ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

CCDC weekly

Vol. 3 No. 7 Feb. 12, 2021

中国疾病预防控制中心周报

ISSN 2096-7071

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Special Issue

Commentary

Commentary

COVID-19 — 2021: A New, Less Predictable Phase of the Pandemic

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It is just over a year ago that what we now know as coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China (*1*). In twelve short months every village, every city in every continent has been affected. Hundreds of millions of people have been infected and recovered and over two million of people have tragically died from COVID-19. In reality, many more have lost loved ones. Yet we may still be closer to the start of this pandemic than to the end.

We knew a year ago that this virus had all the characteristics capable of causing a devastating global pandemic. An animal virus that had crossed the species barrier and could infect humans, for which humanity had no immunity. We knew there was human-to-human transmission, we knew people were infectious when they were asymptomatic or pre-symptomatic, that it could cause a mild illness and also a very severe illness leading tragically to people dying (*2*). We knew the genomic sequences of the virus and we knew we had no diagnostic tests, no specific treatments, or vaccines. We also knew this initially emerged in a very densely populated city with highly connected transport links. Since we had all that information at the end of January 2020, the trajectory of the pandemic has in many ways been highly predictable.

At the dawn of the Lunar New Year, we now face a much less predictable year.

The recent emergence of more transmissible COVID-19 variants with higher case fatality poses a serious threat to efforts to control the pandemic (*3*–*4*). Those variants already identified render anti-viral treatments ineffective, evade immunity from natural infection and, with emerging evidence that some variants reduce efficacy of the first-generation vaccines. It is inevitable that further variants will emerge that pose a more significant threat to vaccine efficacy. Most first-generation vaccines and treatments target a single virus protein, the spike protein, and are very vulnerable to mutations and emergence of new strains. Given that we are currently only finding variants where we have the capability to sequence, and not necessarily where they are occurring, this could already be the case. It is not coincidence that the three new variants have been picked up in the last quarter of 2020, we can expect a more rapid evolution of the virus in 2021 and more new variants as it adapts to humans (biological adaptation) and is now under increasing immunological pressure from infection and vaccination (immunological adaptation).

Since viral mutation is fundamentally a function of global prevalence, there is an imperative to reduce transmission everywhere. Otherwise, mutations will erode the efficacy of our tools faster than we can adapt them. In this instance the adage "no one is safe until everyone is safe" is not just rhetoric, but epidemiological fact. A massive global reduction in prevalence would result in slower evolution and thus make the virus easier to control. We have either to face a vicious cycle of greater prevalence leading to faster mutation and continued reverberation of this pandemic, a pandemic within a pandemic. Or a virtuous cycle of lower prevalence resulting in less mutation and the ability to stay ahead of this pandemic.

Science and international collaboration have always been the exit strategy from this pandemic. That is even more true today. We need to combine the best tools where-ever they may be developed. This could mean combining the best vaccines developed in China with the best vaccines developed in the rest of the world. A global effort to assess these vaccines together and demonstrate which are the best combinations is now urgent. Assessing all possible vaccination strategies is now imperative, for instance priming with an inactivated or other whole virus vaccine followed by a boost with specific targeted vaccine is certainly worth pursuing as part of a matrix of combinations that can elicit the strongest, longest lasting immune response that protects against existing variants and prevents new variants from emerging. This needs international cooperation on an unprecedented scale to bring together the best vaccines for humanity and end this devastating pandemic. The same approach needs to be applied to the development of new treatments,

diagnostics, global genomic surveillance and to the provision of oxygen, personal protective equipment to protect health care workers, and support for health systems to deliver these essential tools.

The first pandemic of the 21st Century has not only had an impact through the direct health consequences of COVID-19. It has impacted every sector of all our societies. This can be framed as four concentric circles: ripples from a stone thrown into a pond. The innermost circle is the immediate impacts of the virus itself, the direct consequences of infection, the illnesses, hospitalizations, and the tragic death toll. That has already been a devastating blow and is still reverberating around the world. However, it may prove to be the smallest of the four circles.

The next, the second larger circle is the indirect health effects; the secondary consequences on all other healthcare. We've already seen in many parts of the world the indirect COVID-19 impact on all other healthcare — heart attacks, tuberculosis (TB) screening and treatment, maternal/child health and for routine vaccinations. The impact on all our well-being and mental health may be even more profound. Other people miss cancer screenings, and cancers will be missed; others, simply fail to get enough exercise, and live shorter lives as a result.

The third circle, rippling out from the second, will be larger still; the social and economic impacts. The economic consequences are perhaps obvious — the joblessness, the shrinking economies; the lack of international trade, increasing debt, fall in remittances, which the International Monetary Fund (IMF) estimates will cost the world 12 trillion USD. More than that, pandemics, like all crises, open up existing fractures in society: they hit the poor harder than the rich; it leads to mistrust between the governed and the governing. The educational impacts of closed schools will hit disadvantaged children and their families the hardest. There is often a fear of outsiders, people "not like us," there often needs to be someone to blame. The political consequences could be severe. If a government is seen as having failed to protect its citizens at a time of crisis there is a loss of trust: the government was not there for its people when it was needed the most. Most of all it amplifies inequalities. And that leads to a fourth circle: the geopolitics. As national governments suffer criticism from their citizens for (perceived or real) failure to protect them, the instinct will always be to blame others, to deflect. This played out in 2020 and is happening again in 2021 as some sought to blame others for the pandemic, the rise in vaccine nationalism, the inequitable access to the critical tools needed to end this pandemic for everyone, everywhere.

None of this is inevitable. For each of the four circles, there are policy responses, nationally and globally. We must improve the public health, clinical, and disease-surveillance measures that can reduce the impact as it continues to reverberate around the world and prepare for future waves. We can also ensure that we invest now in health systems available for all needs, including the resilience to prevent and cope with such inevitable future pandemic shocks.

We can, also, mitigate the third circle, the social and political impacts. We must act on the inequalities in all our societies, rebuild trust in a critical role for government and debt relief for poorer countries would go some way to lessening the economic devastation in the developing world. We need to prepare for the long term changes the pandemic will evoke, invest in education and the training for jobs of the future not the past, opportunities for young people, transition to new, greener economies, fight corruption and value resilience as well as efficiency.

And when it comes to the fourth circle, similarly we face a choice. We can choose to go down a nationalistic, populist routes, blaming others for our problems, amplifying what divides, rather than building on what binds us together and choose to work together to forge a better more equitable peaceful future. There are historical parallels which we can draw on from the 20th century when our parents and grandparent's generation emerged from devastating crisis to forge a much stronger togetherness with the setting up of the United Nations, the World Health Organization, and many others, which bind our small world together

COVID-19 has been and continues to be devastating, but pandemics are not the only global challenges of the 21st Century. In the next few years, we will also need to collectively address the truly global challenges of climate change, access to clean water and green sustainable energy, inequality, antimicrobial resistance, and inevitably more complex and frequent epidemics. Just as with COVID-19, those problems will not be defeated by insular nationalism, blaming others, or by drifting into a more polarized world which makes us all more vulnerable, but by creating and enhancing means of international cooperation. It is not inevitable that the first circle ripples out to the fourth in the most ruinous way possible but avoiding it will take people laying out these problems honestly,

and then being equally honest about our ways out of them. We will face such a choice. A choice that will go a long way to defining how we address all these great global challenges of the 21st Century.

doi: 10.46234/ccdcw2021.032

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Submitted: February 07, 2021; Accepted: February 08, 2021

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Commentary

One Year in: Lessons from China's Fight Against COVID-19

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Since emerging one year ago, coronavirus disease 2019 (COVID-19) has inflicted tremendous suffering on mankind and has devastated the global economy. China was the first country affected by the pandemic and promptly warned the world about this novel coronavirus on January 24, 2020 (*1*). Despite China's efforts to contain the initial outbreak, COVID-19 continues to rampage around the globe, claiming millions of lives in the process. Nevertheless, China's success in limiting the damage inflicted by COVID-19 on its people offers lessons for effective epidemic control and response, both with respect to the ongoing pandemic and future outbreaks of known and unknown epidemic threats.

The Chinese people responded to COVID-19 with solidarity and resilience. They have waged an epic fight against the pandemic, implementing a comprehensive and stringent set of non-pharmaceutical interventions to curb the disease. For example, Wuhan initiated lockdown immediately after health officials announced human-to-human transmission (*2*). In the early stage of the pandemic, China also extended the Chinese Lunar New Year holiday, using this time to impose many social distancing measures, such as school and workplace closures and discouragement of mass gatherings (*3*). Implementation of this "outbreak-control holiday" substantially dampened COVID-19's epidemic spread and bought time to research the new virus, build physical infrastructure, organize medical supplies, and deploy human resources required for long-term epidemic control (*4*). Square-cabin hospitals were also built to isolate, treat, and monitor mild cases, representing an entirely novel concept in humanity's long history of fighting against infectious diseases (*5*). Following China's lead, many other countries adopted a strategy of facility-based isolation of mild cases (*6*–*7*). Taken together, China's multipronged approach of social distancing measures, mass testing, effective contact tracing, quarantine of suspected cases and close contacts, facility-based isolation of all confirmed cases (including asymptomatic and mild ones), and community outreach and health education collectively fueled the successful containment of its national epidemic, saving many lives and minimizing economic harms (*8*–*9*).

The COVID-19 pandemic has triggered many changes in the global geopolitical situation and outlook. First, the pandemic has created an uncertain and potentially volatile state of affairs with respect to economic development both in China and internationally. With the virus lingering, some harbor concerns over rising protectionism and the potential for global economic downturn. Yet, increasingly, forceful calls have also emerged for solidarity, collaboration, and multilateralism. Second, the pandemic has demonstrated the importance of quality medical care for ensuring human health, economic development and wellbeing, and social stability and security. As such, it is crucial to establish an efficient system for promoting high-quality public health research and innovation in medical science and technology. Third, the pandemic has altered many people's perception and behaviors in ways that are likely to persist in the long run. In the future, people may maintain social distancing, reduce unnecessary social contact, and pursue new ways to work and shop remotely, which will in turn boost the development of the digital economy.

Looking forward, China and the global community also continue to face much uncertainty with respect to the course of the COVID-19 pandemic itself. The virus that causes COVID-19 has been mutating, and we will likely see more mutations that could lead to changes in the its infectivity, incubation period, transmissibility, pathogenicity, duration of viral shedding, and antigenicity in the future (*10*–*11*). We may need to tailor our non-pharmaceutical and pharmaceutical interventions to new variants and constantly be alert and responsive to the ongoing pandemic. Under this uncertainty, it is crucial that our surveillance systems, policy decisions, and interventions remain based on science and professionalism.

The COVID-19 pandemic will not be the last pandemic and humans would do well to reflect on and draw lessons from the current moment in order to

better respond to future infectious disease threats. We need to increase investment in healthcare, promote innovation in medical science and technology through efficient research and development mechanisms, improve our relationship with the environment by addressing issues such as climate change, and make an all-out effort to achieve the United Nations Sustainable Development Goals. Accomplishing these aims will ultimately provide future generations with a healthier and safer world.

doi: 10.46234/ccdcw2021.033

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Submitted: January 29, 2021; Accepted: February 01, 2021

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Commentary

COVID-19 in 2021: A Call for Collaboration

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For many years now the world has anticipated a global pandemic. Aware of the devastating impact of pandemic influenza after the first World War, we have been awaiting a similar threat and the changes it would bring to our way of life, health, and the global economy.

Alarm bells rang out loud and clear with significant epidemics in recent years. Outbreaks of severe acute respiratory syndrome (SARS), Ebola, and Zika provided an indication of the health, social, economic, and political impacts that rapid infectious disease spread can have in a globally interconnected world. This did accelerate preparations, but as we have seen, significant weaknesses in global systems have been exposed.

The world has been on a journey to build preparedness and epidemic and pandemic response capacity. The International Health Regulations, which were updated in 2005, provided a clear framework against which countries could assess their capacity to respond, with an 'all hazards' response to potential threats.

However, the World Health Organization's (WHO) Joint External Evaluation (JEE) process helped highlight that significant weaknesses remained after more than 100 countries undertook voluntary assessments of their global health security status (*1*). Efforts to mobilize global resources to strengthen preparedness were underway, and progress was being made, but it is now clear, with the benefit of hindsight, that in many cases preparations were too little, too narrow, and too late.

As I look ahead at the coming year, I am very aware that the challenges of coronavirus disease 2019 (COVID-19) remain high the world over. Whilst there is light at the end of a long and dark tunnel in the form of vaccines and with some good examples of the success of non-pharmaceutical interventions in some countries, it is clear that without successful, global distribution of effective vaccines, the shutting down of international borders and limitations of our social and economic lives will have increasing long term and devastating impacts on our health and wellbeing.

There have however been huge positive developments and innovations, and it is important to recognize and celebrate these. There has been unprecedented international scientific collaboration in support of developing diagnostic tests for COVID-19, in vaccine development and in finding life-saving treatments for patients with COVID-19, such as dexamethasone. We have seen hugely valuable international collaboration and sharing of information and experiences between countries, which have provided a deeper understanding of the nature of the virus and its mutations, and I am immensely proud of the work that the International Association of National Public Health Institutes (IANPHI) has done to facilitate exchanges between National Public Health Institutes from high income and low and middle income countries (*2*). This global collaboration and meeting of minds is something that we must build upon — strengthening the partnerships that have been established to ensure that we not only build back our national systems better, but we also build improved international collaboration.

IANPHI is a partnership between National Public Health Institutes, with China CDC being an active and important member. Sharing of information between countries including on China's national approach has helped to inform IANPHI members and regular exchanges have reinforced the value of peer-to-peer support, which is the glue that binds us together across 100 member countries.

IANPHI now has a vital role to play working alongside partners like the WHO. Over the coming year, one of my greatest priorities as President of IANPHI will be to strengthen that relationship and ensure the collective capability of the world's National Public Health Institutes come together with a common purpose.

In looking forward, I believe we have important choices to make as a global community. We could all prioritize our national interests and turn inwards to protect our own people and economies, or we can recognize that until the world is safe, the global community never can be. It is clear and obvious that we need to reach out, work together, and build on the collaboration that COVID-19 has prompted.

There are some important mechanisms for international collaboration that have been developed and the key one I want to mention is COVAX, which is a global mechanism launched by the Coalition for

Epidemic Preparedness (CEPI), Gavi (the Vaccine Alliance) and the WHO, to ensure that all countries have equitable access to effective COVID-19 vaccines (*3*).

Whilst it is understandable that every country will want to prioritize protecting their own most vulnerable people, over the medium to longer term, it is clear that we will never be safe until COVID-19 is controlled in every country. We have already seen the emergence of some more transmissible mutations of COVID-19 (*4*–*6*), and mutations will continue to develop wherever disease transmission continues unchecked. Therefore, we must work together, through a fair and equitable system, to support access to vaccines.

Those countries that have the money to support countries with less resources should look to mechanisms such as COVAX and seek to pool their financing for the global good. We must resist the temptation to use access to vaccines as a tool for global diplomacy and a vehicle for competition between countries — it is far more important that we work together in solidarity. This is true also for global data sharing, research, and development and for equitable access to diagnostics, treatments, medical goods, and personal protective equipment (PPE). This is something that IANPHI will champion and that I am personally committed to. We must also work together as a global public health community to counter the misinformation that surrounds vaccine hesitancy that damages the public's trust in vaccination.

To ensure we are better prepared for future pandemics we need to fully understand COVID-19 and openly share our findings on the management and science of the virus. We also need to maintain a One Health approach to global public health, which recognizes that human health is connected to the health of animals and the environment and that multiple sectors need to work together to achieve better public health outcomes. This is important not only to counter the threat of zoonotic disease but also to address the wider determinants of health. The link between COVID-19, obesity, and chronic diseases such as hypertension and diabetes highlights the need for global health security to also be linked to broader health system strengthening. The non-pharmaceutical interventions, including lockdowns, which public health systems have employed is another important area for sharing experience and learning, and for developing an evidence base on what has been effective.

Although the year ahead holds many challenges, I believe that we are stronger together, and believe we can build global capability for inclusive, resilient health systems, and champion Universal Health Coverage under UN Sustainable Development Goal 3 (*7*). I am looking forward to using the platform that IANPHI has developed to strengthen global partnerships and to strengthen public health systems globally.

doi: 10.46234/ccdcw2021.034

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Submitted: January 19, 2021; Accepted: January 29, 2021

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Commentary

Lessons from COVID-19 to Help Prevent Future Pandemics

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In just over 12 months since it was first discovered, coronavirus disease 2019 (COVID-19) has caused over 100 million confirmed cases and more than 2.2 million deaths. Its impact on our global economy has been staggering and likely to be in the tens of trillions of dollars by the time vaccines are fully deployed (*1*). COVID-19 has caused significant hardship, mortality, and morbidity across the world, from the lockdowns experienced by the citizens of Wuhan in early 2020, through to the waves of case spikes in European, North American, and other countries. Pandemics of this scale are rare, and many have called COVID-19 a once-in-a-century pandemic, but our research suggests that they are increasing in frequency, driven by a rise in the animal-to-human pathogen spillover events that usually cause them (*2*). Over the last 2 decades, our group has been tracking the origins of emerging diseases, analyzing their causes, plotting their geography, and mathematically dissecting the trends that drive them to emerge. Since 1960 alone, we have recorded over 500 emerging infectious disease (EID) "events" — the appearance of a new disease in the human population for the first time or the sudden rise in caseload of a known disease. By correcting for the underlying biases in reporting these events and testing their correlation with likely causes, we have shown that EIDs are on the rise and that there are predictable patterns in their emergence (*3*). Moreover, these patterns can be used to identify future pandemic risk, set up surveillance and control programs to reduce that risk, and build strategies to ultimately prevent pandemics.

The majority of EIDs, and almost all known pandemics, are caused by zoonotic pathogens, often viruses. They emerge from a large diversity of viruses carried by wildlife and livestock. They are transmitted on a daily basis across the vast human-livestock-wildlife interfaces associated with farming, the wildlife trade, deforestation, mining, road-building, and other activities that increase our contact with animals. This process of spillover is enhanced by our growing global population, our expanding ecological footprint, and our exponentially increasing travel and trade networks that allow diseases like COVID-19 to spread globally within days or weeks (*4*). These are the elements of a prevention strategy.

The first step in any battle is to know your enemy, and in this case identify the size of the threat and where it's coming from. Given that viruses are the predominant group of pathogens and that most viral zoonoses are acquired from mammalian hosts, we repeatedly sampled two species of mammals (a fruit bat and primate) and conducted the same viral discovery protocol on each sample. Using data on the rate of discovery of new strains compared to repeat findings, we were able to estimate the unknown diversity of viruses in all mammal species — around 1.6 million unidentified viruses from all viral families that include zoonotic agents (*5*). We estimate that discovering 71% of these would cost around 1.2 billion USD over a 10-year period and have called for the formation of a "Global Virome Project" to do this (*6*). We envisage countries working together to fund viral discovery programs that upload sequence data in almost real-time, so that it can be used to identify those microbes most likely to be able to cause zoonoses, and the data then can be used to block spillover and create vaccines. To help facilitate the work, we have analyzed every single known viral-animal host assemblage to estimate the global distribution of yet-to-be-discovered viruses in mammals and the host species most likely to harbor them (*7*).

To win a battle, it takes a warrior who can think like their enemy and outwit them. The second step therefore is to think like a zoonotic virus. Viruses are particularly well adapted to zoonotic transfer, particularly those that commonly recombine or mutate more highly than others, like coronaviruses. Once viruses are able to cross the species barrier and spread in people, they rarely are constrained by national boundaries or differences in wealth or social status. Thus, the second step in preventing pandemics is to work together across the animal-livestock-human interface and block the pathways for transmission. This requires cross-sectoral collaboration that is difficult, rarely supported, and often funded by different silo'd

mechanisms. In the USA, Europe, China, and many other countries that lead public health efforts, the ministries of agriculture, health, and environment compete for funding and authority. Using a One Health strategy that brings greater collaboration across these silo'd sectors may be a key way forwards. In a recent report on pandemics and the environment (*8*) and a policy paper aimed at the incoming US administration (*9*), we called for the formation of a high-level intergovernmental council on pandemic prevention and national One Health platforms to strengthen our preparedness. This approach could have direct impacts on reducing pandemic risk. One Health outbreak investigation teams could be formed to rapidly mobilize and investigate case clusters of unusual new illnesses to identify, or rule out, a zoonotic source. One Health policy strategies should be implemented to reduce the drivers of new emerging diseases (e.g. land use change, the wildlife trade, intensification of livestock production) or increase biosafety within these activities.

These programs will require resources, including trained staff and significant funding. However, they will rapidly pay for themselves: we estimate that the cost of programs to reduce deforestation and the wildlife trade to prevent pandemics will cost 10s of billions of dollars, while the cost of pandemics is estimated at 500 million USD – 1 trillion USD each year (*8*,*10*). Likewise, programs like the Global Virome Project or the World Bank One World One Health farm biosecurity initiative are likely to provide returns of at least an order of magnitude for each dollar spent over the long-term (*11*). Finally, the biggest lesson we can learn from COVID-19 is that pandemics exploit our weaknesses. While the pandemic raged, geopolitical forces have chipped away at global collaboration around science and public health. This is untenable if we are to defeat this enemy. Viruses see us as one species to move among and infect. To defeat them, we need global health cooperation more than ever.

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doi: 10.46234/ccdcw2021.035

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Submitted: February 03, 2021; Accepted: February 05, 2021

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Commentary

COVID-19 in 2021: Sharing Responsibility Through Global Solidarity

Chikwe Ihekweazu[#]

Since the beginning of 2020, the world has changed in many ways, but no one predicted the changes that would result from a pandemic. For many years, epidemiologists predicted that this moment would come, but not many people paid attention. People and governments appear astonished to see the impact of a virus on the global economy. The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on our normal way of life, on our economic activities, and on the security of nations. Critically, it has highlighted our collective failure to invest sufficiently in pandemic preparedness and to fill the gaps required for countries to be better prepared.

Remarkably, scientific research and development in response to the pandemic has been unprecedented in terms of speed and the number of new scientific publications (*1*). Global research institutions and vaccine developers have developed new vaccines within one year of the identification of the virus that are now being administered in many countries, albeit mostly in high-income countries. But the science is not our biggest victory yet, because if science serves to accentuate existing inequities, then it cannot really be seen as progress. The biggest success would be if the world can come together in global solidarity to ensure equitable access to the vaccines, therapeutics, and diagnostics required to end the pandemic.

The COVID-19 virus is rapidly evolving (*2*). At least three strains considered variants of concern have already emerged that have massively increased transmissibility of the virus (*3*). Several countries in Southern Africa are recording a higher number of cases (*4*). There is urgent need for rapid new investments in science and development to stay ahead of the natural evolution that will select these variant strains. The current "variants of concern" will not be the last to evolve and could be associated with epidemiological changes in the pandemic or escape from diagnostic tests, treatments, or vaccines. Now, more than ever, countries need to work together to fight this pandemic.

The COVID-19 pandemic and response have brought several inequalities in global health into sharp focus. At the beginning of the pandemic, countries like Nigeria and others in Africa had limited access to diagnostics and therapeutics, which were largely manufactured in high-income countries (*5*). According to data gathered by Bloomberg, more than 94.4 million doses of COVID-19 vaccines in 62 countries have been administered by January 30, 2021. (*6*). Only three of these 62 countries are in Africa-Guinea, Egypt, and Seychelles. At the recently concluded World Health Organization (WHO)-convened Executive Board meeting, WHO Director-General Tedros Adhanom Ghebreyesus said "Rich countries are rolling out vaccines, while the world's least-developed countries watch and wait. Every day that passes, the divide grows larger between the world's haves and have nots." We are confronting a pandemic that presents increasing challenges and as well as opportunities for global solidarity.

In thinking about the year ahead of us, we must be aware of various emerging scenarios and the role we are all playing in defining what the predominant narrative of 2021 will be. Across the world, the number of new cases and infections may remain high, partly driven by new, highly transmissible variants. There is considerable variability across countries in their ability to achieve control without a vaccine. Health systems are increasingly overwhelmed in many countries, and they are experiencing severe budget pressures between demands of investing in COVID-19 versus other priorities. Countries like Nigeria have continued to record outbreaks of other epidemic-prone diseases such as Lassa fever, yellow fever, and cholera (*7*). The number of deaths from COVID-19 and from other causes — including maternal and child mortality — could continue to rise significantly without urgent action. Some low- and middle-income countries may again be forced into strict lockdowns in response to the increasing number of cases. This could cause major disruption to various sectors such as education, businesses, and others and cause immense hardship. The inequality in access to vaccines could further exacerbate these challenges.

Multilateral organizations such as the WHO have continued to provide the required leadership needed for the world to control this pandemic. An important example is the establishment of COVAX, an extraordinary and unique global collaboration with the aim of providing innovative and equitable access to COVID-19 vaccines (*8*). COVAX could represent the world's best hope of bringing the acute phase of this pandemic to a swift end. However, the work of the WHO or similar organizations is impossible without solidarity from countries. It will not achieve its goal if vaccines from COVAX are only available after the needs of rich countries are met.

Finally, we can clearly see from this pandemic that preparedness and response are global issues. Each individual country cannot expect to respond to such a pandemic threat in a vacuum; we cannot end a global crisis at national borders. For COVID-19 and other infectious diseases, the tools we need, such as vaccines, therapeutics, and diagnostics, should be seen first as a common public good and not only as business opportunities. All countries across the world must recognize that no country is safe until every country is safe. Solidarity is our best approach towards controlling the acute phase of this pandemic.

doi: 10.46234/ccdcw2021.036

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Submitted: January 31, 2021; Accepted: February 01, 2021

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Commentary

The Great Coronavirus Pandemic of 2019–2021: the Future and the Requirement for China-America Cooperation

Robert C. Gallo[#]

Over the past century, the great pandemics and most epidemics (defined as virus presence and disease induction presenting more than the expected number of infections in a population) were caused by the sudden outbreak of an RNA virus such as the pandemics of influenza, polio, and HIV/AIDS and the epidemics of influenza, Ebola, Dengue, Zika, West Nile, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Chikungunya. Of course, there are other infections that remain endemic problems in parts of the world, which are caused by bacteria (like tuberculosis) or parasites (like malaria). As everyone knows, the newest and among the most severe pandemic coronavirus disease 2019 (COVID-19) is again caused by an RNA virus, first identified by Chinese medical scientists and shown to be both highly contagious and dangerous (*1–4*). Why its relatives, SARS and MERS, rather quickly declined and disappeared as a global threat, while COVID-19 became global and persisted unabetted is unknown. What is clear are the following: 1) the Chinese scientific and public health groups such as China CDC were quick and effective for China (see references at the end for a few of the key early papers); 2) the rapid publication (January 10, 2020) of the sequence of the genome of the virus enabled the world to rapidly design vaccine plans and more sophisticated diagnostics; 3) their grasp of transmission by aerosols; 4) asymptomatic persons could be infectious; and 5) their identification of numerous coronaviruses in bats as the key carriers benefited all.

As this virus spread globally, medical scientists were quick to see that it could induce a two-phase disease. First is the establishment of infection and showing mild symptoms, but in many cases progressing to a severe inflammatory disease involving numerous organs but especially lung damage and sometimes leading to death. Progress on developing safe, specific, and potent anti-viral drugs for the early first-stage disease has been slow and disappointing, whereas treatment of the inflammatory stage with dexamethasone has had some significant benefit, but this will soon greatly improve (see below).

As to the future, I am proud to state here that a major new advance will soon be announced from our Institute of Human Virology at the University of Maryland School of Medicine made by Professors Yang Liu and Pan Zheng in close cooperation with the company Oncoimmune. They have used the CD24 molecule to target an inflammatory pathway with specificity and with minimal or no side effects. It has shown outstanding success in COVID-19 patients in all preliminary studies, which will soon be reported. This work began decades ago when Yang Liu came from China to work with Charles Janeway at Yale, one of the greatest basic research immunologists in the world. This dramatic and life-saving result will be reported soon. Of interest, these scientists originating from China are true Chinese-Americans, and they collaborate with Chinese scientists and, of course, with Americans.

We speculate that COVID-19 virus may disappear or be controlled while returning seasonally, similar to the flu, but in reality, we have no idea. We have high hopes for the specific preventive vaccines due to some early positive results, but we must remain vigilant for possibilities of lack of antibody durability, virus escape mutations, and difficulties in global deployment. My collaborators and I have strongly suggested that we keep in mind exploiting the power of innate immunity. This can be achieved by the use of "old" non-specific "live" attenuated vaccines (LAVs) like oral polio, "live" measles vaccines etc., to induce off-target that is non-specific but powerful induction of innate immunity. Innate immunity responds immediately to invaders and is our first line of everyday defense against infections. Apparently, it is the mechanism used by bats in order to live with their coronavirus infections, and the genome of COVID-19 virus contains regions that have specifically evolved to try to avoid the innate immune system indicating that these viruses are particularly sensitive to these mechanisms protecting us. Clinical studies with COVID-19 virus infection are consistent with this. There is a direct correlation with

the expression of genes related to innate immune responses and better prognosis, and conversely with bad prognosis when there are deleterious mutations within the innate immunity system. We could have used LAVs at the onset of the pandemic as "stop gaps" until specific vaccines became available. They still can be used if problems occur with the specific vaccines or even with the specific vaccines to enhance them.

Finally, we need better global scientific organization. A "pan" demic means all are affected, and we are all at risk if one member of the global community remains impacted by the virus. All must be together, and that has been far from true so far. I propose that this can best be mediated in part by scientific expertise such as by the deep involvement of the Global Virus Network (GVN), which now consists of 61 Centers of Excellence and 11 Affiliates in 34 countries, containing expertise in virology that covers every type of pathogenic virus and includes animal virology, with a major role for China GVN. During the beginning of the pandemic, we within the GVN had excellent discussions with Chinese colleagues like Yiming Shao and George F. Gao of Beijing as well as Linfa Wang in Singapore, who collaborates closely with Chinese colleagues. It was within the GVN large group discussions that we came to fully realize the importance of innate immunity in controlling COVID-19 virus. Indeed, and above all, we must foster closer ties and collaboration between the US and China, perhaps best mediated by the GVN, which continues to expand its global presence. The world expects this of China and America; the world needs this; the world deserves this. We can accomplish almost anything working together, such as the end of COVID-19 virus and advanced preparation for any future RNA virus threats. Without this, we can be sure such progress has far less chance.

doi: 10.46234/ccdcw2021.037

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Submitted: January 22, 2021; Accepted: January 29, 2021

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Commentary

Countering COVID-19 in 2021 and Beyond: More Cooperation is Required Between the Governments of China and the USA

Richard Danzig[#]

The achievements of the global scientific community in battling coronavirus disease 2019 (COVID-19) have been unprecedented, impressive, and inadequate.

Unprecedented and impressive because this previously unknown virus was sequenced within one month of its appearance (*1*) and because safe and efficacious vaccines to counter it were developed within the year. Impressive also because, though they were imperfect, drugs and therapeutic interventions were developed to reduce morbidity and mortality and non-pharmaceutical interventions (lockdowns, distancing, masks (*2*), and other measures) were implemented to retard the spread of the virus.

The People's Republic of China and the United States of America were leaders in all these efforts. China has particular cause for pride in its remarkably effective control of an exceptionally challenging pandemic (*3*) and in its efforts to help other countries by exporting its vaccines and medical supplies.

Clearly though, even herculean efforts have not protected the global community. By even conservative reckonings more than two million people have died from COVID-19. The global pandemic continues. Present mutations (*4*–*5*) are likely to expand contagion and present risks to the effectiveness of our medical and non-pharmaceutical countermeasures. Economic damage, already immense, is expanding and likely to be long-lasting for many.

The area where we have most underperformed is political. The United States and China — the two countries with the most resources and deepest pools of technical talent — have the greatest responsibilities in this respect. This is true not just about what has occurred, but also about what will occur as this pandemic continues and as it is succeeded by other pandemics.

Probably everyone who reads this short article understands that COVID-19 is a challenge to humankind, not just to one nation or continent. And what is undeniable about this dynamic pandemic will be true of the next one and the one after that until we treat epidemics and pandemic threats as global problems that require global solutions (*6*). Stepping up to that requires not just the collaborations of individual scientists and organizations but as governments.

The United States and the Soviet Union achieved cooperation in this regard. Even in the worst days of the Cold War, testing and development of the polio and smallpox vaccines were, for example, shared between the two nations (*7*). China and the United States similarly worked side by side on every pandemic since severe acute respiratory syndrome (SARS). But our governments have failed to cooperate in our responses to COVID-19.

The vaccines in which both nations can take much pride were developed with no bilateral coordination and little sharing of trial data, production techniques, and distribution plans. This contrasts with the technical support provided by Western organizations to help put the first Chinese vaccine — for Japanese encephalitis — on the global market. Both nations would benefit from cooperation on COVID-19 vaccines — for example, by sharing detailed data on serious adverse effects as these vaccines are deployed and by having regulatory agencies in both countries review and validate these and other pharmaceutical products for global use.

The American mRNA vaccines provide a new technology that is unusually precisely targeted and that can be adapted rapidly to new viruses (or variants of COVID-19) as they emerge. The leading Chinese whole virus-inactivated and attenuated viral vaccines have the strengths of being more broadly targeted. China is developing its own mRNA vaccine capabilities and the US is funding some attenuated viral vaccines, but each country could help the other towards these ends. Diversity in our vaccine armamentarium may be particularly rewarding as the virus mutates.

Global distribution is a hodgepodge of arrangements that shortchange the world. Cooperative purchasing through the World Health Organization (WHO) and non-governmental organizations like Global Alliance for Vaccines and Immunisation (GAVI) and the Coalition for Epidemic Preparedness Innovations

(CEPI) will save lives. It will also benefit China and the United States by reducing and then extinguishing the pandemic, reducing the likelihood of viral mutations spreading from a global reservoir back into our countries. The US and China have not, though, found a way to make these organizations a very fruitful arena of cooperative activity between our countries.

Cooperation is most important with respect to surveillance. Both nations recognize that zoonotic diseases are on the rise and that this pandemic — not this century's first — will not be its last. Sentinel systems and zoonotic investigations — including about the origins of COVID-19 — need to be conducted with shared information and expertise that is transparently, rapidly, and cooperatively employed (*8*).

We know that wherever it starts, a fire can destroy the whole forest. Accordingly, we fight fires by providing surveillance throughout the forest and we respond by focusing and coordinating all our resources to stamp out small fires before they become catastrophic. We need to treat the threat of pandemics the same way.

And — should one more example be desired — we now have different data derived from different experiences with COVID-19. China has longer experience with victims and wider experience with the rewards of non-pharmaceutical interventions and some treatments. America has many more cases and much more diversity in its non-pharmaceutical measures. Therefore, it has much more data. We need to pool our understanding.

Better cooperation will yield what science was designed for: the growth of knowledge and improvements in human health. Beyond this, it can achieve something that transcends science. It can be an example of how the best educated and most collaborative amongst us can cooperate for the betterment of mankind.

In 2020 politics undermined science. In 2021 let us have science improve our politics.

doi: 10.46234/ccdcw2021.038

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Submitted: January 28, 2021; Accepted: February 01, 2021

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Commentary

The COVID-19 Pandemic: Global Asymmetries and Challenges for the Future of Health

Nísia Trindade Lima[#]; Carlos Grabois Gadelha[#]

The coronavirus disease 2019 (COVID-19) pandemic reveals economic, social, and environmental trends that have been present since the last two decades, and it is characterized as a new phenomenon that qualitatively alters contemporary global and national dilemmas — not only because it was caused by a hitherto unknown virus, but by the magnitude of the crisis and the transformations that shape the lifeworld. It marks a disruptive and threatening historical period in the face of the foundations of modern sociability built during the post-war period.

Social and economic inequality between countries, territories, and population groups has increased during the pandemic. Its impacts are unevenly distributed, revealing the interface between the biological, economic, and social worlds. There is a threat of a humanitarian crisis due to the concrete differences between those who have full access to products, services, and health and those who can be left behind. In Latin America alone, the income of more than 30 million people has fallen below the poverty threshold less than a year after the arrival of the pandemic to the continent (*1*).

In terms of international relations, the pandemic highlights the tension between a vision of global health and the interests of the nation states and regional blocs. Vulnerability is observed even in developed countries, manifested in the lack of fundamental health items such as ventilators, essential medicines used in treatment, and even more basic items such as masks and personal protective equipment for health providers. Within the scope of the relationship between the nation states, the dispute over health products, with the imposition of trade barriers by more developed countries that could lead a solidarity action in health, has resulted in a limitation of access, generating global inequity. At present, limiting the supply of vaccines to less developed countries and vulnerable populations undermines the impact of essential mechanisms, such as the COVAX Facility [the initiative led by World Health Organization (WHO), Global Alliance for Vaccines and Immunization (GAVI) and the Coalition for Epidemic Preparedness Innovations (CEPI)], which is aimed at ensuring equal access to immunization.

In Brazil, this debate has motivated the strengthening of an approach developed at the Oswaldo Cruz Foundation (Fiocruz) — the main health science, technology and innovation institution in Latin America — in the last decades, which conceives health as development, understood in the concept of the Health Economic-Industrial Complex (HEIC) (*2*). A set of public policies for partnerships between the state and the private industries was established, including the strengthening of local production of state-of-the-art diagnostic tests, drugs, and vaccines. This conception shows that the production, science, technology, and local innovation bases are essential to give economic sustainability to the universal Brazilian health system (The Unified Health System — SUS), also favoring global cooperation guided by the solidary exchange of technologies. This virtuous link in the relationship between local technological training in the least developed countries and global cooperation has been demonstrated by the experience of Brazil's cooperation with Africa in the area of vaccines and medicines, including the transfer of technological and productive capacity and not just the sale and the supply of products.

The economic, production, and innovation basis in health must be seen as an essential element for national health systems and for global health, as evidenced in the COVID-19 pandemic, which demonstrated that primary healthcare actions, epidemiological surveillance, and hospital treatment depended on the availability of health products and services, without which the objectives of universal and equitable access could not be achieved (*2*). With this view, as emphasized in a recent publication in the *China CDC Weekly*, the availability of critical health products and services is also seen as an essential factor in health national security (*3*).

The integration of the social, economic, and environmental dimensions of development is,

therefore, essential to enable a healthy life, considering that health is understood as quality of life. Once again, the COVID-19 pandemic shows that the countries best placed to face it were those that managed to integrate the organization of health systems, social protection, the provision of basic services, programs to mitigate the effects of the economic crisis, the policies of social cohesion and community resilience, and a strong reinforcement of the responsiveness of the systems of science, technology, and innovation in health.

Based on this context, it is possible to show the major challenges that must be faced so that the future of health contributes to a more equitable and fairer world guided by sustainable development:

1) The strengthening of universal health systems, with strong evidence in both the international and Brazilian experiences in that public health and collective action are essential for the resilience of the countries and preparedness to face future pandemics and health issues, including both communicable and chronic diseases (*4*–*6*).

2) The core relevance of strengthening science, technology, and innovation for a new vision of public health in the knowledge society. It becomes necessary to face the mother of all inequalities: the inequality of knowledge, innovation, and the production base. In addition, without a more symmetrical distribution of productive and innovation capacities, the growing concentration and monopolization of health will render national and global responses based on universality and equity unfeasible (*7*).

3) The global effort to guide the economic, productive, and technological base in health, from different countries with different levels of development, towards social and environmental needs. The demands of society and the sustainability of the planet must guide all public policies and be integrated into the principle that the ultimate meaning of development is the promotion of quality of life and environmental preservation. The 4th technological revolution presents the risk of rupture and structural reproduction of inequalities, leading to work and people being in a precarious situation. However, it also represents an enormous opportunity to place the world of artifacts and technology at the service of the greater goals of society and the planet.

Dealing with these challenges requires the definition of a strategic agenda of commitments that reduce asymmetries between countries and consider the global vulnerability to face the unequal conditions of response to health emergencies as revealed by the COVID-19 pandemic.

doi: 10.46234/ccdcw2021.039

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Submitted: January 30, 2021; Accepted: February 02, 2021

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Commentary

Global Perspectives: The COVID-19 Pandemic in 2020–2021 and Beyond

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While coronavirus disease 2019 (COVID-19) cases have reached 100 million across the globe with more than 2 million deaths as at January 26, 2021, over 50 countries have initiated vaccinations against the disease. Vaccinations began within a year from January 12, 2020, when the China CDC shared the new virus genomic sequence with the World Health Organization (WHO) and globally, following the first complete genome sequencing of the novel β genus coronavirus on January 3 (*1*). This must be the most remarkable achievement in vaccine research and development since the English physician Edward Jenner pioneered the concept of smallpox vaccination in the 18th century. It truly is an outcome of joint efforts between interconnected scientific communities, the leading roles played by the WHO, Global Alliance for Vaccines and Immunisation (GAVI), and Coalition for Epidemic Preparedness Innovations (CEPI), and the contributions of many global health partners.

In 2015, in the aftermaths of the Ebola and Middle East respiratory syndrome (MERS) outbreaks, the WHO created a dedicated research team under the name "the R&D Blueprint to Prevent Epidemics." The intended aim was to facilitate research and development activity during the time of any outbreak. The R&D Blueprint organized the First Global Research and Innovation Forum on February 11–12, 2020, less than a fortnight after the declaration of a Public Health Emergency of International Concern (PHEIC) by the WHO Director General, which happened on January 30, 2020. This testifies to the WHO's strong commitment to play a coordinator role in research and development. The First Forum resulted in a coordinated global research roadmap for COVID-19, which was published on March 12, 2020. This roadmap proposes an immediate goal of accelerating research to contain the COVID-19 epidemic and a mid- to long-term goal of supporting research priorities that can lead to the development of a global research platform to better prepare for future epidemics and pandemics. There is no doubt that the research and development preparedness coordinated by the WHO R&D Blueprint network has facilitated the development of COVID-19 vaccines in 2020.

To end the COVID-19 pandemic, we need an equitable distribution of safe and effective vaccines on a global scale. The WHO, GAVI, and CEPI launched COVAX with a view to ensuring global equitable access to COVID-19 vaccines. However, COVAX's aim of delivering vaccine doses to at least 20% of the population of each participating country, regardless of the country's income level, as early as possible seems to be difficult to achieve given the foreseen insufficiency of global supply in 2021. At the 148th session of the WHO Executive Board Meeting on January 18, 2021, the WHO Director General made a statement emphasizing the importance of equitable distribution. He called on all countries to work together in solidarity to ensure that, within the first 100 days of 2021, vaccination of health workers and older people is underway in all countries, and requested vaccine producers to prioritize supplying to COVAX rather than through bilateral deals with countries (*2*). GAVI's forecast that as many as 1.8 billion doses will be available to 92 lower-middle and low-income economies participating in COVAX can only come true when the COVAX Advanced Market Commitment (AMC) proves to be fully functional.

There are still many unknowns in the newly developed COVID-19 vaccines - *inter alia* the duration and characteristics of vaccine-induced immunity, long-term safety, and efficacy against COVID-19 virus variants. Recent reports of Phase 3 clinical trials from Johnson & Johnson and Novavax show a reduced efficacy for UK and South African variants (*3–4*). With expert discussions underway, vaccine manufacturers need to be prepared for the reformulation of vaccines against the currently circulating and upcoming variant strains.

While we need to confirm the efficacy and long-term safety of vaccines that are available and will be available, it can take at least some months to see any decreasing trend of confirmed cases even in countries that have begun vaccination. Furthermore, we may not

be able to go back to the lifestyles of the pre-COVID-19 era even after herd immunity for COVID-19 is achieved. It will take some years to have answers for many unknowns in COVID-19 science. Researchers from academia, industries, governments, non-governmental organizations (NGOs), and public health partners will have to work together to find those answers. This pandemic has brought us many formidable challenges, but has also provided a precious opportunity to advance science and global cooperation.

doi: 10.46234/ccdcw2021.040

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Submitted: January 31, 2021; Accepted: February 01, 2021

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Commentary

Towards Societies Living with COVID-19

Peter Piot[1]; Julia Spencer[1,#]

The coronavirus disease 2019 (COVID-19) pandemic is undoubtedly the greatest challenge in peacetime facing the world for more than 100 years. No country is untouched with more than 100 million confirmed cases and over 2 million deaths as of January 28, 2021 (*1*), and the actual number of infections is probably closer to one billion as few countries had sufficient testing capacity to identify all cases, particularly throughout early 2020.

The effectiveness of national responses to the pandemic has been very unequal. Whereas some countries, particularly in East and Southeast Asia and Oceania, have been able to bring the epidemic provisionally under control though with continuing outbreaks, much of the rest of the world is still struggling with expanding epidemics and an escalating death toll. In addition to the physical and mental health impact and disruptions to health services, it is likely that the social and economic devastation will be with us for years to come. The sobering reality is that we are only at the end of the beginning, not the beginning of the end.

While dealing with the acute stage of the pandemic, we need to start planning for the long-term and shift our thinking to societies living with COVID-19, even if we should benefit from the protection of vaccines. The future trajectory of the pandemic will vary by country and depend on a combination of at least five factors: societal and public health responses, vaccine coverage, the duration of natural and vaccine-induced immunity, seasonality, and future mutations of the virus (*2–3*).

The recent emergence of new variants of the COVID-19 virus is at the same time expected, since RNA viruses mutate and the number of people infected in the world is enormous, and a major concern since this is probably only the beginning and evolutionary pressure from vaccination, particularly incomplete vaccination, may provide a breeding ground for escape mutants. It seems that at least the B.1.1.7 British variant is inactivated by the current vaccines and both Novavax and Janssen reported protection against the South African 501Y.V2 variant. However, other, more divergent and complex mutations may render vaccines less effective. It may also mean that vaccines have to be redesigned regularly, that multivalent vaccines may need to be developed, and that, just as for influenza, countries may need to periodically vaccinate — all this at a high cost.

The silver lining is that unprecedented scientific collaboration has achieved in months what would normally take decades with several safe and effective vaccines on the market, as well as diagnostics and, to a lesser degree, therapeutics. But scientific innovation alone is insufficient. Sustained progress in bringing the virus under control requires continued compliance with all non-pharmaceutical measures alongside the global rollout of equitable and efficient vaccination programmes and vaccine uptake.

With our increasing understanding of the virus and our new armamentarium of tools against it, the likely scenario is that most countries will gradually begin to control COVID-19 with very low mortality but with occasional flare-ups, possibly seasonal outbreaks because of waning immunity or the emergence of new variants of concern.

However, the crisis is not over anywhere until it is over everywhere. Some countries are not yet sufficiently protected and widespread testing and contact tracing, including for international travel, will be essential. We must also ensure that everyone, everywhere, has equitable access to safe and effective vaccines starting with the most vulnerable, including in low- and middle-income countries. This is not only a moral imperative, but as long as one country in the world is affected by COVID-19, no country is safe. Equitable access to COVID-19 vaccines is becoming one of the most pressing geopolitical issues of our time.

As we rapidly roll-out vaccination programmes to save lives and livelihoods, we must also address the long-term health and socioeconomic challenges ahead of us. But there is also an opportunity to make our societies and systems more resilient and more just by accelerating much need changes in many areas such as health, education, workplace policies, urban planning, food production, and environmental policy.

Although it is unlikely that we can eradicate COVID-19 in the foreseeable future, we have the tools and strategies to prevent COVID-19 outbreaks from spiralling into major epidemics while protecting those most at risk of developing severe disease. As we have seen in many settings, hard-won gains are easily reversed and there will always be a risk of resurgence. Success hinges on action at all levels — to protect ourselves we must protect our communities.

We must also learn critical lessons to better prepare for the next epidemic, and important efforts are under way in this regard (*4*). It may well be that we are entering an age of pandemics due to our increasing inability to live in harmony with natural ecosystems in our interconnected world (*5*). Indeed, infectious diseases are emerging at an accelerating rate and more than 60% of those emerging in humans are zoonoses, most of which originate in wildlife (72%) (*6*). The risk is further compounded by the profound health impacts of the global climate crisis (*7*).

International collaboration is vital for epidemic preparedness and response as "public health goes global" (*8*). In addition to the global leadership of the World Health Organization, regional bodies are playing an increasingly important role in providing political leadership and strengthening resilience and preparedness tailored to unique national contexts, from the African Union to the European Union and the Association of Southeast Asian Nations. Regional entities should also rapidly embrace much needed cross-sectoral strategies beyond the health sector. China's support through COVAX [the initiative led by World Health Organization (WHO), Global Alliance for Vaccines and Immunization (GAVI) and the Coalition for Epidemic Preparedness Innovations (CEPI)] and bilateral supplies of vaccines should play a major part in ensuring equitable access.

Now more than ever we must break the vicious cycle of panic and neglect associated with pandemics and sustainably invest in prevention and preparedness (*9*). As COVID-19 has amply demonstrated, epidemics can trigger major economic and security crises, and effectively managing them therefore requires a whole-of-society approach, underpinned by robust and well-resourced public health systems. We must also work to overcome the silos between human, animal, and environmental health, investing in systems that embrace the critical intersection between these fields as advocated by the One Health approach (*10*). The COVID-19 pandemic is a profound tragedy and we must act now to ensure we are better prepared when the next epidemic inevitably strikes.

doi: 10.46234/ccdcw2021.041

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Submitted: January 29, 2021; Accepted: January 30, 2021

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Commentary

A Return to BC19: From Virtual to Real International Travel — the Road is Long

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Virtual meetings, virtual travel podcasts, and virtual family reunions — a 21st century shift forced upon us by the coronavirus disease 2019 (COVID-19) pandemic — are an urgent leap forward to a new way of working and socialising.

But the dialogue is now changing in anticipation of a shift back to the way it was before COVID-19 — to the era some are calling "Before COVID-19" or BC19. This anticipation is occurring because the epidemiology of the COVID-19 virus* has become more clearly understood — given a kickstart by the extensive research done by Chinese researchers early in the pandemic and continuing today; and because there are now an astounding number of easier to use diagnostic tests, vaccines, and therapeutics that were only a hope one year ago.

But will this shift back to BC19 benefit from what we have learned from living in the virtual world during the past year — that virtual meetings can have the hoped for outcomes, that travel podcasts can provide new thoughts and experiences, and that virtual reunions can keep families close together across long distances. Will there be a mix of virtual and real international travel in BC19, and will this prolong the glimpse of benefits that the decrease in international travel has brought to our environment and to our own well being (*1*)? Or will the pandemic have been a glitch in our usual way of life that rapidly disappears — in fact, there is an omen that this might be true.

Though it is too early to know how the shift to BC19 will finally play out, especially as variants of the COVID-19 virus continue to evolve, there is clearly a sense of great urgency to get back to international travel (*2*). International travel is perceived to be as important today as it has been since the establishment of the great trade routes in history including the Silk Road, the trade route that linked people and goods from the Middle East and China to the Western world. The Silk Road, and many other networks of human travel and trade, were often interrupted by pandemics — plague, cholera, and smallpox — yet they came back and continued to evolve and increase as new means of public conveyance were developed.

Yellow fever is a good recent example of how an infectious disease slowed and disrupted international travel and trade, such as in the early 20th century when yellow fever outbreaks disrupted the construction of the Panama Canal. They had become a concern for international travel within the Americas in the late 19th century when major urban outbreaks occurred where yellow fever had not been previously recorded (*3*). Innovation prevailed, however, and in the 1930s a yellow fever vaccine was developed that prevented its infection and transmission and all was changed (*4*).

Along the road to BC19, late last year Hong Kong, China and Singapore conceived a way of ensuring safer international travel between each of their massive urbanised areas — what they called a "travel bubble." But by the end of December the travel bubble had burst (*5*). One of the perceptions for creating the bubble appeared to be that equal risk of infection and equal detection and response capacity, along with strategic testing for COVID-19 virus, could lead to decreased risk of infection during travel and upon landing. An increase in reported infections in one of these two urban areas, however, caused a perceived imbalance in the risk and plans were abandoned. The mantra of equal risk and equal response capacity and safe travel was shown to be difficult to implement but is a goal still being sought. And as a follow up, the World Health Organization is developing a risk assessment framework to help countries estimate and compare their travel risks.

And today there are vaccines as well. Just as in the 1930s when the newly developed yellow fever vaccine led to prevention of infection and transmission and to safer international travel in the Americas, COVID-19 vaccines are giving the same hope — that international travel will again become safe, returning the world of international travel to its BC19 level.

* Also know as SARS-CoV-2 in some researches.

In fact there is talk of "vaccine or immunity passports" and of international vaccination cards as a means of ensuring safe international travel, minimising both the risk of transmission in airports and airplanes (*6*).

But while vaccines provide almost complete personal protection against serious illness and death — the end point in the studies conducted for licensing — there is still not evidence as to whether these vaccines prevent infection or whether they modify infection once it has occurred. And there is not yet evidence to help understand how long the protective effect of these vaccines will last, and whether new variants of the virus will impact on protection though evidence is accumulating (*7*).

These answers will rapidly become available as more and more persons are vaccinated and post-vaccination surveillance and research continues. For now however, patience is the byword. We know for example that persons vaccinated against polio are protected from infection, but they can still carry wild poliovirus in the gut and transmit to others. And we also know that for some bacterial vaccines — the polysaccharide meningitis vaccine for example — nasal carriage of meningitis bacteria was possible and only rectified by innovation of a conjugate vaccine that eliminates this carriage.

Though there is some evidence that some of the COVID-19 vaccines decrease nasal carriage of COVID-19 virus from small subsets of persons studies in clinical trials, more information is required along with that about duration of the protective response.

So returning to BC19 for international travel is still a cautious journey — there is a need for continued understanding and innovation using the tools we have today, and the will that we can and must return in a more environmentally friendly way. But there is one caveat — and that relates to an unsubstantiated report of neighbour who recently returned on an international flight. His certification of a negative test for COVID-19 came from a template in the virtual world of the internet — not from a medically authorised laboratory.

The road is long for the return to international travel BC19 and presents many challenges along the way.

doi: 10.46234/ccdcw2021.042

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Submitted: January 30, 2021; Accepted: February 01, 2021

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Commentary

Getting Ahead of the Virus

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The world has recorded more than two million deaths from coronavirus disease 2019 (COVID-19) and is approaching one hundred million confirmed cases (*1*). Both numbers are underestimates of the true toll of the pandemic. Many countries in the Northern Hemisphere are in the grip of a large winter wave and have reintroduced lockdowns and intensified other nonpharmaceutical interventions to reduce stress on fragile healthcare systems. Vaccination campaigns have begun in a growing number of countries, but supplies remain scarce. And new variants of COVID-19 virus, which appear to increase its transmissibility and perhaps confer resistance to available countermeasures, have been documented in dozens of countries.

This is the state of the pandemic in late January 2021. We now have tools with the potential to bring the pandemic to an end, but the pandemic itself is slippery and continues to evolve. Just when we thought the end was in sight, we now face the prospect of new, more intense epidemics. In most countries, the response in 2020 trailed behind the pandemic. What can we do, in 2021, as a global community to get ahead of the virus?

With respect to the vaccines, our most important tool, four things can be done, principally.

First, we must ensure that the vaccines are shared globally as quickly as possible. We are fortunate in that several vaccines have already been shown to be safe and effective and we can anticipate that others will follow. Nevertheless, relative to global need, the vaccine will remain in short supply throughout 2021. If we can ensure that the vaccine is shared equitably to protect the most vulnerable, we can substantially reduce the number of deaths caused by COVID-19, limit the stress on healthcare systems, reduce the need for lockdowns, and speed global economic recovery. COVAX, the initiative led by Global Alliance for Vaccines and Immunisation (GAVI), Coalition for Epidemic Preparedness Innovations (CEPI), and World Health Organization (WHO), represents the world's best chance to ensure that all countries achieve the critical threshold of protecting their most vulnerable populations in 2021. All nations should support it.

Second, we must do everything we can to use the vaccines we have as effectively and efficiently as possible. That means maximizing their benefit for individuals as well as populations. Manufacturers have reported efficacy rates of between 50 and 95 percent for the vaccines that have completed Phase 3 clinical trials, and all vaccines have demonstrated a reduction in the severity of disease, but the variability in efficacy rates raises questions about how best to use the vaccines we have. In a related vein, and somewhat controversially, the UK's Joint Committee on Vaccination and Immunisation has issued guidance recommending an extended dosing interval for both the Pfizer and AstraZeneca vaccines in order to increase the number of individuals receiving a first dose of vaccine (*2*). Other strategies, such as the sequential use of different vaccines in heterologous prime-boost regimens, might allow vaccines with different efficacy to be combined in ways that optimize the individual and population benefits they provide while allowing greater numbers of people to receive at least one dose of the most effective vaccines. All such strategies should be evaluated rapidly and prospectively to understand their benefits and tradeoffs in terms of the protection they afford.

Third, we must prepare for the eventuality of viral evolution and be prepared to implement strain changes in existing vaccines much more rapidly than we do with influenza, where 9–10 months is the norm. The emergence of new variants demonstrates the potential of COVID-19 virus to accumulate numerous adaptive and biologically significant changes that lead to increased transmission and potentially immune evasion or escape. These variants have spread globally within months of their emergence, accelerating national epidemics in the UK, South Africa, and in Manaus, Brazil, a region thought to have achieved herd immunity by virtue of a largely unmitigated outbreak (*3*–*4*). Preparing for strain changes will entail increased global viral surveillance and sequencing, immediate and transparent reporting of new variants or concerning epidemiologic and clinical patterns, a low

threshold to develop candidate vaccine seeds, and agreement with regulators on the clinical, manufacturing, and regulatory requirements — and these requirements may differ by platform. Manufacturers should aim to be able to release a revised vaccine within 100 days of the decision to develop a candidate vaccine seed.

Fourth, we should build on the vaccines we have to construct an armamentarium for the future. We do not yet know where COVID-19 will find its epidemiologic niche, but we can anticipate that it will become endemic and we must ensure that we have vaccines that can address the needs of all segments of all populations in all geographies. In the first instance, that means determining the safety and efficacy of the current vaccines in special populations, such as children, pregnant women, the immunocompromised, and the elderly. In the second, it means developing low-cost vaccines with favorable attributes, such as thermostability, that facilitate administration (and even self-administration) in a wide variety of settings. And finally, if vaccines targeting the whole spike protein or its receptor-binding domain cannot keep up with viral evolution, it may mean broadening our approach and investing in COVID-19 vaccines that present multiple structural and non-structural proteins that have the potential to elicit an immune response. Ultimately, we should aspire to develop broadly protective coronavirus vaccines targeting epitopes preserved across many different coronaviruses.

If we are to defeat the pandemic we must get ahead of the virus and doing that will require a sustained global effort that cuts across every level of the response. The solidarity that the scientific community has demonstrated over the last year must become the governing norm. We are all in this together.

doi: 10.46234/ccdcw2021.043

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Submitted: January 24, 2021; Accepted: January 29, 2021

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Commentary

Vaccination Uncertainties and COVID-19 Prospects in 2021

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As we pass the first anniversary of the World Health Organization's (WHO) declaration of a Public Health Emergency of International Concern (*1*), we look back at the impact of coronavirus disease 2019 (COVID-19) in 2020 and the prospects for the pandemic in 2021.

The almost inverse correlation between pre-COVID-19 assessed preparedness (*2*) and actual performance (*3*) one year since the world first learned of the pandemic potential of the COVID-19 virus (*4*) is a stark reminder of Robert Burns's "The best laid schemes o' Mice an' Men / Gang aft agley." Going forward, we clearly need to bridge this disconnect and identify reliable indicators of true preparedness that are widely applicable and can stand the test of a real outbreak.

In the past year we have observed unprecedented public health and social measures (PHSMs) including lockdowns and travel restrictions (*5*). The health impact could have been much larger without these sustained drastic interventions, but the societal and economic cost has still not yet been fully realized. Although affected earliest in the pandemic, the rapid implementation of effective measures in China resulted in domestic elimination of infections by March 2020 (*6*) with only very occasional case clusters observed thereafter, leading to one of the lowest rates of infection per capita worldwide (*7*) and without the need for sustained PHSMs since.

COVID-19 vaccines are eagerly anticipated to bring an "end" to the pandemic, although the virus may continue to circulate and is likely to cause seasonal epidemics in the post-vaccination era (*8*). We must be vigilant for the emergence of new variants, especially those arising from convergent evolution, that are more transmissible, virulent, or could escape vaccine immunity. As administration of COVID-19 vaccinations is rolled out in more countries, we should begin to see reductions in case numbers and hospitalizations, and the opportunity to relax some PHSMs that have been in place for much of the past year. However, with delays in vaccine availability and fatigue with physical distancing measures, we are concerned that there could be more COVID-19 deaths in 2021 than 2020. With a resurgence in case numbers in many parts of the world, we urgently need to vaccinate older adults, other target groups such as healthcare workers and front-line workers in essential services and ultimately the whole adult population.

If high vaccination coverage is achieved and vaccines have high effectiveness against infection, we should see herd immunity preventing large epidemics although smaller outbreaks would remain a risk. On the other hand, even if coverage of a vaccine with insufficiently high efficacy reaches high levels, herd immunity will be difficult to achieve. In China, vaccination efforts have so far focused on high-risk working populations (*9*), leaving older adults vulnerable to infection if outbreaks recur. However, if vaccination coverage does not reach high levels, or if the vaccines prevent disease development but not infections (*10*) and specifically do not limit transmission, a more concerning scenario may play out where PHSMs need to be maintained for much longer to protect healthcare systems against surges in cases. Achieving high vaccine coverage will be hindered by vaccine hesitancy (*11*), which can be a particular problem with novel vaccines against a coronavirus that are licensed under emergency approvals with a rapid development timeline.

While we are encouraged by the successes of several promising vaccines with high efficacy against symptomatic disease in interim analyses of phase 3 trials, others have unsurprisingly been reporting more variable data. Even amongst those that have already been approved for emergency rollout, studies addressing extended use in population subgroups (e.g. the extremes of age, immunocompromised groups, and pregnant mothers), the optimal dosing interval between prime and booster, head-to-head comparisons between vaccines, and possible mixed use of vaccines between different technology platforms as first or second booster are ongoing. Therefore, many uncertainties remain as the pandemic threat

necessitates immediate vaccine deployment. Post-marketing pharmacovigilance and safety monitoring, as well as vaccine effectiveness studies, will help us further finetune immunization strategies.

As such, openness and transparency are the only sure way of countering vaccine hesitancy. Full and systematic disclosure of data from clinical trials and post-rollout empirical studies is needed to determine the safety and efficacy of each vaccine for different population groups, preferably in the international peer reviewed literature in parallel with regulatory submissions at the national level.

It is expected that the protection from vaccination against COVID-19 would not be lifelong, although data on waning of the neutralizing antibody after vaccination have been mixed (*12–13*). It is worrying to see a surge of COVID-19 cases in countries with high attack rates in their first waves (*14–15*). Revaccination may be needed sooner or later to prevent vaccinated or infected individuals from reinfection, although development of new vaccines would become essential if new virus variants emerge capable of escaping from vaccine-induced immune protection (*16*).

Despite the uncertainties in efficacy and safety, vaccines are expected to be the single most effective intervention to bring the COVID-19 pandemic to a resolution. To achieve fair and equitable access to vaccines, ethical principles should be upheld to overcome vaccination nationalism and, at the same time, to guarantee efficient access for individuals/countries in greater need (*17–18*). The moral imperative for equitable access to vaccines ultimately also serves the utilitarian purpose of self-protection by vaccinating others.

Funding: The Health and Medical Research Fund, Food and Health Bureau, Government of the Hong Kong Special Administrative Region (grant no. COVID190118). BJC and GML are supported by the AIR@innoHK program of Hong Kong SAR Government.

Conflicts of Intrest: BJC consults for Roche and Sanofi Pasteur. The authors report no other potential conflicts of interest.

doi: 10.46234/ccdcw2021.044

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Submitted: January 27, 2021; Accepted: January 31, 2021

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Commentary

Bats and Coronaviruses in the Context of COVID-19

Linfa Wang[1,2,#]; Matae Ahn[1]; Danielle E. Anderson[1]

In the Chinese zodiac, 2020 was the Year of the Rat. But it was remembered more as a "Year of the Bat" due to the great attention in the general public and scientific community on the role of bats as the reservoir of emerging zoonotic viruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) (*1*) and the coronavirus disease 2019 (COVID-19) virus, also known as SARS-CoV-2 (*2*). Here we provide a summary of our current knowledge on the relationship between bats and viruses, particularly coronaviruses, and discuss the various hypotheses for the origin of the COVID-19 virus.

EMERGING ZOONOTIC VIRUSES OF BAT ORIGIN

In the last 2–3 decades, the world has experienced 6 major viral disease outbreaks caused by emerging zoonotic viruses of bat origin. These include Hendra virus in Australia in 1994, Nipah virus in Malaysia/Singapore 1998/1999, SARS-CoV in China 2002/2003, Marburg in Africa in 2005, MERS-CoV in the Middle East in 2012, Ebola virus in West Africa in 2013, and COVID-19 virus in 2019 in China (Table 1). In addition, there have been many other "less impactful" emerging viruses of bat origin from Australia (Menangle virus) to Malaysia (Tioman virus and Melaka virus) and Africa (Sosuga virus). For more information on this rapid growing area of research, please refer to reviews and books published recently on this topic (*3*–*4*).

BAT IMMUNITY AND ITS SPECIAL STATUS AS VIRUS RESERVOIR

Bats are unique as the only mammals capable of powered flight. During their 65 million years of adaptive evolution, bats have displayed several unique biological features including long lifespan relative to their body size, decreased susceptibility to cancer, and ability to host various viruses without suffering from clinical diseases. In particular, the asymptomatic viral reservoir status of bats has attracted increasing interest and efforts to study their immune system.

Although research into bat immunity is still at its infancy, significant progress has been made in the last ten years. Bats exhibit a unique balance between enhanced host defense responses and immune tolerance (*5*–*6*). Mechanisms of enhanced host defense include constitutive expression of some interferons and/or interferon-stimulated genes, higher expression of heat-shock proteins, and efficient drug efflux via the ATP binding cassette subfamily B member 1 (ABCB1) transporter. On the other hand, dampened stimulator of interferon genes (STING) and inflammasome signaling are key examples of immune tolerance in

TABLE 1. Emerging zoonotic virus outbreaks related to bats. Cumulative infected humans is the sum from all outbreaks.

Viral Disease	Year	Country (initial)	Infected	Deaths	Cumulative infected (deaths)	Origin	Intermediate host
Hendra	1994	Australia	2 (+19 horses)	1	7 (5)	Bat	Horse
Nipah	1998–1999	Malaysia	265	105	704 (412)	Bat	Bat*/Pig
SARS	2003–2004	China	8,098	774	8,098 (774)	Bat	Civet
Marburg	2005	Angola	252	227	474 (380)	Bat	Monkey/Bat†
Ebola	2013	Guinea/West Africa	28,646	11,323	34,975 (15,253)	Bat	Bat/Monkey
MERS	2014	Saudi Arabia	255	93	2,494 (858)	Bat§	Camel
COVID-19	2019	China	99,931	4,810	98,280,844(2,115,759)¶	Bat*	X**

* Direct bat to human transmission via urine in palm sap as well as bat to pig, pig to human transmission.
† Either macaques (intermediate) or bats (direct) believed to be hosts.
§ Ancestral origin believed to be bat based on close genetic relatedness to bat-borne viruses and evolutionary trajectory.
¶ Data current on 27 January 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update---27-january-2021.
** Currently unknown.

bats. Strikingly, recent studies demonstrate multiple mechanisms of dampened inflammasome activation at different levels of the signaling. These include the loss of PYRIN and HIN domain (PYHIN) gene family including absent in melanoma 2 (AIM2), dampened transcriptional priming and protein function of NLR family pyrin domain containing 3 (NLRP3), and reduced downstream caspase-1 activity and/or IL-1 β cleavage, which results in an overall reduction in virus-induced or age-related inflammation (*5*). A deeper understanding of how bats fine-tune this balance will provide valuable lessons for combating viral diseases, aging, and cancer in humans.

BAT CORONAVIRUSES

The association of coronaviruses (CoVs) with bats started with the discovery of SARS-related CoVs in bats during the investigation for the origin of SARS-CoV (*1*). Since then, bats have been identified as a rich source of genetically diverse CoVs all around the world. Bats are undoubtedly the richest source of CoVs, displaying greater genetic diversity of CoVs from any other animal hosts (*7*).

CoVs contain the largest ssRNA genome (>30 kb) of all known RNA viruses and are members of the order *Nidovirales*. It is well documented that replication of large DNA genomes is less error prone due to proofreading capacity of the DNA polymerase. In contrast to DNA polymerase, RNA-dependent RNA polymerases (RdRp) lack replication fidelity. This is believed to be one of the reasons that RNA viral genomes tend to be smaller and viruses such as influenza virus use genome segmentation as a means of increasing genome-coding capacity. This paradigm was revisited after the discovery of a 3'-to-5' exoribonuclease (ExoN). ExoN, a homolog of canonical DNA proof-reading enzymes, which is exclusively encoded by nidoviruses with genomes larger than 20 kb (*8*). While the nidovirus-unique ExoN can explain why CoVs can maintain such a large RNA genome, the special "affinity" of CoVs towards bats remains elusive.

IS THE COVID-19 VIRUS A BAT VIRUS?

One year after the first detection of COVID-19 infection and more than 100,000 scientific publications on the COVID-19 pandemic, there are still many key questions remaining unanswered. One major question involves the origin of the causative agent of COVID-19. To address this question, it is important to differentiate the following viral terms. 1) Outbreak virus: the virus which was directly responsible for causing the outbreak, such as the first isolate (Wuhan-Hu-1) of COVID-19 virus. 2) Progenitor virus: this refers to a very closely related virus which is not identical to the outbreak virus, but could have evolved into an outbreak virus with minimal mutation(s). 3) Ancestral virus: this is the ancestor of both the progenitor virus and the outbreak virus residing in its natural reservoir host for a long time.

COVID-19 virus is a member of the species SARS-related coronavirus (SARSr-CoV) which includes SARS-CoV and many other CoVs of bat origin. The species is currently composed of two lineages or clades, one related to SARS-CoV and the other more related to virus causing COVID-19 (*2*). More than 10 COVID-19-virus related coronavirus genome sequences have been reported and over 80% of them originated from bats (*9*), including the RaTG13 sequence which has a genome that identifies 96% with COVID-19 virus. It is therefore most likely that the ancestral virus is from bats (*10*). The origin and geographic distribution of the progenitor virus remains elusive. In Table 2, alternative hypotheses of key events related to the origin of COVID-19 virus are summarized.

TABLE 2. Uncertainties surrounding key events relating to the origin and early transmission of COVID-19 virus.

Event	Hypothesis-1	Hypothesis-2
First human infection time	December 2019	Months earlier
First human infection location	Wuhan	Other site in China or outside China
Introduction of virus to Wuhan	By infected animal	By infected human
Type of virus introduced to Wuhan	The progenitor virus	The outbreak virus
The role of the Huanan Seafood Wholesale Market	The site of spillover (i.e., animal to human transmission)	The site of spillback-then-spillover (i.e. human to animal transmission, which led to amplification/adaptation in animal and followed up by animal to human transmission)
Host of the progenitor virus	Animal	Human

CONCLUSION

Bats are undoubtedly one of the most important mammalian reservoir hosts for emerging viruses. This can most likely be attributed to their unique immunity formed as part of the long-term adaptation to flight. CoVs seem to have a special co-evolutionary relationship with bats and the ancestral virus of COVID-19 virus also originated from bats. The origin of COVID-19 virus or its progenitor virus and the early transmission event from animal(s) to human remain elusive. The scientific community needs to keep an open mind in searching for the origin of COVID-19 virus as alternative hypotheses have been postulated for each of the key events from sources, timing to geographic locations.

doi: 10.46234/ccdcw2021.045

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Submitted: February 02, 2021; Accepted: February 03, 2021

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The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 3 No. 7 Feb. 12, 2021

Responsible Authority
National Health Commission of the People's Republic of China

Sponsor
Chinese Center for Disease Control and Prevention

Editing and Publishing
China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN
ISSN 2096-7071
CN 10-1629/R1