What We Need to Consider During and After the SARS-CoV-2 Pandemic

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Abstract

Even though extreme containment and mitigation strategies were implemented by numerous governments around the world to slow down the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the number of critically ill patients and fatalities keeps rising. This crisis has highlighted the socioeconomic disparities of health care systems within and among countries. As new CoVID policies and responses are implemented to lessen the impact of the virus, it is imperative (1) to consider additional mitigation strategies critical for the development of effective countermeasures, (2) to promote long-term policies and strict regulations of the trade of wildlife and live animal markets, and (3) to advocate for necessary funding and investments in global health, specifically for the prevention of and response to natural and manmade pandemics. This document considers some of these challenges.

Keywords: SARS-CoV-2, CoVID-19, pandemic, biodefense

Introduction

FOR DECADES, HUNDREDS OF SCIENTISTS and specialists working on emerging infectious diseases have warned about the risks of dangerous pathogens crossing the animal–human species barrier and the threat of a pandemic. Despite our close encounters with various endemics such as Ebola, SARS-CoV-1, and Middle East Respiratory Syndrome (MERS-CoV), and even a pandemic such as H1N1, most citizens of developed countries and living in urban areas considered these warnings exaggerated as most of these diseases occurred in foreign and geographically remote locations (Reed Hranac et al. 2019, Wong et al. 2019). Although we have been aware for a long time that a particular pathogen infecting a human being in a remote area in Africa, Asia, or in the Amazon can be transported and spread within any region in the world in <36 h, these warnings were dismissed and considered overstated.

Even though hundreds of publications established that—besides deforestation, climate change, urbanization, and others—travel and trade are the main factors in the spread of infectious diseases, and several mathematical models estimated the catastrophic economic impact of a pandemic, the call for the implementation for strong biosecurity and global health programs did not result in wide political support and

sufficient funding for research (Cohen 2000, Wilson 2020). Under these circumstances, the entire public health prevention and response system in most countries became complacent and unprepared for the “perfect storm,” which came upon us in early January 2020 with the advent and spread of a previously unknown respiratory illness, caused by a novel CoV now called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

The novel coronavirus disease (CoVID-19) was first reported by the WHO in the city of Wuhan, Hubei Province, China, at the end of December 2019. CoVID-19 is caused by the SARS-CoV-2 (Gorbalenya et al. 2020, Zhou et al. 2020). Symptoms of the disease caused by SARS-CoV-2 range from mild to severe illness and death. Onset of symptoms (fever, cough, and shortness of breath) may appear in infected individuals within 2 to 14 days after infection, with a median incubation period of 5 to 6 days (Wölfel et al. 2020). Based on current data, ~81% of infections are mild, 14% of cases are severe, which include pneumonia and shortness of breath, and 5% of cases are critical, which can result in respiratory failure, septic shock, multiorgan failure, and death. The case fatality rate increases with age (especially older than 70 years) and in individuals with pre-existing conditions, and relatively few cases were recorded among children. All these data are preliminary and may change when more information is available (Chen 2020).

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By the end of January 2020, Australia, Malaysia, Japan, Canada, Thailand, Singapore, Philippines, and Russian reported their first cases of imported SARS-CoV-2. By February, the Chinese whistleblower Li Wenliang died with CoVID-19, whereas Italy, Spain, and Iran began to report a rapid increase of deaths caused by the virus. In <5 months, due to travel and regular physical contact, SARS-CoV-2 has spread to >212 countries and territories, affected >4.3 million people, and caused >291,000 fatalities (as of May 12, 2020).

By the end of March 2020, >120 countries established strict and unprecedented isolation measures for their citizens, including physical/social distancing to mitigate the spread of the virus and to significantly decrease the demand for hospital services, especially in intensive care units. Physicians in Italy and Spain started to prioritize medical attention to patients with a higher chance of survival. By March 27, the chief of International Monetary Fund, Ms. Kristalina Georgieva, declared that the pandemic is already causing a global economic recession. By the end of April, the U.S. Department of Labor reported an unprecedented 26.4 million people applying for unemployment benefits. More than 3000% than the prepandemic levels. This is the highest number ever on records. By May, the overall reduction of the global industrial output was 18%, and the price of agricultural commodities fell by 20% as the stock market index reached a historical decline that led to drastic deterioration of the liquidity levels in many countries (Ivanov 2020, Nicola et al. 2020).

Even though extreme containment and mitigation strategies were implemented by numerous governments around the world to slow down the spread of SARS-CoV-2, the number of critically ill patients and fatalities keep raising. This crisis has highlighted the socioeconomic disparities of health care systems within and among countries. As new CoVID policies and responses are implemented to lessen the impact of the virus, it is imperative (1) to consider additional mitigation strategies critical for the development of effective countermeasures, (2) to promote long-term policies and strict regulations of the trade of wildlife and live animal markets, and (3) to advocate for necessary funding and investments in global health, specifically for the prevention of and response to natural and intentional pandemics.

We need to expand our understanding of CoV genomic plasticity

Coronaviridae are a large family of RNA viruses commonly infecting people and different species of domestic and wild animals, including cattle, swine, horses, dogs, cats, camels, and bats. Until 2019, six pathogenic CoVs were known to infect humans (hCoV-OC43, hCoV-229E, hCoV-NL63, hCoV-HKU1, SARS-CoV-1, and MERS-CoV) (Zaki et al. 2012, Fehr and Perlman 2015, Lim et al. 2016). DNA sequencing and phylogenomic analysis of the 29,903 nucleotides genome SARS-CoV-2 indicate that it belongs to the subgenus *Sarbecovirus* of the genus *Betacoronavirus* (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020, Andersen et al. 2020). The SARS-CoV-2 genome shares ~80% identity with SARS-CoV-1, and its sequence shares ~90% identity with a betacoronavirus isolated in 2015 from horseshoe bats (*Rhinolophus affinis*) and pangolins (*Manis javanica*) (Andersen et al. 2020); however, the natural reservoir and host range of SARS-CoV-2 have not been determined yet.

Despite their similarities, neither bat nor pangolin beta-coronaviruses have the polybasic cleavage sites found in the furin cleave site in SARS-CoV-2 (Andersen et al. 2020). SARS-like CoVs have been identified from four horseshoe bat species within the genus *Rhinolophus* in both northern and southern China (Wong et al. 2019).

Researchers studying bats agree that *Rhinolophus* bats have a wide geographical distribution in tropical and temperate regions throughout Asia, Africa, and Europe, and they are rather poorly studied (Hayman 2016, Demos et al. 2019). In addition, recent studies have found SARS-like CoVs in Malayan pangolins (*M. javanica*); they belong to two sublineages of SARS-CoVs, including one that exhibits a high homology to SARS-CoV-2 in the receptor-binding domain region (Lam et al. 2020). Analysis of the genomic information has led to the hypothesis that the novel SARS-CoV-2 might be a recombined virus, with its genome backbone evolved from a bat SARS-like CoV closely related to that of the RaTG13 isolate and its receptor binding domain (RBD) region acquired from a pangolin SARS-like CoV (Paraskevis et al. 2020).

As SARS-CoV-2 still infects daily significant number of people belonging to different genetic backgrounds throughout the world, it will be critical to improve sampling and RNA detection techniques in doctor's offices and drive through field stations to obtain a better understanding of the distribution of SARS-CoV-2 in various populations. Next-generation sequencing (NGS) technology should also be applied to determine the molecular evolution of SARS-CoV-2 in different populations and different ecosystems. This could help to elucidate the mechanisms of virus adaptation to various host species and to identify the capacity of SARS-CoV-2 for recombination with other CoVs; the latter might have a significant impact on the host range SARS-CoV-2 and tropism (Graham and Baric 2010, Luk et al. 2019, Lamers et al. 2020).

CoVs have the propensity for interfamily, interspecies, and intraspecies recombination. For example, heterologous interfamily recombination event between a single-stranded positive-sense RNA bat CoV and a double-stranded segmented RNA orthoreovirus has been reported (Huang et al. 2016). There are several potential regions within the SARS-CoV-2 genome that have the ability to recombine through homologous RNA recombination (Rehman et al. 2020). Within the SARS-CoV-2 genome, these recombination hotspots include the region 11083–20953 of the ORF1a/ORF1b gene, region 25745–25862 of the ORF3a gene, region 16693–17932 of the helicase gene, region 15504–16692 of the RdRp gene, and positions 22077–22124, 22299–22435, 22397–2316, 23117–23270, 23519–23787, 23897–24342, and 24716–24790 including the RBD of the S-glycoprotein (Rehman et al. 2020, Susanna et al. 2020, Yi 2020).

Recombination of SARS-CoV-2 with other CoVs can lead to rapid adaptation to new host and ecological niches and can potentially shift the tropism of the virus and transmission across the species barrier from humans to companion or food animals (Rest and Mindell 2003, Zhang et al. 2005). Therefore, rapid detection of genetic mutation and potential recombination through NGS of the entire genome will provide valuable information to advert the emergence of novel SARS-CoV-2 variants in new animal hosts (Chen et al. 2005b). Testing of pet animals (cats, dogs, rabbits, pet pigs, ferrets, etc.) in close contact with CoVID-19 patients should also be considered, especially in view of the recent reports that

especially young cats are highly susceptible to SARS-CoV-2 infection (Chen 2020, Shi et al. 2020). Clearly, the rapid detection and whole genome characterization will provide valuable information to advert the emergence of novel variants for which countermeasures are not available (Chen et al. 2005a).

In addition to the mentioned *in vitro* data, *in vivo* experiments and epidemiological studies in the field will provide valuable information on the spread of the virus within certain communities and the involvement of intermediate hosts, such as companion animals or livestock (McNamara et al. 2020). Human to animal transmission of SARS-CoV-2 has been reported for cats and dogs living in the same household as CoVID-19 patients, but establishing clear links of transmission and replication in companion animals will provide key information for policy makers, epidemiologists, physicians, and veterinarians.

Scientists and policy makers should use the SARS-CoV-2 pandemic impact on global health, trade, and security to impose strict controls on wildlife (legal and illegal) and live animal markets (wet markets) around the world. This is particularly challenging in countries where wildlife distribution and consumption represent a market worth billions of dollars. In 2017, in China, the wildlife market value has been estimated at USD \$74 billion. Swift measures to close legal loopholes for online trading of wildlife products, and improvement of the harmonized trade code describing these products to enhance the interception capabilities of custom and border protection agencies, could be first steps toward a more robust response. At the same time, a revision of the United Nations' *Convention on International Trade in Endangered Species of Wild Fauna and Flora* is required to properly implement country-specific responses at ports of entry and in virtual markets in the deep web.

Vaccines elicit protective immune responses against CoVs

For the near foreseeable future, safe and efficacious vaccines for SARS-CoV-2 will not be available (Amanat and Krammer 2020). Vaccine development will greatly benefit from the scientific progress made during the preclinical evaluation of vaccines (and therapeutics) for both SARS-CoV-1 and MERS-CoV (Shang et al. 2020, Tse et al. 2020). Inactivated and attenuated CoVs, subunit, virus-like particles, DNA plasmids, and vector-based system have been used to produce vaccine candidates expressing different regions of the SARS-CoV and MERS-CoV genome (Graham et al. 2018, Shang et al. 2020, Walls et al. 2020).

Because the spike-glycoprotein (S) mediates host–receptor binding and virus entry and is the major target of neutralizing antibodies (nAbs), it has been used to induce protective humoral and cell-mediated immune responses (Lin et al. 2007, Enjuanes et al. 2008, Lokugamage et al. 2008, Martin et al. 2008). A modified vaccinia Ankara (MVA) expressing the SARS-CoV-S (rMVA-S) generated strong nAb responses and protected rhesus monkeys against lethal challenge (Chen et al. 2005a). Vaccination with recombinant adenovirus encoding the SARS-CoV-S protein (rADV-S) also induced protective immunity (Shim et al. 2012). Furthermore, different vaccination regimens of an S-based DNA vaccine, rMVA-S, and rADV-S in mice and rabbits revealed that heterologous immunization strategies with rMVA-S used as prime and rADV-S as boost induced the highest and most persistent level of nAb responses.

When the entire ectodomain of the S protein was produced in baculoviruses, and applied without adjuvant, the vaccine elicited the production of highly effective nAbs in mice (Feng et al. 2006). The baculovirus platform was also used to express a chimeric SARS-CoV-1 S and influenza-M1 protein, which induced nAbs and protective immunity against lethal challenge in mice (Liu et al. 2011). DNA plasmids encoding a modified SARS-CoV-1 S glycoprotein elicited protective immunity after intramuscular injection into BALB/c mice. A dose of 25 μ g of a DNA vaccine based on the S protein induced nAb responses that inhibited pulmonary viral replication (Yang et al. 2004). These examples of vaccine development and efficacy studies against related betacoronaviruses (*e.g.*, SARS-CoV-1 and MERS-CoV) revealed that the S glycoprotein of CoVs can induce protective immune responses.

Vaccines are an important aspect for SARS-CoV-2 mitigation; however, there is also evidence that certain vaccine formulations produced to protect against CoVs can negatively affect the outcome after virus infection and lead to enhancement of disease (vaccine-associated enhancement of respiratory disease, VAERD). Also, using attenuated vaccines can lead to recombination events with wild-type viruses and the emergence of new strains with potentially different virulence and host range (Fehr and Perlman 2015).

SARS-CoV vaccines based on inactivated virus preparations or the full-length recombinant S and/or N proteins applied with or without adjuvant to mice, ferrets, and non-human primates (NHPs) induce Th2-type mediated immunopathology with eosinophil infiltration after virulent challenge (Yasui et al. 2008, Tseng et al. 2012). Venezuelan equine encephalitis virus replicon particles expressing the SARS-CoV-1 N region failed to protect mice from homologous or heterologous virus challenge, and resulted VAERD-like immunopathology mainly in the lungs (Deming et al. 2006). There is also mounting evidence that under selective pressures CoVs can mutate, which could lead to a change in the receptor binding domain (Liu et al. 2007, Luk et al. 2019), the protease cleavage site (Simmons et al. 2013, Zhou et al. 2019), and the carbohydrate sites on the S protein (Millet and Whittaker 2015).

As the virus continues to adapt to the human host (and maybe to new intermediate hosts such as the cat), the interaction of the viral S-glycoprotein with other attachment factors or cofactors could lead to enhanced infection. For example, the C-type lectins DC-SIGN and DC-SIGNR (also termed L-SIGN), which are commonly expressed in sinusoidal endothelial cells and on placental macrophages, have been shown to facilitate viral transmission and enhanced infection of SARS-CoV-1 (Marzi et al. 2004). This adaptation could lead to the advent of mutant viruses with different tissue and cell tropisms (*e.g.*, respiratory tract to enteric tract shift), host range, and pathogenesis (Rest and Mindell 2003, Millet and Whittaker 2015). Novel mutants with different host cell susceptibility, infection, and transmission dynamics of SARS-CoV-2 in humans, companion animals, or even livestock could render available vaccines ineffective.

There is an unprecedented global race to develop vaccines against the SARS-CoV-2 (Dhama et al. 2020, Gao et al. 2020). According to the WHO, there are >103 public and private vaccine development efforts worldwide, of which 2 lipid nanoparticles encapsulated mRNA vaccine candidates, 1 adenovirus type 5 vector vaccine candidate, 3 inactivated vaccines, and 1 DNA plasmid vaccine candidate are currently

FIG. 1. Current State of biosurveillance systems.

undergoing Phase-I and Phase-II human clinical trials in the United States, Europe, and China. Vaccine approval for human use is a long and complex process that requires not only investments in the immunogenic product delivery technology, but also research on preclinical animal model development, adjuvant effects, and manufacture systems capable to scale up the vaccine production according to the expected demand.

Despite the investment of billions of dollars, and like other CoV vaccines, SARS-CoV-2 vaccine platforms could face a series of challenges associated with adverse effects for both human and animal health (Graham 2020). The diversity of the S-glycoprotein, the selection pressure induced by a vaccine on the virus could lead to vaccines with only partial cross-protection against heterologous virus strains. Incomplete virus inactivation, reversion to virulence or recombination of attenuated vaccine strains with wild-type strains could produce more virulent or highly transmissible virus strains. Induction of immune-mediated enhancement of disease and immunopathology and the decline of immune protection coupled with limited vaccine efficacy within senescent populations could represent a narrow efficacy range and limited margin of profit for vaccine development enterprises (Decaro and Lorusso 2020, Gao et al. 2020, Graham 2020).

A better understanding of the immune responses induced by different vaccine candidates, which on one hand can be safe and efficacious or on the other hand can induce VAERD, will require detailed studies on the humoral and cellular immune responses to SARS-CoV-2. In addition, innovative strategies for the design and expression of immunodominant epitopes that are targets for nAbs are clearly needed. Finding a vaccine that is safe and efficacious and at the same time also able to deliver that vaccine to all the people who need it, will require an unprecedented level of international engagement. As more vaccine candidates are developed, there are concerns that this could disrupt existing vaccine development, vaccine production pipelines, and supply chains for other vaccine preventable infectious diseases.

Capability assessment and response capacity must be improved

Zoonotic disease emergence is a complex process dependent on various extrinsic and intrinsic conditions that allow microbes to mutate, expand, and adapt to new hosts. Since 1970,

>1500 new pathogens have been discovered and 75% novel emerging infectious diseases in humans are zoonotic in nature. Using health, security, and economic risk matrices, some nations have developed a list of 30 zoonotic pathogens that can be considered important threats to human health (Morse 2015). Despite this, tracking zoonotic pathogens and spillover events to humans in remote areas of the world and assessing their risk for future global emergence continue to present a significant challenge to researchers and government agencies.

Although the assessment of the risk of SARS-CoV-2 has been considered as a failure of intelligence agencies worldwide, the arguments about this matter are contentious and politicized. Nonetheless, it is about time to readdress (i) how countries can generate early warnings of infectious disease outbreaks, (ii) how we use these indicators to assess country capability to respond to epidemics, and (iii) how evidence- and science-based decision making and recovery efforts are evaluated in near real time (Valdivia-Granda 2019). This not only includes the sharing of information, but also the development of autonomous systems that discriminate, identify, and counter accidental or intentional disinformation. Although several government agencies have invested significant resources in the development of automatic biosurveillance systems (Fig. 1), it is imperative to change not only how these resources are distributed but also how these systems are designed and implemented.

Re-engineering automatic biosurveillance for automated and autonomous systems will require minimum standards on data exchange formats and can be easily shared among countries to report critical information about an outbreak. These multidimensional and dynamic data types should include international classification of disease nomenclature, clinical and molecular diagnostics, georeferentiation, mobile telephone signal data, and genomic information. The exchange format should allow machine learning and artificial intelligence to dynamically perform risk assessment, classification, and outbreak scenario forecasting. These types of analyses could allow policy makers worldwide to assess and maintain regional stockpiles of medicines and equipment required to quickly implement a response to mitigate a high-risk infectious disease threatening global health, trade, and security.

After the CoVID-19 pandemic, many things will change—we hope that proper responses of individual governments and the international community will significantly alter the curse

of a future pandemic or the intentional development of a bioweapon (Valdivia-Granda 2010, 2013, 2019). Critical resources must be allocated for the implementation of policies allowing biosurveillance validation and verification following an approach as summarized in the *Open Sky Treaty* developed to verify nuclear proliferation. Global exercises simulating the emergence of a pathogen with pandemic potential will be necessary to address the challenges that many countries face in coordinating a multisectoral response to public health threats, update policies and pathways of efficient information exchange between human, veterinary, and agricultural local, national, and international officials. This approach will lead to a higher resilience of countries and to a better logistical readiness for the distribution of food, medicines, protective equipment, diagnostic kits, vaccines, and therapeutics during a pandemic while maintaining the social structure and peace.

Conclusions

The emergence of a zoonotic CoV causing a worldwide pandemic threatening global health systems, trade, and security for which neither vaccines nor therapeutics are available was a warning foretold for decades by hundreds of scientists. The health and socioeconomic crisis caused by SARS-CoV-2 is experienced by countries and territories worldwide, the long-term effects including re-emergence remain unknown. Nonetheless, current situation demands an urgent response from the international scientific, medical, regulatory, and political community to impose strict control on the sale of live (and slaughtered) wildlife and other exotic animals in wet markets around the world. This must be conducted within the framework of the international health regulations, international and bilateral treaties. The time for action is now.

Although there are hundreds of SARS-CoV-2 vaccine candidates in development, the question whether such vaccines are safe and efficacious and not able to induce VAERD remains unanswered. Preclinical animal models that can show VAERD after vaccination and challenge with SARS-CoV-2 are urgently needed. Such models need to be employed to determine the safety of SARS-CoV-2 vaccines before they are utilized in human clinical trials. We should not circumvent these steps because it could jeopardize the health of human volunteers and our citizens. Failure to do so might lead to the usage of a SARS-CoV-2 vaccine that induces immunopathological immune responses. Such scenario would be devastating to the human vaccine industry and a strong argument for those supporting global antivaccination (“anti-vax”) movement against medicines that have been saving millions of lives in the past century.

As new diagnostic technologies are deployed, secure data exchange systems are required to allow for autonomous biosurveillance systems to provide a deeper understanding of the distribution of SARS-CoV-2 infection and other known and unknown pathogens. Global health security efforts must embrace artificial intelligence and machine learning algorithms to perform real-time and dynamic disease tracking and risk assessment to trigger evidence-based responses by decision makers. Studies on interspecies transmission and host shift, and the role of coinfections with other pathogens, will

provide critical information for epidemiologists, physicians, veterinarians and regional and international health organizations. The mitigation of SARS-CoV-2 and future biothreats will also require international engagement, dynamic capability response scoring, and accurate communication to counter censorship and misinformation unless we are willing to continue to be unprepared. There is always the possibility of the global emergence of another more deadly contagion with even greater human and economic losses. We are unmistakably warned.

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