

Editorial

Covid-19 — An Epic Pandemic is on the Loose!

Received: 2 April 2020 Accepted: 30 April 2020

doi: <https://doi.org/10.3329/jemc.v10i2.53530>

For the third time in as many decades, a zoonotic enigmatic coronavirus (COVID-19) in recent history has crossed species to infect human populations. This up-to-the-minute threat to global health is raging across the globe with fierceness; thereupon, WHO declared the coronavirus crisis, a pandemic. Parallel to other pandemics, the outbreak of coronavirus is expected to bring catastrophe to the human civilization as an uncharted arena.

The viral agent (SARS-Cov-2) of COVID-19 belongs to the genus Coronavirus in Coronaviridae family and are pleomorphic enveloped with a positive sense single-stranded RNA genome (26–32 kilobases), 80–160 nm in size characterized by crown-shape peplomers emanating from the surface.¹ Adaptation to cells of different host species readily occurs since coronaviruses possess error-prone RNA-dependent RNA polymerases, fostering mutation and frequent recombination events. Along with its high mutation rate, coronaviruses are present in diverse species of animals, e.g., bats, camels etc, infecting humans with the manifestation of a wide range of clinical features from mild illness to fatal respiratory issues causing imminent threat of hospitalization.²

In December 2019, novel Coronavirus-2019 has emerged in the Huanan Seafood Market, where livestock animals were also traded, in Wuhan State of Hubei Province in China and has been the sheer global attention due to clusters of pneumonia cases with unknown cause.³ Chinese authorities announced on 7 January 2020 that a new type of coronavirus was evolved from those reported cases and the virus was named as 2019-nCoV by WHO on January 12 for an interim period and the disease as COVID-19 on 11 February 2020. The increase in the number of cases

in Wuhan city and internationally, even after closing the market and evacuation of the cases in China, has imposed an insight to trace the human-to-human transmission.⁴ New cases were identified, primarily in other Asian countries followed by some trans-oceanic countries such as the USA and France.

The human transmission of the disease primarily occurs when an infected person coughs, sneezes and then through the respiratory droplets produced just as the spread of influenza and other respiratory viruses. These droplets can settle in the mouth or nasal mucosa and lungs of other people during inhalation while considered to be highly contagious when people are mostly symptomatic.⁵

On 22 January 2020 novel CoV has been declared to be originated from wild bats which belong to Group 2 of beta-coronavirus that contains SARS-CoV. The genome of SARS-CoV-2 is similar to that of typical CoVs and contains at least ten open reading frames (ORFs). The first ORFs (ORF1a/b), about two-thirds of viral RNA, are translated into two large polyproteins (pp1a and pp1ab) and sixteen non-structural proteins (nsp1-nsp16), which generate the viral replicase-transcriptase complex 1. Those nsp(s) rearrange membranes originating from the rough endoplasmic reticulum (RER) into double-membrane vesicles where viral replication and transcription occur. The remaining one-third of ORFs of the genome encodes four main structural proteins: spike (S), envelope (E), membrane (M) proteins and nucleocapsid (N). The infection is initiated with the interaction between spike proteins and reciprocal receptor of human cells. It has been implied that the spike proteins of the coronavirus fundamentally get attached to human angiotensin converting enzyme 2 (hACE2) proteins

of the host cells.⁶ Being within the cells, the newly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi, and the nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Finally, the vesicles containing the virus particles fuse with the plasma membrane to release the progeny viruses by exocytosis which can infect cells of lower respiratory tract, kidney, liver and the intestines where they instigate the symptoms and signs.⁷ The hACE2 may play a role in the regulation of cardiovascular function and renal function while people with hypertension and impaired renal function are prone to be more vulnerable to COVID-19. Additionally, researchers emphasized that spike protein of the virus is 10 to 20 times more efficient in binding with hACE2 compared to the SARS-like virus from 2002; hence the COVID-19 appeared more contagious than the earlier SARS-like viruses.⁶ Moreover, the rapid genomic changes emanated from recombination, gene exchange, gene insertion, or deletion are frequent among CoVs which will be correlated with future emergence of the outbreaks with new strains or reemergence of the previous strains as in past epidemics.

The virus damages the function of CD4+ T cells accelerating activation and possibly subsequent exhaustion of CD8+ T cells; together, this may eventually wane host antiviral immunity.⁸ Similar to other SARS-CoV, the infection shows elevated levels of IL-6, IFN- α , and CCL5, CXCL8, CXCL-10 in serum. The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and eventually lead to death in severe cases of SARS-CoV-2 infection.⁹ The offshoot of infection by SARS-CoV-2 depends on the interaction between the virus and the individual's immune system. In connection to the aforesaid content, the viral factors include virus type, mutation, viral load and in vitro viability of the virus while the

host immune system factors include genetics, e.g., HLA genes, age, nutritional status, neuroendocrine-immune regulation and physical status.

The first non-Chinese case, that has spread to the Chinese provinces, and then to the Asian continent, was reported from Thailand on 13 January 2020. The case reported a Chinese tourist who has traveled to Thailand and had no epidemiologic connection with the marketplace.⁵ Other cases from overseas countries such as the USA and France have continued to be reported. In this context, people from South Asian countries such as India and Bangladesh, which are densely populated, have started fearing. According to the Institute of Epidemiology, Disease Control and Research (IEDCR), in Bangladesh, currently 56 people reported to be infected and 6 died. Meanwhile, the death toll from the Covid-19 has reached 49,186 globally as of April 2. It has so far infected around one million people around the world, according to *worldometer*. Till the write up, 252,433 cases had an outcome and of them, 81% recovered and 19% died. In total Covid-19 is affecting 203 countries and territories around the world.

The diagnosis of COVID-19 is based on a history of detailed contact, travel, and precise laboratory testing. The laboratory modalities used to diagnose are molecular methods, immunological tests and viral culture. The suspected cases should be screened for the virus with nucleic acid amplification tests (NAAT), such as RT-PCR. The PCR technique, in the combination of fluorescent dye, gives real-time data about the amount of DNA present. However, for coronavirus, single-stranded RNA has to be converted into DNA using reverse transcriptase (RT) enzyme and as such the technique is called rRT-PCR with confirmation by nucleic acid sequencing when necessary.¹⁰ The rRT-PCR is performed using viral RNA from respiratory samples; for instance oropharyngeal swabs, sputum, nasopharyngeal and tracheal aspirates and bronchoalveolar lavage. In particular, lower respiratory tract samples can offer

significantly higher viral load and genome fraction than upper respiratory tract samples.¹¹ Laboratories are advised to seek authentication of any conflicting results from an international reference laboratory.

Immunological surveys can aid investigation of an ongoing outbreak and retrospective assessment of the extent of that outbreak. In cases where NAAT assays are negative and there is a strong epidemiological link to Covid-19 infection, paired serum samples (in the acute and convalescent phase) could support diagnosis once reliable tests are available and serum samples can be stored accordingly.¹² Cross reactivity to other coronaviruses can be challenging, but the tests are currently under investigations. Moreover, the role of rapid assessment for antigen detection for Covid-19 needs to be evaluated. The immunological identification technology point-of-care testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA) are also under trial and practice. Additional clinical specimens may be collected as the virus of Covid-19 can be detected in blood and stool.¹⁰ On a similar note, viral culture is a more time consuming method to reach a diagnosis but can be used in the in-vitro and in-vivo antiviral treatment and vaccine evaluation trials.²

On chest radiography or thorax CT imaging of the examined patients, unilateral or bilateral lung involvement compatible with viral pneumonia was evident and bilateral multiple lobular and sub-segmental consolidation areas were observed in patients admitted in the intensive care unit.¹¹ The patients with underlying comorbidity exhibited a more severe clinical course, as speculated by the experience gained from the previous epidemics.

The gravity of the situation in terms of spread and severity of the virus is substantially considerate with around 3–5% current mortality rate. It is apparent that the longer the outbreak will last the greater would be the overall deface globally considering both social and economic aspects. Those who depend on a tiny

sum of wages and daily earnings are left in an even more helpless and miserable state. The situation is even more terrifying as there is no vaccine or effective treatment to contain Covid-19 infection.⁵

There is however a thin line of hope as there are drugs like favipiravir that blocks RNA-dependent RNA polymerase and remdesivir, a ‘nucleotide analogue’ drug that has shown some promise in the treatment. In addition to this, good results have been obtained for coronavirus infection from the lopinavir and ritonavir medications against HIV in Thailand and Japan; yet no concrete protocol of medication or procedure to effective cure is available. Apart from these medicines, some of the drugs boost the immune system by increasing the production of interferons. Studies evaluating the antiviral activity of interferon-beta (IFN- β) showed that it, as the most potent interferon, was reducing in-vitro MERS-CoV replication.⁶ The pegylated interferon and ribavirin argues to generate successful viral clearance. Moreover, the generation of recombinant human monoclonal antibody (mAb) is a fairly straightforward path to neutralize SARS-CoV. The mAb is assumed to bind potently with the receptor-binding domain (RBD) of SARS-CoV-2 and has the potential to be developed as candidate therapeutics of SARS-CoV-2 infections.¹³

Scientists all over the world are working relentlessly to find a solution. In this regard, an investigational vaccine was espied using a genetic platform called mRNA which directs the host cells to elicit a specific immune response. The mRNA-1273 vaccine has depicted its ability in animal models. In human model, a phase 1 clinical trial has begun at Kaiser Permanente Washington Health Research Institute (KPWHRI) in Seattle. The open-label trial was designed to enroll 45 healthy adult volunteers, age range between 18 to 55 years, over approximately 6 weeks (NIH Clinical Trial of Investigational Vaccine for COVID-19 Begins. <https://corona.kpwashingtongresearch.org/>).¹⁴ The study is evaluating different doses of the experimental vaccine for safety and its ability to induce an immune

response among participants. According to Anthony S. Fauci, NIAID Director, finding a safe and effective vaccine to prevent infection with Covid-19 is an urgent public health priority.

The CDC, Atlanta reminds basic measures such as hand washing, using disinfectant solutions, avoiding proximity with patients and social distancing of people in order to prevent the spread of viruses. Precautionary actions including the provision of medicines supply chains, personal protective equipment (PPE), and availability of hospital supplies should be assured in a short time for the protection of the people.¹⁵ The reason for escalating awareness is that there are reported cases of infected hospital personnel. Therefore healthcare staff should be informed about taking personal protective measures such as the use of gloves, eye masks and N95 masks during the examination of patients with a history of Covid-19 contact or travel history.¹⁶ According to the logistical modeling studies performed by combining daily numbers from Covid-19 cases with data obtained in SARS epidemics, rapid diagnosis with quarantine and integrated interventions will have a great effect on future trends of the outbreak. With increased scientific collaboration, scientists may have more powerful means of fighting against this disastrous disease, in which they would catch on the genome structure very well in the future.

As we are dealing with an obscure malady, the focus should be given on containing it by strengthening widespread surveillance, conducting thorough investigations to identify contacts and applying appropriate measures to prevent further spread. Several factors underlie the emergence of such diseases including increased population, poverty, malnutrition and global connectivity, economic factors leading to population migration, social practices, unplanned urbanization, deforestation and change in agricultural practices.⁵ On a different consideration, this subcontinent has extremely geo-climatic

diversity; as a result countries face a sustained threat of emerging and reemerging viral infections of public health importance. At the same time, there is also a pressing need to gain detailed insights into disease biomics, including genomic architect and cell biology of natural (animal) and accidental (human) hosts and environmental factors influencing the viral adaptation for favoring replication.

Lastly, it is also important to enact the emergency preparedness for these diseases and response by focusing on 'one health' approach and avoiding pointless panic to develop cognizance during the critical juncture in the outbreak. We hope that global awareness and cooperation among all walks of people along with the enormous effort of the scientists will remain vibrant in coming days. This would trigger and ensure a less damage and in doing so we would want to see Covid-19 free world, a real way to combine the drifts of survival, which so far the human civilization has been developed from previous experiences, by compulsion.

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