New coronavirus outbreak: Framing questions for pandemic prevention

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The new coronavirus, severe acute respiratory syndrome (SARS)–CoV-2, has caused a rapidly spreading outbreak centered in China. This new betacoronavirus, similar to those in bats, has appeared in at least 83 other countries and infected over 94,200 people with more than 3200 deaths as of March 4, 2020 (https://systems.jhu.edu/research/public-health/ncov/). To understand the unprecedented challenges posed by SARS–CoV-2, which causes the newly described "coronavirus disease 2019" (COVID-19), it is insufficient to rely exclusively on confirmed cases and their geospatial spread. It is valuable, but also insufficient, to report statistics on mild (80.9%), severe (13.8%), and critical (4.4%) cases (1). Instead, we must understand and quantify the dominant variables that govern the current outbreak.

An infectious disease outbreak can be characterized by its reproductive number, R_o. If this number is greater than one, $R_o > 1$, cases are statistically capable of transmitting an infection to secondary cases. If it equals one or less, $R_o \leq 1$, chains of secondary transmission soon end. Although preliminary, current estimates of R_o for the SARS–CoV-2 outbreak in China range from 2.5 to 2.9, with an associated all-age case fatality ratio estimated to be 2.3% (1,2). In comparison, the 1918–1919 Spanish influenza pandemic that killed about 50 million people worldwide is estimated to have had an R_o ~1.8 and a case fatality ratio of 1 to 2%. These estimated numbers for the SARS–CoV-2 outbreak are concerning, but such data alone do not enable expert assessment of the continuing COVID-19 threat.

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Both the 2002–2003 SARS and the 2012–2015 Middle Eastern respiratory syndrome (MERS) coronavirus outbreaks were associated with variable numbers of transmitted secondary nonhospital (community) and hospital-based cases, but subsequent estimates suggest an $R_o < 2$ (3). In contrast, the current COVID-19 pattern of spread appears concerning because of similar or greater R_o in combination with similar or possibly shorter doubling times.

Many relevant questions, however, remain unanswered. What pathogen-associated variables account for these amplification dynamics? What society-based variables are different from, or have changed since, the SARS and MERS events? Which population areas will sustain $R_o > 1$, and what are the determinants of this degree of transmission? In addressing these questions, there are two domains of variables and several types of interventions that should be studied.

Variables pertaining to the pathogen-host interaction include the following: duration of viral shedding (time), titer of viral shedding (number of infectious particles released), duration of viral stability (environmental), and heterogeneity of viral shedding (e.g., "superspreaders"). Moreover, changes to the viral genome, should ongoing human adaptation occur, could conceivably alter the average value of these variables over time. Variables pertaining to society-based mixing include the following: people per area (densities), daily commuting (housing and workforce structure), close contact interactions (greater travel opportunities), and new behavior patterns (urbanization and greater mobility), among many others.

Interventions to consider include the impacts of quarantine, case and contact isolation, hand hygiene, face masks, public education about personal protection, therapeutics (antivirals and antibodies), and future vaccines. Recent reports suggest that COVID-19 exhibits a mild or even "preclinical but communicable" period of viral shedding and spread of infection (4). Such features are observed for human influenza viruses and many other respiratory viruses but not for the SARS and MERS coronaviruses. In addition, there are suggestions that people who are asymptomatic or "subsymptomatic" can transmit SARS–CoV-2 as well.

Basic mathematical models of epidemiological outbreaks are used to estimate R_o, but they cannot determine the pathogen-based variables. These estimates will require clinical observations and "shoe-leather" epidemiology. Society-based variables can be extracted from existing demographics, transportation, and telecommunications data. Already, health authorities in China have started using time-dependent locations of mobile phones over geospatial regions to provide some of the necessary data. Because of privacy and security issues, however, collecting agencies in other countries may be unwilling to share such data —even during disasters or public health emergencies.

Mathematical models that offer real-time forecasting of COVID-19 cases over several weeks have begun to appear in published papers and online resources. Yet more comprehensive mathematical models that include complex pathogen- and society-based variables may require considerable time and effort to develop and validate (often months to years). Nevertheless, we can use existing mathematical models developed for previous influenza pandemics or SARS and MERS outbreaks. They include those developed by the U.S.

National Institute of General Medical Sciences for the Models of Infectious Disease Agent Study (5). Such differential equation models account for the variations in pathogen, society, and intervention-based variables. Obviously, their accuracy for forecasting the spread of COVID-19 will depend on the quality of the transmission model and underlying data.

We believe that scientific efforts need to include determining the values (and ranges) of the above key variables and identifying any other important ones. In addition, information on these variables should be shared freely among the scientific and the response and resilience communities, such as the Red Cross, other nongovernmental organizations, and emergency responders. Establishing one data bank that organizes information according to pathogen-host, society-based mixing, and intervention-impact modules may offer the most efficient means for sharing such disparate information. Such a resource would connect all of the existing networks of data banks. In addition, such a "centralized exchange" bank could introduce automated tools to find, assemble, and evaluate data for subsequent curation and linkage.

Many mathematical modeling groups in the United States, China, and Europe are working independently to predict the spread of COVID-19 infections. We believe that coordinating aims among these groups is essential and should be supported by government agencies. On 12 February 2020, the World Health Organization (WHO) took the lead by organizing a Global Research and Innovation Forum and announcing an associated R&D Blueprint with objectives (6). We emphasize three specific aims that encompass WHO's objectives: (i) predicting further spread of COVID-19 in China, (ii) predicting its potential for spread to and further transmission within other locales under various conditions, and (iii) predicting the effectiveness of different mitigation strategies (e.g., quarantine, contact isolation, hand hygiene, and use of face masks).

Multiple clinical trials are now under way to find therapies for COVID-19. Unfortunately, on the medical front, there are no currently approved vaccines or antiviral drugs for treating coronavirus infections. Supportive care, including hospitalization and intensive care unit management, is the only therapeutic option. Furthermore, the possibility that pneumonia caused by SARS–CoV-2 could, like influenza, potentiate fatal bacterial secondary infections needs to be urgently investigated. Fortunately, on the public health front, interventions may exist for protecting large populations, including travel restrictions, quarantine, and case/contact isolation. Identifying optimal measures, however, will require understanding the dominant factors that drive the COVID-19 outbreak and monitoring how these factors change over time and location.

Through 2019, WHO has declared five "Public Health Emergencies of International Concern." On 30 January 2020, it declared a sixth one for the expanding COVID-19 outbreak. In this unfolding epidemic, the world needs actions guided by expert consensus and, as emphasized in this Editorial, further guided by data-driven models.
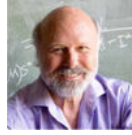
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