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EDITORIAL

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The 2019 coronavirus: Learning curves, lessons, and the weakest link

In the space of just six weeks, a new coronavirus, from a family that his torically was not viewed as a global health concern, has become daily headline news around the globe. The 21st century marked its arrival with the emergence of three previously unknown coronaviruses. SARS-CoV (severe acute respiratory syndrome coronavirus) was recognized in November 2002,[1,2] MERS-CoV (Middle East respiratory syndrome coronavirus) in June 2012,[3,4] and 2019-nCoV in December 2019.[5] Previously, human coronaviruses, known since the 1960s, were viewed as being only marginally relevant to the clinic, except for infants, the elderly, and immunocompromised individuals.[1,6,7] What these, and several other recent outbreaks have in common, is how fast they circled the world. Outbreaks that centuries ago needed weeks or months to spread globally can today reach any continent within days.[8] The first, spring wave of the 1918 Spanish Flu, at a time when travel by ship was the fastest way of transportation around the world, spread through the United States, Europe, and possibly Asia over six months.[9,10] The pandemic affected over a quarter of the world's population, caused 50-100 million deaths, more than the two World Wars combined, and caused life expectancy at birth in the United States to drop by 11.8 years between 1917 and 1918.[9,11,12] In comparison, in 2002-2003 the SARS-CoV spread to 5 countries within 24 hours,[13] and in 2009 the H1N1 influenza virus spread to 30 countries within 6 weeks.[14]

In the most recent of the three coronavirus outbreaks, several clusters of patients with pneumonia started to be reported on December 8, 2019 from Wuhan, China, and most of them were epidemiologically linked to the Huanan Seafood Wholesale Market.[5,15-17] The market was closed on January 1, 2020.[5] By February 11, 2020, the virus, 2019-nCoV, was reported from >28 countries and special administrative regions, affected >43 000 people, and caused 1018 deaths.[18] The ability of the virus to spread by human-to-human transmission was confirmed.[19] A preliminary epidemiological analysis indicates that the incubation period of 2019-nCoV is similar to that of SARS, but with a wider confidence interval, and longer than the one for the 2009 H1N1 influenza strain.[20] On February 11, 2020, the disease caused by 2019-nCoV was named COVID-2019, for coronavirus disease in 2019.[21-23]

Real-time information about the outbreak is available via an online virus tracker developed by researchers at Johns Hopkins University, based on information collected from the World Health Organization (WHO), the United States Centers for Disease Control and Prevention (CDC), the European CDC, China CDC (CCDC), China's National Health Commission (NHC), and DXY (a Chinese website that aggregates NHC and local CCDC).

The prompt availability of the viral genome was critical for allowing comparisons with coronaviruses from previous outbreaks and helped make initial predictions. After the 2019-nCoV was isolated on January 7, 2020, its sequence was published on January 12, 2020.[24,25] The virus shares >70% genetic similarity with the 2002-2003 SARS-CoV strain,[5] is most closely related to coronaviruses of bat origin,[17] its spike glycoprotein gene appears to have emerged by recombination between a bat coronavirus and a coronavirus of unknown origins, and relative synonymous codon usage bias analyses indicate that snakes may be a potential reservoir.[26]

The SARS-CoV spike protein receptor binds the angiotensin-converting enzyme 2 (ACE2) on host cells, an interaction that shapes cross-species and human-to-human transmission.[27,28] ACE2 is a metallopeptidase expressed in numerous tissues, including alveolar epithelial cells and enterocytes.[29-32] Sequencing indicates that the 2019-nCoV might also use ACE2 as a receptor.[33] The 2019-nCoV spike receptor-binding domain is 73%-76% similar at the genomic level to the one from the SARS-CoV from human, civet, or bat viruses.[33] In late 2003-early 2004, after the first coronavirus outbreak, a second coronavirus outbreak was reported in Guangdong, China, in four individuals in contact with animals, all of whom recovered, and the strain was different from the one that caused the first outbreak.[34-36] Amino acid analyses indicate that 2019-nCoV uses human ACE2 less efficiently than the 2002-2003 SARS-CoV but more efficiently than the 2003-2004 SARS-CoV. In 2019-nCoV, the presence of asparagine at position 501, which is compatible with, but not ideal for binding human ACE2, suggests that the virus has acquired the ability for human-to-human transmission, but this appears to be more limited than that of the 2002-2003 SARS-CoV strain.[26] The mutation of this asparagine to threonine in 2019-nCoV was predicted to significantly increase the ability of the virus to bind the human ACE2 receptor and should be closely monitored for.[33]

One of the earliest interventions during the 2019-nCoV outbreak involved quarantining an estimated 50-60 million people in multiple Chinese cities, in what appears to be the largest mass quarantine in history.[37,38] It is still too early to visualize the impact of this initiative on the global dynamics of the outbreak, and retrospective analyses will be critical. Quarantines, even though they are controversial, come at a high cost, and have been viewed with suspicion, were historically found to delay and slow the spread of various outbreaks.[39-43] Quarantines are one of the non-pharmaceutical

interventions, which also include personal hygiene measures, cancellation of mass gatherings and public events, school and workplace closure, and travel restrictions.[44-46] What all these interventions share is that at least during the initial stages of a new outbreak, particularly when a novel pathogen is involved and therapies are not yet available, they are one of the few options available. A lesson that flu taught us is that non-pharmaceutical interventions are at least as important as drugs or vaccines in controlling a pandemic.[47] A comparison between St. Louis and Philadelphia during the 1918 flu pandemic is relevant in this respect. After St. Louis experienced its first cases of flu on October 5, it closed schools, theaters, and banned public gatherings on October 7.[47,48] Philadelphia experienced its first cases on September 17, but allowed a city-wide parade to be held on September 28, and only implemented measures on October 3.[47,48] During the September 8-December 28, 1918 period, the peak weekly excess pneumonia and influenza death rate was 251 vs 31/100 000 in St. Louis and Philadelphia, respectively.[48]

Another intervention, albeit of controversial value, that was implemented in the wake of some outbreaks, including the current coronavirus one, is thermal screening at some airports.[49] An analysis of airline passenger screenings during the 2009 H1N1 pandemic emphasized that many national authorities usually focus on preventing the import, but not the export of pathogens, even though from a contemporary perspective interventions would be globally most impactful if implemented as close as possible to the sources of an epidemic, by exit screening.[50] Entry screening did not detect any of the confirmed SARS cases in Australia, Canada, and Singapore during the 2002-2003 outbreak, but is believed to have discouraged ill people from traveling and raised awareness.[51-53] During the SARS outbreak in Taiwan, among 80 813 travelers arriving on flights from WHO-designated SARS-affected areas who were quarantined for 10 days, probable or suspected SARS was diagnosed in 21 (0.03%) but none of them was identified by thermal scanning upon entering Taiwan.[54,55] In Italy, even though entry screening was conducted at two international airports, none of the 72 individuals, including four probable SARS cases, that were admitted for clinical evaluation, were referred to the hospitals by airport authorities.[56] Some of the limitations of screening measures, in the wake of an outbreak, include denying contact with ill individuals, taking antipyretic medication to conceal fever,[51] and its reliance on the length of the incubation period of the infectious disease.[57]

About 400 new infectious diseases were identified since 1940, and new pathogens emerge at faster rates.[10,58-60] Every outbreak brings something new, provides opportunities to reap the benefits gained from past epidemics and pandemics, and provides novel lessons that will shape the framework to manage emerging infectious diseases. One aspect that all outbreaks share is their potential for rapid global dissemination through air travel. As we attempt to predict and quantitate the impact of international travel on an infectious disease outbreak and visualize the host, environmental, and microbial factors that make some outbreaks spread faster and others have higher mortality, it is worth noting that in 2013, for the first time, the annual number of passengers exceeded three billion.[8] An estimated one million people travel internationally every day, one million people travel between developing and developed countries every week,[61] and the volume of airline passengers increases annually.[62] In 2014, for the first time, the daily number of flights exceeded an annual average of 100 000.[8] It has become increasingly easy to reach any continent within 24 hours, a period that is shorter than the incubation time of most contagious diseases.[63] This brings us closer to the inevitability of future pandemics that experts have long warned about, whether influenza[64] or SARS.[65]

On the bright side, despite the inevitability of future pandemics that could quickly spread globally due to the escalation of air travel, science reached the point where it can quickly identify a pathogen, learn about its biology, and protect global health. For example, as 2019-nCoV illustrated, modern science can identify and sequence new viruses within days. Thus, even though future pandemics are inevitable, embracing technological advancements and learning from the past will make the consequences of epidemics and pandemics less inevitable.

The 2019-nCoV outbreak has brought an element of déjà-vu, plenty of fears, some assumptions, and a relentless race to better understand this novel virus. Critical questions include identifying the reservoirs, understanding the transmission route(s), defining the incubation period and the time when the virus can be transmitted, characterizing the clinical spectrum of the disease, exploring the potential of long-term health effects, and learning more about susceptible populations. As we approach mid-February, we don't know yet much about the epidemic curve of the outbreak. Its morbidity, mortality, mental health impact, and psychological effects are impossible to predict. The existence and the contribution of super-spreaders, defined as contagious hosts that create more secondary contacts that most others in the population, will be a critical component of retrospective analyses, and there is an indication that super-spreading might already have occurred in the current outbreak.[66]

An important consideration, for this and future outbreaks, is understanding the types of different non-pharmaceutical interventions, their combined benefit, and the best timing for their implementation. This is both a learning curve and a new lesson in the wake of every epidemic, most likely riddled with differences even between two nearby cities impacted by the same outbreak. However, this is also the weakest link and the one that will indisputably assume a critical role in the management of zoonotic infectious diseases, a world where, as we know by now, history keeps repeating itself.

NOTE ADDED IN PROOF

As of February 26, 2020, >82,000 COVID-19 infections and 2,798 deaths were reported. The first major outbreak in Europe, and the largest one outside of Asia, was reported in Italy, with 453 cases and 7 deaths as of February 26, 2020. In Italy, the difficulty to trace the chain of the outbreak to the first infection in the country represents a huge setback in terms of the public health interventions that could help contain the spread of the virus. The

SARS-CoV-2 (previously referred to as 2019-nCoV) outbreak has brought to prominence another topic related to epidemic and pandemic preparedness, which involves transmission of the virus, the management of an outbreak, and the role of quarantines aboard cruise ships.

DISCLOSURE

None.

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