoming endemic in the human population? Important questions regarding any emerging virus are, What is the shape of the disease pyramid? What proportion of infected people develop disease? And what proportion of those seek health care? These three questions inform the classic surveillance pyramid (see diagram).[4] Emerging coronavirus-

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Table 1. Pathogenicity and Transmissibility Characteristics of Recently Emerged Viruses in Relation to Outbreak Containment.

Virus	Case Fatality Rate (%)	Pandemic	Contained	Remarks
2019-nCoV	Unknown*	Unknown	No, efforts ongoing	
pH1N1	0.02–0.4	Yes	No, postpandemic circulation and establishment in human population	
H7N9	39	No	No, eradication efforts in poultry reservoir ongoing	
NL63	Unknown	Unknown	No, endemic in human population	
SARS-CoV	9.5	Yes	Yes, eradicated from intermediate animal reservoir	58% of cases result from nosocomial transmission
MERS-CoV	34.4	No	No, continuous circulation in animal reservoir and zoonotic spillover	70% of cases result from nosocomial transmission
Ebola virus (West Africa)	63	No	Yes	

* Number will most likely continue to change until all infected persons recover.

es raise an additional question: How widespread is the virus in its reservoir? Currently, epidemiologic data that would allow us to draw this pyramid are largely unavailable (see diagram).

Clearly, efficient human-to-human transmission is a requirement for large-scale spread of this emerging virus. However, the severity of disease is an important indirect factor in a virus's ability to spread, as well as in our ability to identify those infected and to contain it — a relationship that holds true whether an outbreak results from a single spillover event (SARS-CoV) or from repeated crossing of the species barrier (MERS-CoV).

If infection does not cause serious disease, infected people probably will not end up in health care centers. Instead, they will go to work and travel, thereby potentially spreading the virus to their contacts, possibly even internationally. Whether subclinical or mild disease from 2019-nCoV is also associated with a reduced risk of virus spread remains to be determined.

Much of our thinking regarding the relationship between transmissibility and pathogenicity of respiratory viruses has been influenced by our understanding of influenza A virus: the change in receptor specificity necessary for efficient human-to-human transmission of avian influenza viruses leads to a tropism shift from the lower to the upper respiratory tract, resulting in a lower disease burden. Two primary — and recent — examples are the pandemic H1N1 virus and the avian influenza H7N9 virus. Whereas the pandemic H1N1 virus — binding to receptors in the upper respiratory tract — caused relatively mild disease and became endemic in the population, the H7N9 virus — binding to receptors in the lower respiratory tract — has a case-fatality rate of approximately 40% and has so far resulted in only a few small clusters of human-to-human transmission.

It is tempting to assume that this association would apply to other viruses as well, but such a similarity is not a given: two coronaviruses that use the same receptor (ACE2) — NL63 and SARS-CoV — cause disease of different severity. Whereas NL63 usually causes mild upper respiratory tract disease and is endemic in the human population, SARS-CoV induced severe lower respiratory tract disease with a case-fatality rate of about 11% (see table). SARS-CoV was eventually contained by means of syndromic surveillance, isolation of patients, and quarantine of their contacts. Thus, disease severity is not necessarily linked to transmission efficiency.

Even if a virus causes subclinical or mild disease in general, some people may be more susceptible and end up seeking care. The majority of SARS-CoV and MERS-CoV cases were associated with nosocomial transmission in hospitals,[5] resulting at least in part from the use of aerosol-generating procedures in patients with respiratory disease. In particular, nosocomial super-spreader events appear to have driven large outbreaks within and between health care settings. For example, travel from Hong Kong to Toronto by one person with SARS-CoV resulted in 128 SARS cases in a local

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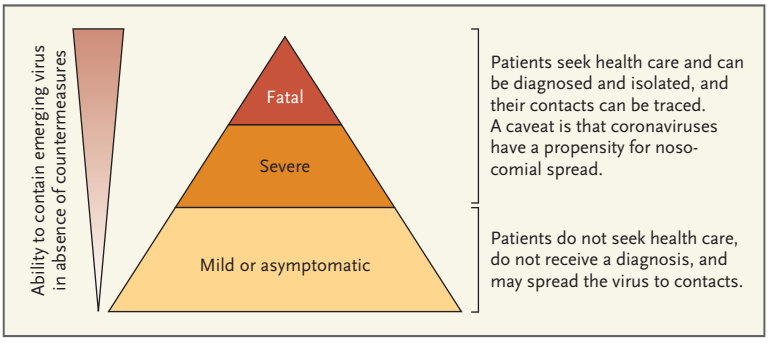

Figure 1. Surveillance Pyramid and Its Relation to Outbreak Containment.

The proportion of mild and asymptomatic cases versus severe and fatal cases is currently unknown for 2019-nCoV — a knowledge gap that hampers realistic assessment of the virus's epidemic potential and complicates the outbreak response.

hospital. Similarly, the introduction of a single patient with MERS-CoV from Saudi Arabia into the South Korean health care system resulted in 186 MERS cases.

The substantial involvement of nosocomial transmission in both SARS-CoV and MERS-CoV outbreaks suggests that such transmission is a serious risk with other newly emerging respiratory coronaviruses. In addition to the vulnerability of health care settings to outbreaks of emerging coronaviruses, hospital populations are at significantly increased risk for complications from infection. Age and coexisting conditions (such as diabetes or heart disease) are independent predictors of adverse outcome in SARS-CoV and MERS-CoV. Thus, emerging viruses that may go undetected because of a lack of severe disease in healthy people can pose significant risk to vulnerable populations with underlying medical conditions.

A lack of severe disease manifestations affects our ability to contain the spread of the virus. Identification of chains of transmission and subsequent contact tracing are much more complicated if many infected people remain asymptomatic or mildly symptomatic (assuming that these people are able to transmit the virus). More pathogenic viruses that transmit well between humans can generally be contained effectively through syndromic (fever) surveillance and contact tracing, as exemplified by SARS-CoV and, more recently, Ebola virus. Although containment of the ongoing Ebola virus outbreak in the Democratic Republic of Congo is complicated by violent conflict, all previous outbreaks were contained through identification of cases and tracing of contacts, despite the virus's efficient person-to-person transmission.

We currently do not know where 2019-nCoV falls on the scale of human-to-human transmissibility. But it is safe to assume that *if* this virus transmits efficiently, its seemingly lower pathogenicity as compared with SARS, possibly combined with super-spreader events in specific cases, could allow large-scale spread. In this manner, a virus that poses a low health threat on the individual level can pose a high risk on the population level, with the potential to cause disruptions of global public health systems and economic losses. This possibility warrants the current aggressive response aimed at tracing and diagnosing every infected patient and thereby breaking the transmission chain of 2019-nCoV.

Epidemiologic information on the pathogenicity and transmissibility of this virus obtained by means of molecular detection and serosurveillance is needed to fill in the details in the surveillance pyramid and guide the response to this outbreak. Moreover, the propensity of novel coronaviruses to spread in health care centers indicates a need for peripheral health care facilities to be on standby to identify potential cases as well. In addition, increased preparedness is needed at animal markets and other animal facilities, while the possible source of this emerging virus is being investigated. If we are proactive in these ways, perhaps we will never have to discover the true epidemic or pandemic potential of 2019-nCoV.

Disclosure forms provided by the authors are available at NEJM.org.

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