Editorial

One mutation away, the potential zoonotic threat – NeoCoV, planetary health impacts and the call for sustainability

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Background

A recent study entitled "Close relatives of MERS-CoV in bats use ACE2 as their functional receptors" posted on the bioRxiv preprint server has identified two close relatives of the Middle East Respiratory Syndrome coronavirus (MERS-CoV) in South African bats – NeoCoV and PDF-2180-CoV which can efficiently use Angiotensin-converting enzyme 2 (ACE2) in bats but less so in humans. However, researchers suggested that NeoCoV could be infectious to humans via one key mutation – T510F mutation on the receptor-binding motif. As suggested that the origin of MERS-CoV might be a result of intra-spike recombination between a NeoCoV-like virus and a DPP4-using virus, the nonhuman infectious NeoCoV firstly identified in 2011 is seen as a time boom,[1] and this alarms the zoonotic potential of possible "MERS-CoV-2" using ACE2 in the future. As coronavirus outbreak is part of human causes of global change,[2] recommendations are no longer limited to be preventive, but instead, sustainability should be planned to safeguard planetary health.

Overview of coronaviruses

Coronaviruses are enveloped positive-strand RNA viruses that belong to the family Coronavirinae and are classified into four genera, namely: Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus and Delta-coronavirus.[3,4] To date, researchers have discovered seven Human Coronaviruses (HCoVs), and at least three have led to major public health threats and deadly outbreaks, which include Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle-East Respiratory Syndrome coronavirus (MERS-CoV) that caused epidemics in 2003 and 2012 respectively, and most recently in March 2020 – SARS-CoV-2, which marked the first coronavirus pandemic.[3–5] Alpha-coronaviruses such as HCoV-229E and HCoV-NL63, and Beta-coronaviruses such as SARS-CoV, MERS-CoV, HCoV-OC43 and HCoV-HKU1, are primarily associated with infections in mammals, while Gamma-coronaviruses and Delta-coronaviruses mainly infect birds.[6] Among all the HCoVs, MERS-CoV which belongs to the subgenus Merbecovirus (lineage C) under the genus Beta-coronavirus, is associated with the highest mortality rate of 37% compared to SARS-CoV and SARS-CoV-2, 10% and 1.4%, respectively.[7,8] This further supports the importance of identifying the close relatives of MERS-CoV that could be potential zoonotic threats to humans.

About NeoCoV

NeoCoV is a bat coronavirus that was first discovered in 2011 from South African *Neoromicia capensis* bat.[1] This species is widespread in sub-Saharan Africa and common in all provinces of South Africa, as well as Lesotho and Swaziland.[9] NeoCoV has an 85% genome sequence similarity to MERS-CoV, making it the closest known relative of MERS-CoV.[1]

Potential zoonotic threat

Generally, coronaviruses primarily infect the respiratory and gastrointestinal tract of animal species such as mammals and birds.[10] Genome sequencing and phylogenetic analysis revealed that coronaviruses own the ability to bypass host species barriers.[11,12] In the past 20 years, the world has witnessed three major zoonotic events – the SARS-CoV epidemic in 2003, the MERS-CoV outbreak in 2012 and SARS-CoV-2 that has escalated into a pandemic in March 2020.[3–5] Indeed, most human coronaviruses are originated from bat coronaviruses (BtCoVs) and are transmitted to humans directly or indirectly via an intermediate host.[13–17] Cross-species transmission was the root for the SARS-CoV epidemic that found its origin in the Chinese Guangdong province in 2002, which spread from bat to intermediate host civet cats, then to humans.[13] In 2012, MERS-CoV in the Arabian Peninsula spread from bat to dromedary camels, then to humans.[14,15] Besides that, another four human coronaviruses may also have originated from cross-species transmission events: HCoV-NL63 and HCoV-229E from bats, HCoV-HKU1 from rodents and HCoV-OC43 from bovine.[16,17] Controversially, the origin of SARS-CoV2 remains enigmatic as the study under the NIH suggested that although BtCoVs (RaTG13 and BANAL-52) are 96-97 per cent identical to SARS-CoV-2 at the nucleotide level, the difference

Significance for public health

The emergence of new zoonotic infections like coronaviruses is inevitable with human activities, industrialization and urbanization, the presence of cross-transmission, the nature of viral replication, and antigenic drift. Therefore, it is high time for world leaders to recognize the possible upcoming impacts of coronaviruses related outbreaks and drive strategies for the prevention of future pandemics, as well as policy planning for sustainable living.

represents decades of evolutionary divergence from SARS-CoV-2.[18] However, phylogenetic analysis suggested a likely origin for SARS-CoV-2 in bats (Rhinolophus spp.).[19] Therefore, it is inevitable that more zoonotic infections will occur in the future.

A recent study entitled "Close relatives of MERS-CoV in bats use ACE2 as their functional receptors" posted on the bioRxiv preprint server demonstrates the first case of Angiotensin-converting enzyme 2 (ACE2) usage as a functional receptor in MERS-CoV close relatives – NeoCoV and PDF-2180-CoV. Although the ACE2 receptor usage by NeoCoV is efficient in bats but less so in humans, the researchers suggested that a single T510F mutation on the receptor-binding motif is sufficient for NeoCoV to infect ACE2 expressing human cells. As the study results suggested the origin of MERS-CoV might be a result of intra-spike recombination between a NeoCoV-like virus and a DPP4-using virus, this shed light on a potential zoonotic threat of a "MERS-CoV-2" using ACE2. Furthermore, neutralizing antibodies against SARS-CoV-2 or MERS-CoV elicited by the current COVID-19 vaccines did not exhibit cross-neutralization with the NeoCoV infection. In view of the extensive mutations in the receptor-binding domain regions of the SARS-CoV-2 variants, particularly the heavily mutated omicron variant, the study underlines that these viruses may pose a latent zoonotic potential with further adaptation through antigenic drift. Therefore, the next COVID variant might be more contagious than Omicron, but the question is whether it will be more deadly?

Planetary health impacts and zoonosis

Recognizing and responding to the adverse human health impacts of global environmental change will be a prime concern for public health professionals in the twenty-first century. Failure to account for the long-term adverse impacts of human activities on the earth's natural systems have resulted in upheavals to public health and health care delivery system.[20] A notable example is the global pandemic of COVID-19 that has claimed over 5.8 million lives,[7] which had long been predicted due to increased urbanization, changing land use patterns, climate changes, natural evolution, and human encroachment in formerly undisturbed habitats.[2]

The impact of the environment on the spread of infectious diseases has already been established with mounting evidence. The repercussions of climate change, such as extreme weather patterns, droughts, deforestation and destruction of wildlife habitats have increased contact between humans and other species, resulting in an increase in the number and frequency of zoonotic diseases.[21] In the wake of the current pandemic, mounting evidence reveals that places with disproportionate air pollution have attributed to the spread of the disease. As evident by data and research, in places with worse climates, the coronavirus tends to stay further in the air, causing more disastrous consequences to the human body. Moreover, a potent example from Greece, where coronavirus was documented in wastewater, rigorously back up the evidence that the environment may act as a favourable factor for the disease to remain undetected and continue spreading in the environment.[21] Hence, a bad climate compounded by the spread of zoonotic diseases can be of critical danger to human lives. Therefore, investing in planetary health and improving the environment can help reduce the spread of zoonotic diseases.

Sustainability: Three holistic approaches to health

As its nature, any potential zoonotic disease can irritate the sustainability of life, health, and economy. The current pandemic has revealed with compelling evidence that countries with a declining Gross Domestic Product (GDP) were facing recession and had a higher mortality rate, suggesting that economic status may be a useful predictor for COVID-19 related mortality, which has been disproportionately recorded worldwide.[22] Around the globe, specifically in Low- and Middle-Income Countries (LMICs), the pandemic's impact overwhelmed the fragile healthcare systems. Most of the people living in these countries, could not receive regular health attention due to the country's priority on COVID-19. Moreover, healthcare workers living in LMICs have also reportedly indicated burnout, depression, and anxiety due to workload pressure.[23] Despite the plethora of challenges posed by the pandemic, it is paramount to consider the pandemic as an opportunity to scale up sustainability to prevent future pandemics, health crisis, socioeconomic crisis, psychosocial crisis, and food crisis.

Ever since the COVID-19 pandemic started, public health approaches have been widely practiced for disaster management to curb the spread of COVID-19 and its impacts. One fundamental strategy being the need to strengthen the healthcare systems, as well as investment in disease surveillance systems to detect any potential zoonotic disease—particularly in countries with the highest burden of zoonotic diseases and with the lowest healthcare infrastructures. Primary prevention by vaccination is a key public health tool that should be provided on time to countries where the virus is spreading and mutating to curb further infection. But how well can future COVID variants evade the COVID-19 vaccine? How many more vaccines do we need and how soon will a vaccine be ready? Is this new COVID variant the result of vaccine inequity or inefficiency in policy implementation? Thus far, many earlier studies were perplexing and remain unexplained. If two years of public health preventive measures have been seen to be not sufficient to push forward "sustainable living", are there other possible approaches to be applied?

The sustainability of human lives should be considered wisely – countries should enforce restrictions when the probability of disease contraction is high and lose the restriction when the infection rate is decreased. This may reduce the extreme inflation in the economy and help people to maintain their provision and sustenance.

Currently, there are three holistic and interdisciplinary approaches to safeguard health, namely, One Health, EcoHealth and Planetary Health.[24] The three concepts of health are all interconnected. One Health approach includes obtaining timely response to reduce devastating impacts of diseases occurring at the intersection of human, animal, and the environment.[24] For instance, One Health approach starts with stopping animals that carries coronaviruses to enter the wet market, which can eventually prevent COVID-19. Secondly, One Health approach monitors human activities to prevent habitat loss and human contact with animals, thereby preventing virus spillover events and zoonosis. Thus, One Health approach could have stopped people from getting COVID-19, which has costed trillions of Dollars and millions of human deaths. To ensure effective response, One Health should be integrated with EcoHealth by having strong multidisciplinary and multiple communities' participation.[24] Unless the community members are involved in decision making together with policy makers, researchers and related professionals, any planned approach will never be sustainable. Thus, participation to gather people's knowledge is the way forward for sustainability, and in fact – participation is prerequisite for sustainable future.

Planetary health is essential for sustainable development. It is the integration and interconnectedness between human, animal, environment, as well as the Earth's natural system.[24] Nature exploitation has disrupted climate regulation which helps to keep our planet as a livable temperature. Over the past decades, the climate and environment has played a powerful role in the spread of infectious diseases.[25] By initiating Planetary health approach, deforestation and habitat destruction can be stopped to keep the diseases within the wildlife, to prevent human contact with animal, and the emergence of zoonotic diseases. Countries with worse climates should also be constantly monitored to prevent the spikes of communicable diseases.

In a nutshell, if we want to lead sustainable lives, we need our planet to be a healthy home. However, we have damaged the Earth, our own health, and the home for our future generations. Creating a sustainable world is a shared responsibility. To better protect ourselves from zoonosis, we must have multidisciplinary and multiple communities' involvement. Collaborative efforts anchor better understanding on potential hazards and allow us to seek the best way for sustainable living. After all, it's about ensuring the Earth – a healthy home for humanity. It is therefore, vital to introduce planetary health in the curriculum even at the primary level to inculcate the value and address the impacts of human disruptions to earth's natural systems on human health and all life on earth.

Thus, are the current preventive measures and vaccination sustainable in the long run? Are we resilient enough to more emerging and re-emerging infectious diseases in the future? If we are not ready for the COVID-19 transition from pandemic to endemic, how can we prepare for the post-COVID era? Lastly, how to build back better?

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