EDITORIAL

The COVID-19 pandemic

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The world has experienced pandemics over many millennia — be it smallpox, plague or cholera — that have decimated populations in every continent. Today we are in the center of another brutal onslaught by a novel virus named SARS Cov-2 that originated in the city of Wuhan in China. On February 11, 2020 WHO named the disease Covid-19 (COronaVIrusDisease-2019) and on March 11 WHO declared it a pandemic, as over 118,000 cases were identified in over 110 countries and territories around the world on that day. Many more cases, deaths and countries have been added since.

The Corona virus (CoV) belongs to a large group of the Nidovirales order, Family Coronaviridae. It is a single-stranded, positive-sense RNA virus with a large genome, primarily infecting birds and mammals. The human CoV affect the respiratory tract of humans, and are known to mutate and recombine frequently. Much of our understanding comes from the epidemics of Sever Acute Respiratory Syndrome (SARS) in 2002-2003 and Middle East Respiratory Syndrome (MERS) in 2012 that caused extraordinarily high mortality.[1-3] The SARS Cov-2 closely resembles SARS and MERS corona viruses, not only in its homology and taxonomy, but also the epidemiology and clinical symptomatology.

The manifestations of Covid-19 range from no symptoms, or mild upper respiratory tract symptoms such as fever, rhinorrhea, dry cough and myalgia that are self-limiting, to moderately severe disease accompanied with high fever, tachypnea and O_2 saturation of < 94% on ambient air, abnormalities on chest X-ray; the condition may progress to critical illness with bilateral pneumonia and often with multi organ involvement or failure, resulting in high mortality.[3] New and convincing information through postmortem studies indicates that surge of inflammatory cytokines, particularly IL6, is responsible for the cascade of events leading to thromboembolic events, shock and multiorgan failure. 80% of affected patients suffering mild symptoms recover with no specific treatment; 14% presenting with moderate infection are sick enough to be hospitalized, and may recover with supportive care and oxygen supplement. The 5% critically ill require admission into intensive care units for breathing assistance on a ventilator, and nearly half of them may die. It is alarming how rapidly the SARS Cov-2 continues to ravage European countries and the USA with case fatality rates (CFR) ranging from 10-15%, while in Asia the CRF is still less than 3%. However, these figures are a moving target while the epidemic continues, and the CRF will ultimately depend upon the total number of persons tested positive, and the number of persons who will die from Covid-19.

The Reproduction number (R0) indicates the number of people a single infected person can transmit, and depends on the population vulnerability, population density, and the virulence of the pathogen. If R0 is less than 1, the disease will die out in time. In the case of SARS in 2002 the R0 was 2.75. With intense quarantine and isolation activities the R0 dropped below 1, after which the infection gradually disappeared and the last case reported was in 2004. During the early stage experienced on the Diamond Princess cruise ship the R0 of Covid-19 was found to be 2.28 (2.06-2.52).[4]

The established method of diagnosis of SARS Cov-2 is by obtaining secretions from the respiratory tract via naso- or oro-pharyngeal swabs, or in ventilated patients by direct lung secretions. Nucleic acid detection based on nucleic acid sequencing by real time Reverse transcriptase (RT) PCR has 75 % sensitivity and 100 % specificity, while false negative tests may occur within the window period of 1-3 days.[5] RT-PCR detects 10-100 copies/μml. Although the test is completed in 2-4 hours, the turnaround time is 24-48 hours due to logistical delays from steadily increasing workload. It would be advantageous to test universally, as asymptomatic carriers are capable of transmitting the virus, and diagnosing carriers would facilitate contact tracing. At this time there is insufficient testing in Pakistan, although there is potential for more coverage.

Numerous rapid diagnostic tests that identify specific

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IgM and IgG antibodies are in process of development and marketing, and would help to determine immunity.[6,7] Covid-19 specific IgM antibody is detectable in the blood very early after infection and lasts a few days; IgG antibody is detectable once IgM starts to decline, and remains detectable, indicating immunity; however, based on experience with SARS it is uncertain how long immunity will last in the case of Covid-19. These tests are rapid and easy to perform. Three ELISA assays and six point of care (POC) lateral flow tests are in the pipeline, using serum samples of patients with early Covid-19 disease. Control sera was taken from healthy volunteers before the epidemic in China, from patients recovered from other corona infections, and finally from patients with non corona viral infections such as dengue, cytomegalovirus and Epstein Barr virus. The specificities of ELISA assay tests ranged from 93-100%, while sensitivities ranged 65-90%; results of POCT varied widely among various manufacturers.[7] The tests must be independently validated before receiving approval and release into the market even while clinicians are eagerly waiting for a conclusive, rapid and affordable test.

Covid-19 has not been around long enough to assess its seasonality, i.e. how it will fare in extreme climatic conditions. Indications are that summer temperatures will not ameliorate the pandemic. It is also likely that the pandemic will continue through winter months when influenza usually peaks, adding another dimension in differentiating between the two viruses that belong to two different genera, yet present with almost identical symptoms and outcomes.

Worldwide, desperate attempts have been made to ameliorate severe disease. Anti malarials, antivirals, antibiotics in various combinations, steroids and anti cytokines for disease modulating effects have been tried in varying combinations, but none has proven to be effective. More than 300 active randomized control trials (RCTs) are underway, but there is no conclusive evidence yet that any therapy improves outcomes in patients with confirmed COVID-19. Neither does any trial support prophylactic therapy.[8]

Not enough is known about Covid-19 to conclude whether a single attack will confer permanent immunity, or if it can recur in an individual. More confounding is whether it will make a comeback in areas where its presence has been reduced or even eliminated. Much depends on furtherance of research of Neutralizing antibodies (NAbs) that are the protective immune responses to viral infections.[9] NAbs bind to viral particles and block them from entering the host cells. Many CoVs are potent inducers of Nabs, but it is not established whether neutralizing antibodies or non-neutralizing antibodies are produced after infection with SARS Cov-2. Intense research is ongoing to develop effective SARS Cov-2 specific NAbs for prophylactic and therapeutic agents to prevent and treat Covid-19. Development of NAbs would also determine the success of anti SARS Cov-2 vaccine.[9]

Attempts were made to produce a vaccine against SARS in 2003-2004, but success was limited.[10] Presently, scientists in many countries are feverishly endeavoring to produce a vaccine against SARS-2 CoV. The process of developing an effective and safe vaccine is complex. Once produced in the laboratory and after getting tested on animals, trials on human volunteers are done in three phases. Barring unacceptable adverse events, production will speed up. However, making enough doses for 7.3 billion people around the globe is a daunting challenge. Assuming all hurdles are crossed, it is only realistic to expect that the vaccine will be deployed not before late 2021.

As treatment and vaccine are still distant visions, one must learn from the lessons of SARS and MERS: the only way to diminish spread were early detection by massive testing, isolating those infected, social distancing and hygienic measures for droplet precaution using masks and hand hygiene that ultimately controlled the epidemics.[11]

We need to strictly implement these codes to flatten the curve and ultimately mitigate Covid-19 in Pakistan. Like the Russian roulette, only chance picks the next victim.

(Social conditions in different parts of the world, data, pathogenesis, symptomatology guidelines, progress in treatment and vaccine development may change by the time this journal is published)

References

1. Drosten C, et al. Transmission of MERS-coronavirus in household contacts. N Engl J Med. 2014;371:828-835.
2. Assiri A, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med. 2013;369:407-416.
3. Zaki AM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814-1820.
4. EZhang S, Diao M, Yu W, Pei L, Lin Z, Chen D Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: A data-driven analysis. Int J Infect Dis. 2020 Feb 22;93:201-204. doi: 10.1016/j.ijid.2020.02.033. [Epub ahead of print]
5. Vijgen L, et al. Development of one-step, real-time,

quantitative reverse transcriptase PCR assays for absolute quantitation of human coronaviruses OC43 and 229E. J Clin Microbiol. 2005;43:5452-5456

6. FDA. Accelerated emergency use authorization (EUA) Summary COVID-19 RT-PCR https://www.fda.gov/media/136151
7. Ria Lassaunière, Anders Frische, Zitta B Harboe, Alex CY Nielsen, Anders FomsgaardKaren A Krogfelt, Charlotte S Jørgensen Evaluation of nine commercial SARS-CoV-2 immunoassays doi:https://doi.org/10.1101/2020.04.09.20056325
8. James M. Sanders, PhD, PharmD; Marguerite L. Monogue, PharmD; Tomasz Z. Jodlowski, PharmD; et al James B. Cutrell, MD Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19JAMA.doi:10.1001/jama.2020.6019
9. Nie Yuchun, Wang Guangwen, Shi Xuanling, Zhang Hong, Qiu Yan, He Zhongping, Wang Wei, Lian Gewei, Yin Xiaolei, Du Liying Neutralizing Antibodies in Patients with Severe Acute Respiratory Syndrome-Associated Coronavirus Infection The Journal of Infectious Diseases, Volume 190, Issue 6, 15 September 2004, Pages 1119-1126, https://doi.org/10.1086/423286
10. Groneberg DA, et al. Treatment and vaccines for severe acute respiratory syndrome. Lancet Infect Dis. 2005;5: 147-155.
11. Seto WH, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet. 2003;361:1519-1520.