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The continued epidemic threat of SARS-CoV-2 and implications for the future of global public health

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A new coronavirus (CoV) called SARS-CoV-2 emerged in Wuhan, China in December 2019 as the etiological agent of a viral pneumonia called COVID-19. The global spread of SARS-CoV-2 has been so extensive that the WHO declared COVID-19 a pandemic on March 11, 2020. Below, we discuss the emergence of SARS-CoV-2 and provide the historical context, which strongly suggests emerging CoVs provide an immediate threat to global public health and will continue to do so in the future.

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Previous emerging coronavirus discoveries

Coronaviruses infect many different mammals and birds [1••]. Before 2002, coronaviruses were not known to cause severe human disease and instead were primarily of agricultural and domestic animal importance. A new paradigm for human coronavirology was born with the emergence of severe acute respiratory syndrome CoV (SARS-CoV) in November 2002 in Guangdong Province, China. The epidemic strain of SARS-CoV, is believed to have emerged from a bat reservoir through a civet intermediate host in live animal markets and then spilled over into humans [2]. At that time, viruses similar to SARS-CoV were found in a variety of species in live animal markets in China including racoon dogs and ferret badgers [2]. This notion of CoV emergence was further solidified with discovery of the novel highly pathogenic Middle East respiratory syndrome CoV (MERS-CoV) in 2012, which also likely emerged from an ancestral bat-CoV but through a camel intermediate host which continues to seed human MERS-CoV infections to this day [2,3]. Given the diversity and prevalence of CoV circulating among wild birds and mammals, it is not surprising that the potential for emerging CoV to cause severe disease outbreaks and epidemics is not limited to humans. In the past century, three porcine CoV have emerged. First in the 1970s with porcine epidemic diarrhea virus (PEDV), in 2012 with porcine deltacoronavirus (PDCoV) and in 2019 with severe acute diarrhea syndrome CoV (SADS-CoV), which together have killed millions of piglets worldwide [4–6]. Like SARS-CoV, SADS-CoV is believed to have emerged from Chinese horseshoe bats [6]. Now, with the current emergence of SARS-CoV-2, the paradigm of CoV as a family with emergence potential and a consistent ability for spillover into new species to cause diseases never before seen has truly been solidified. Thus, while attempting to control the global pandemic of SARS-CoV-2, we must prepare for the continual emergence of new coronavirus in the future.

With the recognition of the potential for CoV emergence from wild animal reservoirs came the realization that we lacked a deep understanding of CoV diversity as well as animal reservoir ecology. Coupled with the advent of deep sequencing technology as SARS-CoV was emerging, various metagenomic surveys have drastically changed our understanding of the CoV sequence diversity, geospatial distribution, and animal reservoir diversity. These surveys have found CoV sequences in bats in the North and South America, Europe, Asia, Australiasia and Africa [7–14]. Interestingly, CoV similar to both SARS- and MERS-CoV have been found in bats in China [9,15,16]. Using isolates or reconstructed viruses in the lab, these bat viruses have been shown to readily infect human cells without adaptation [16–19]. Thus, future spillover of a SARS-like or MERS-like virus continues to be real possibility.

SARS-CoV-2 emergence

A novel coronavirus emerged from Wuhan in Hubei Provence in China with the first cases being identified at the end of November and presenting symptoms at the beginning of December 2019 [21]. A large cluster of ~40 cases were identified and associated with the Huanan Wholesale Animal Market in Wuhan in the first week of January 2020, which grew to 198 laboratory confirmed infections with three fatal cases by January 20th, 2020 [21]. Since then, the virus has spread to 192 countries with over 4 million cases and over 280 000 deaths as of May 11, 2020.

Early clinical cases

In an early study of 41 patients confirmed to have SARS-CoV-2, patients that were admitted to Wuhan Hospital presented with fever (98%), cough (76%), dyspnea (55%), and fatigue (44%) [20•]. In all of these patients they had pneumonia with abnormal findings on a chest X-ray and computed tomography (CT) scans. As cases began to increase across the Hubei Province additional clusters of cases were identified. A family cluster of seven individuals was analyzed where after the index case was infected, the virus spread to the other six family members [22•]. This cluster highlights two important features of SARS-CoV-2. First, virus was transmitted following minimal contact with the infected individual suggesting the virus is highly transmissible. Second, one individual had no respiratory or fever symptoms however was positive for the virus by nasopharyngeal swab. This alerted the medical community to the potential spectrum of infection scenarios which could include asymptomatic infection.

As the outbreak began to spread in Hubei province and to other countries, the potential for epidemic spread outside of China was realized. In a case in Vietman, a couple traveled through Wuhan but said they did not visit any animal markets however they were identified as symptomatic and positive for SARS-CoV-2 [23••]. They subsequently spread the virus to their son who had not left Vietnam, demonstrating transmission outside of the China. The first case exported to the United States was identified on January 20, 2020 where a man returning to the US on January 15, 2020 from visiting China began developing respiratory symptoms and went to the hospital for assessment on January 19, 2020 [24••]. Since this first case, there have been over 1.3 million cases in the US. Two of the initial cases in the US were the result of direct transmission between the infected patient and a close contact. These cases serve as examples for the potential transmission of virus before quarantine and foreshadow the potential for spread before the implementation of public health measures complicating containment and mitigation globally.

Current state of knowledge of coronavirus spread and diversity

Since SARS-CoV emerged in 2002, there has been a large interest in emerging coronaviruses which was spurred again in 2012 with the emergence of MERS-CoV. There has been significant interest in understanding how these viruses cause disease, why they tend to cause the most severe disease in older people, how the virus and host response to infection collaborate to cause severe lung disease, and for the development of antivirals, antibodies and vaccines. There are no approved vaccines or therapies for any human coronavirus. This is in part due to perception that there is not a need for medical counter measures for emerging viruses which can rapidly emerge, cause devastating epidemic disease and then seemingly disappear from the human population as happened with SARS-CoV in 2003. Given that three new human CoV have emerged in the past 20 years, this may finally provide the activation energy needed to motivate the development of broad-spectrum therapeutics and vaccines. Since it is unknown what viruses will emerge in the future, broadly acting antivirals targeting conserved viral proteins, like the RNA polymerase, or targeting host proteins that many viruses require for replication, are the most effective therapeutic category for the current and future outbreaks. For instance, the broad-spectrum antiviral, remdesivir, targets the viral RNA dependent RNA polymerase and is potently antiviral against Ebola, respiratory syncytial virus, Nipah and Hendra viruses and multiple endemic and emerging CoV in cell culture models [25–28,29•,30]. Remdesivir is currently being evaluated in randomized control trials in China (Clinicaltrials.gov, NCT04257656, NCT04252664) and in the United States (Clinicaltrials.gov, NCT04292899, NCT04292730, NCT04280705). Alternatively, a pan-CoV antibody approach could be tested on all current Coronavirus strains to aid in the assurance that it will work for future outbreaks. The difficulty is in the targeting of the Spike protein which is wildly divergent across the CoV lineages (i.e. alph, beta, delta, gamma). For example, SARS-CoV-2 spike protein is 90% similar to that of SARS-CoV but these viruses are both beta CoV. When comparing CoV of unrelated lineages, SARS-CoV and alpha CoV 229E, spike proteins are approximately 50% similar. However, group specific antibodies or vaccines could be used to protect against many types of coronaviruses at once given the inherent intra-lineage spike protein conservation. Future therapeutic developments would hinge on the ability to test these therapeutics in humans in controlled trials such as human challenge models where an individual gets infected with hCoV-OC43 under observation while also being given either a vaccine or antibody that has been shown to be broadly active *in vitro* or in mouse models, should they exist.

Four of the seven known human CoV are endemic in the human population (i.e. OC43, 229E, NL64, and HKU1) and continually circle the globe typically causing the common cold. For the cold causing coronaviruses (CCC), which are responsible for 10–26% of seasonal colds, we know very little about their longitudinal genetic variation, effects on the host and CoV immunity [31,32]. Thus, there are large gaps in knowledge that would be useful to have answers to in the context of understanding this current outbreak. The current outbreak of SARS-CoV-2 has the hallmarks of becoming a seasonal cold causing coronavirus. Thus, we have an unprecedented research opportunity to not only better understand SARS-CoV-2 but to also glean insights into the constellation of events that fostered the emergence, spread and eventual endemicity of the previously known CCC. From this pandemic, we will have a deep understanding of the

degree of viral genetic drift and if this virus does become endemic, sequence variation from year to year can be compared to the volumes of sequence data being generated from the virus' initial passage in the human population. In addition, epidemiological and clinical data in conjunction with animal models should help elucidate why there is increased viral pathogenesis with increasing age. Because of the widespread nature of this pandemic, there is also the potential for human genome wide association studies which could uncover both susceptibility and resistance alleles. These human genetic studies coupled with virus and host interaction studies may reveal host molecules or pathways that could be exploited for host targeted antiviral therapies. Lastly, an exhaustive survey of wild and domestic animal species should help elucidate the animal reservoir of SARS-CoV-2 which is needed to prevent future introduction of SARS-CoV-2-like viruses into the human population. This new body of knowledge in conjunction with the development of broadly active vaccines, drugs and antibodies should better position humanity to deal with inevitability of CoV emergence in the future.

Conclusion

This current outbreak has highlighted that: 1) CoV diversity is much more complex that realized pre-2002, 2) CoV reservoirs are diverse, not geographically constrained globally and some have the potential for rapid and distant global transit like bats and birds 3) Some CoV found in animal reservoirs are similar to known human epidemic strains, 4) genetic and antigenic diversity may make broad-spectrum therapeutics difficult to design and 5) broad-spectrum therapies effective against currently known CoV as well as those that may emerge in the future are desperately needed. The emergence of SARS-CoV-2 is the global public health emergency we have been predicting and preparing for since the advent of SARS-CoV yet still we are not adequately prepared.

Conflicts of interest statement

Nothing declared.

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