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GUEST EDITORIAL

COVID-19: is there an end in sight

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In a recent report in the journal *Cell,* a team of investigators of Los Alamos National Laboratory led by Bette Korber et al. suggested that 614G, the latest variant of SARS-CoV-2 virus is responsible for the increasing global transmission of COVID-19. It was also reported that the main reason for the higher rate of transmission is that the mutated virus replicates faster in the upper respiratory tract in the human body, thus increasing the viral load in the infected individuals. It has also been observed that this does not increase the case severity, but certainly increases the infectivity.[1]

Although the outbreak of an influenza-like illness caused by a new coronavirus in Wuhan, China was reported as early as December 2019, the World Health Organization (WHO) took a considerably long time to declare it as a Public Health Emergency of International Concern only on January 30, 2020, and also to declare it as a new epidemic under the name of COVID-19 on 11 February, 2020.[2] Consequent to this there has been widespread criticisms from various countries regarding the role of WHO in containing COVID-19, as WHO declared it as a Global Pandemic as late as on 11 March, 2020.[3] By that time alarm bells have started ringing across the globe as the disease has already spread to many countries of the world.

The rapid spread of the disease during February and March 2020 across several countries of Europe and other continents led to research about the mode of transmission. Initially thought to be from droplet infection at close contact with an infected individual, other routes of spread are also being investigated. Scientists from different countries of the world have suggested that airborne transmission of micro-droplets which may persist in a close environment in the form of aerosol for a longer time and may spread up to a distance of several meters may be one of the probable cause of the faster rate of spread of SARS-Cov-2 virus, and adequate control measures must be taken in this direction.[4] They have expressed the opinion that changes in the physical environment in the workplaces, markets and departmental stores, gyms, places of worship, educational institutions, hospitals and clinics with physical distancing and adequate ventilation of the premises will be essential soon.

How the present pandemic is likely to progress is a matter of speculation. But our experience of similar events may offer some insights into the future. Perhaps we will have to learn to live with the disease; the most recent example of this in the history of the world was the Spanish Flu caused by H1N1 influenza virus pandemic of 1918-20.[5] Another pandemic in 1957, caused by H2N2 virus removed whatever was remaining of the previous pandemic. As some experts have put it in the right way, "What Nature can do it, we cannot".[5] SARS epidemic of 2003 caused by a coronavirus, was fortunately limited to a few countries because of very aggressive efforts of containment. This was thought to be possible because most of the people infected by the virus had serious symptoms and they transmitted the virus only after getting sick. But with SARS-CoV-2 the situation is different. Here persons infected by the virus have a wide spectrum of clinical presentations, from totally asymptomatic cases to mild, moderate and severe illness with respiratory distress, bilateral lung consolidation, cytokine storm, DIC like picture and death. Fortunately, the percentage of asymptomatic cases and persons with mild influenza-like illness is quite high; but at the same time, they continue to spread the virus before becoming symptomatic, or even before becoming positive on swab test. This is the reason for the rapid spread of the disease despite the global efforts for containment, with the imposition of lockdowns, and various other methods like social distancing, use of masks and hand hygiene.

The last few months in the history of COVID-19 has seen the evolution of a standard treatment of the disease. In the initial period of the pandemic, there was a lot of confusion regarding the use of drugs like hydroxychloroquine and azithromycin. Gradually a clear picture emerged regarding the pathophysiology of the disease process and these drugs are no longer accepted in the treatment module. The role of steroids to stabilize the excessive immune response as evidenced by the rise in IL-6 was widely discussed and accepted as a part of the standard treatment regime. Also, the role of low molecular weight heparin to combat intravascular coagulation was established. Antivirals like

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Remdesivir is now used in many centres routinely. To combat cytokine storm, monoclonal antibodies like Tocilizumab is now being increasingly administered with good results. High flow oxygen therapy essentially remains the primary treatment once the oxygen saturation starts falling. Improvement in the ICU care with ventilation has also contributed to the lowering of the case fatality ratio. The latest addition to the armamentarium is convalescent plasma therapy. In a systematic review of several publications in PubMed, EMBASE and Medline databases up to April 2020, Rajendran et al., concluded that convalescent plasma therapy (CPT) may reduce mortality in critically ill Covid-19 patients by increasing the neutralizing antibodies, clearance of the virus, and beneficial effect on the clinical symptoms.[6] Li et al. (June 2020) published their first report of a randomized clinical trial of convalescent plasma therapy in 7 medical centres in Wuhan, China, where they concluded that convalescent plasma therapy added to the standard treatment compared to standard treatment alone did not result in a statistically significant clinical improvement. This study was prematurely terminated because of non-availability of the required number of severely sick patients, as the epidemic was already on the decline in Wuhan by that time.[7] More research is necessary to establish the role of CPT in the treatment of severe COVID-19 cases.

The previous SARS outbreak in 2003 caused by a closely related coronavirus may have slowed down because of mutation. This is Nature's way of controlling the epidemic. In case of SARS-CoV-2, the recently reported change in the amino acid at position 614 of spike protein from aspartic acid (D) to glycine (G) has caused the emergence of the 614G variant which is the prevalent strain now.[1] The mutated strain is reported to be more infective, although increased ability to infect a cell line in the laboratory does not necessarily mean increased infectivity in the human body or the community as a whole. However, scientists all over the world are worried about the SARS-CoV-2 virus not undergoing enough mutations as expected at the beginning of the outbreak. Perhaps there is not enough influence of natural selection, as the virus is racing through the continents in millions of non-immunized people with very little resistance.[8] Probably an effective vaccine will be the only answer, which hopefully may force it to evolve into a less infective variant.[8]

Meanwhile, the incidence of COVID-19 has rapidly declined in the country of its origin (China). Those countries of Europe which had devastating effects of the disease in February and March 2020 are already showing the decline in the incidence of new cases and also in the mortality. In countries like the USA, India and Brazil, the pandemic is currently showing a rising curve, although the death rate is now significantly lower than that in the initial period of the disease, probably due to improvement in the standard treatment regime.

Case Fatality Ratio (CFR) is an important way of assessing the severity of an epidemic. It generally refers to the total number of reported deaths divided by reported cases on any particular point of time.[9] This is in contrast to Infection Fatality Rate (IFR), which is the number of reported deaths divided by the total number of infected cases (including the reported as well as the unreported cases). In the case of Covid-19, IFR is almost impossible to compute because the actual number of infected cases is not known as a large number of infected people are either asymptomatic or not tested, and therefore hidden in the community. Even CFR is also not a correct measurement, as, for the number of deaths occurring up to a certain point of time, the corresponding number of patients were infected a variable period of days ago. This lag period is observed to be different from country to country. An average lag period may be calculated which can be taken into account while estimating the CFR, and this is called LagCFR, which is more close to reality.[10] Wilson et al. has calculated an average lag period of 13 days from confirmation of the diagnosis to the day of death.[11] According to the authors, this gives a more realistic view of the case fatality during the epidemic. For example, in the Indian scenario, the total number of deaths due to COVID-19 till 19 July 2020 was 27,503; and the corresponding number of confirmed cases till this date was 11,18,780. Hence the CFR on this date was 2.49. However, if we take the average lag time from initial diagnosis (hospitalization) to the date of death to be about 2 weeks, then the lag case fatality rate (LagCFR) will be 3.94, as the total number of confirmed cases on 5 July 2020 was 6,97,836.[12] Thus if we do not consider the lag period, it gives us a false idea of a low fatality rate, particularly with the incidence of confirmed positive cases on a rising curve. Once the curve reaches a plateau, this difference between CFR and LagCFR will get minimized, and we will have a more realistic figure. With the rapid improvement in technology and availability of diagnostic facilities in the country, particularly after the introduction of rapid antigen testing kits and TrueNat equipment, the number of tests done in India has crossed 19 million by the end of July 2020. During this time, the number of confirmed test positive cases exceeded 1.6 million.[12] Fortunately, the majority of the test positive cases are asymptomatic or mildly symptomatic. The opinion is gradually building up in the country whether the asymptomatic and mild cases can be quarantined at home, thereby making available scarce hospital beds for the moderate, severe and critically sick cases in an already highly stressed health care system in the country.

In India, the disease started spreading only from the middle of March 2020. Initially, the spread was slow, which was thought to be due to the timely intervention by the government in the form of nationwide lockdown. The unprecedented displacement of the migrant population in the aftermath of lockdown was probably the biggest disaster in the history of independent India. It not only produced extreme hardships to the life of millions of poor people but also helped in spreading the disease to the nook and corners of the country. In our country, prolonged lockdowns are bound to inflict untold miseries to the poor section of the population. Ultimately the choice between life and livelihood stares in the

face of the common people, and they gradually start getting desperate to have their livelihood restored.

How does a pandemic like COVID-19 end? There are only a few possibilities. In the absence of an effective and specific antiviral therapy, we have to expect that an effective vaccine will be available in the earliest possible time. Epidemiologists hope that sooner or later a mutation will occur with which the virus is going to lose its 'Sting'. In the natural course of the disease, herd immunity will take a very long time to develop, and until it develops there will be a lot of sufferings to mankind. There is a fourth possibility of "Social end" of the pandemic when the people, in general, will be no longer afraid of the disease and they will learn to live with COVID-19.

The Oxford COVID Vaccine Trial Group has published the initial report of phase 1/2, single-blind, randomized controlled trial of ChAd0x1nCoV-19, which showed an acceptable safety profile, increased antibody response, and T-cell immune response against SARS-CoV-2.[13] This is an encouraging report, perhaps the first of many more similar efforts currently being undertaken in various other research centres across the world. On the other hand, Ibarrondo et al. reporting from University of California School of Medicine, Los Angeles has cautioned against "immunity passports", herd immunity, and perhaps vaccine durability in light of their finding of short-lived immunity against human coronaviruses, as their findings suggested rapid decay of IgG antibodies in mildly symptomatic Covid-19 patients.[14]

Initial reports of ongoing research work on an effective vaccine against SARS-CoV-2 are pouring in from several other countries including India, USA, China and Russia. These are reported to be in the advanced stage of human trials. Hopefully, by the end of the year 2020, the events will take a turn for the better. Until then, we have to accept social distancing, masks and hand hygiene as part of our life and hope for the best.

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