

## COVID-19: A game of drugs, vaccines, hope and... death!

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The turn of this decade has seen perhaps one of the deadliest diseases modern science has ever encountered. Declared a pandemic in January 2020, coronavirus disease (COVID)-19 has been responsible for almost 3.7 million deaths and many more occurring as this editorial is being written.<sup>[1]</sup> To be on the bright side, this pandemic has brought to the fore the dedication, sincerity and resilience of all the healthcare workers right from the general workers, paramedics, nurses and treating physicians, apart from a vast majority of researchers engaged day and night in finding a cure and a preventive vaccine for this disease. The spread of the pandemic has been so rapid, that it has put the entire health system of the country on acid test.

The journey of this disease in the last 1 year and 3 months has been nothing less than an epic though. Originating from a wet market in Wuhan, China, where the first case was first reported in October 2019, the disease was originally thought to be transmitted by bats. It assumed epidemic proportions in the Hubei province and later spread around the world thanks to the age of globalisation. Many conspiracy theories abounded regarding the origin of the disease, the horrors in the hospitals, social ostracisation of the diseased, and even rumours of the assassination of persons affected by the disease in one of the most closed countries of the world.

From an Indian perspective, things were slow to start, so to say, with the first cases appearing in February

2020. What followed was the largest and strictest lockdown in the world as a measure to contain the spread of the disease in the second most populous nation of the world and build upon the health infrastructure. The lockdown was not without its own demerits, in the sense that it contained the disease to a certain extent with the hope of few drugs working against the virus. The start was with hydroxychloroquine, azithromycin, favipiravir,<sup>[2]</sup> an antiviral and ivermectin, an antihelminthic.<sup>[3]</sup> Though the disease ravaged Europe, South America and the United States of America (USA), the intensity was not felt to that extent in India and all projections, given the population and inadequate health infrastructure in the country, which had prophesied a death toll exceeding all other countries combined were negated.

In the meantime, convalescent plasma and then remdesivir showed an initial promise and were approved for the treatment of the disease in the early phase. Commonly used inflammatory markers such as lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (PCT), interleukin -6 (IL-6) and D-dimer were pushed to the fore. For the subsequently arising complications such as cytokine storm, tocilizumab was approved with few precautionary guidelines for its use.<sup>[4]</sup> An increase in sudden deaths in Europe even after the supposed cure of the disease led to the discovery of new pathophysiology of the disease severity, and the scientific community opined that

the disease was in fact highly vasculo-inflammatory and thrombogenic in nature<sup>[5]</sup> and could lead to complications such as pulmonary thromboembolism, myocardial infarction and stroke. Thus, the role of low molecular weight heparin emerged so as to prevent thrombotic complications. Over a period of time, it was further realised that the severe inflammatory reaction caused by the infection could be suppressed by the seemingly innocuous dexamethasone given either orally or intravenous,<sup>[6]</sup> and it has remained the only proven therapy along with supportive oxygen therapy to mitigate the severity of the disease.

The so-called first wave of the disease in India, which emerged after gradual opening up, was tided over successfully with the disease remaining mild to moderate in presentation. A combination of steroids, favipiravir, ivermectin and awake proning allowed that the sick could be treated at home while in isolation thus reducing the burden on the healthcare system. Hospitalisation was reserved only for cases with moderate to severe disease requiring oxygen supplementation and those with complications. The entire healthcare system was thus divided into a three-tier system: COVID care centres: mainly for infected people who were asymptomatic or mildly symptomatic with no facilities for isolation at home, COVID Health Care Centres: for patients with mild to moderate disease requiring oxygen through face masks/venturi masks at <10 Lpm and COVID hospitals: for patients with moderate to severe disease requiring non-invasive or invasive ventilation. The American and European experience was beneficial for India in the sense that it was seen that non-invasive ventilation decreased mortality vis a vis invasive ventilation.

The disease peaked in August–September and was on the downslope by November–December of 2020. Remdesivir, steroids and low molecular weight heparin became the mainstay of treatment. Steroids, being easily available, are being prescribed unscrupulously even in those who do not require it. The long-term effects are yet to be seen, but the increasing incidence of mucormycosis is being attributed to it.<sup>[7,8]</sup> As the news of increasing fungal infections spread through the news media and social networks, there was an unscrupulous prophylactic prescription of antifungals, not unlike that of steroids in mild and asymptomatic disease, which led to strict control of amphotericin B by the government, so much so, that it has become tedious to procure it even for

diagnosed cases. Much of it can also be attributed to hoarders and black marketers who have not let go of this chance to make some easy money at the expense of the life of others.

As we write this editorial, the current pandemic due to severe acute respiratory syndrome coronavirus (SARS-CoV-2) might have crippled few more lives in India. The currently prescribed antiviral and anti-inflammatory measures have limited efficacy. Though the magnitude of the pandemic can be influenced in some way by the COVID appropriate behaviour, the only hope to halt this pandemic seems to be large-scale vaccination. With no definite treatment available, efforts were channelised to protect the race by means of vaccination.

Never in the history of medicine has a vaccine been developed and authorised for use within a year of the emergence of a disease. There are currently seven vaccines available, the first from China, three from the USA, one from India, one from Russia, and one from the United Kingdom (UK). There are, however, several more in phases of development and clinical trials. Trials are also underway for vaccination in the age group of 2–12 years, while rollout has already occurred for 18+ years.

The beginning of this year saw the biggest ever vaccination drives in the world. In India, currently, three vaccines have been granted approval for emergency use. India's vaccine rollout began with the availability of two jabs- Covishield® (AstraZeneca's vaccine manufactured by Serum Institute of India) and Covaxin® (manufactured by Bharat Biotech Limited). Both vaccines were granted emergency use authorisation (EUA) by the Central Drugs Standard Control Organization (CDSCO) in India. Later, one more vaccine added to this list is Sputnik V developed by Moscow's Gamaleya Institute. Sputnik V was granted emergency use authorisation in the month of April 2021.<sup>[9]</sup> All these vaccines were issued under "emergency use authorisation" considering that known and potential benefits outweigh the known potential risks of the vaccine as per the safety record evaluated from phase 1 and 2 studies and part/whole of phase 3 study.

India has witnessed a large-scale vaccine hesitancy among its population in the initial phase of rollout unlike the wider acceptability of vaccination drive in other countries.<sup>[10,11]</sup> This vaccine hesitancy slowly

faded up with proactive steps taken by the different social platforms, the medical community and political parties. The vaccine rollout was initially for the healthcare and frontline workers and later expanded to more than 45 years age group.

The end of March, however, saw the beginning of one of the most devastating medical crises the country has ever witnessed. With daily cases touching about 4 lakh per day with a positivity rate of as high as 30%, the reported deaths were at one time 4000 a day! Special teams comprising of public health and anaesthesiology experts were formed by the Ministry of Health and Family Welfare, Government of India and dispatched to the affected districts to aid and formulate plans for containment of the disease in April 2021.

With the sick thronging the healthcare facilities, the sudden deluge of hypoxic patients created a shortage of almost everything, the worst being the lifesaving drug: Oxygen! This shortage was not without its toll. There were horrifying stories of the death of patients and the helplessness and frustration of treating physicians who had been sent to war without ammunition. The entire bureaucratic machinery rose to the occasion to ensure adequate oxygen supply as soon as the oxygen SOS was raised by many hospitals from across the country.

All through this crisis, the medical fraternity worked relentlessly, tirelessly and with utmost sincerity to treat and find a cure. This path is not without thorns. The antiviral drug remdesivir initially came with a promise to halt viral replication *in vivo* but failed to stand strong over time. A prospective randomised study from India did not find any clinical benefit of remdesivir use in terms of mortality reduction in patients with moderate to severe COVID-19 even after adjustment for baseline clinical status.<sup>[12,13]</sup> The other drugs, which promised a remarkable recovery (hydroxychloroquine, azithromycin, tocilizumab) were later found to be not effective<sup>[14]</sup> and new drugs such as 2-deoxy-d-glucose (2DG),<sup>[15]</sup> tofacitinib,<sup>[16]</sup> baricitinib<sup>[17]</sup> and pifrenidone<sup>[18]</sup> are being revisited. 2-deoxy-d-glucose, the latest entrant as an adjuvant, available as an oral sachet developed by the Defence Research and Development Organisation (DRDO), acts on the glycolytic pathway and glycosylation of the viral protein. In preliminary studies, it has shown reduced oxygen requirement and shorter hospital stay, but whether or not it stands the test of time remains to be seen. Novel methods such as

low dose radiation therapy alone and in combination with 2DG are also being explored.<sup>[19]</sup>

Oxygen, the mainstay of the treatment has been explored through the conventional delivery devices and amongst the recent ones, high flow nasal oxygenation (HFNO) and extracorporeal membrane oxygenation (ECMO) have shown promise. Apart from conventional oxygen therapy, hyperbaric oxygen therapy appears to be an interesting approach for refractory hypoxaemia and post-COVID sequelae. Senniappan *et al.*<sup>[20]</sup> in a recent review, put forth the benefits of using hyperbaric oxygen therapy (HBOT) in patients with COVID-19 with the assumption that it will help in the oxygen-carrying capacity of dysfunctional haemoglobin in COVID-19 patients. Several smaller case series in effect to this found that HBOT not only increases the oxygen-carrying capacity, but also reduces the inflammatory markers responsible for causing vascular thrombosis,<sup>[21]</sup> however, concerns regarding oxygen toxicity remain.

Another challenge unique to India is the rise of business houses slandering and belittling the efforts of healthcare workers using the shield of alternative medical systems. Certain medications have been brought out in the market which claim to cure the disease, however, without any scientific rationale or basis. The sad part is the inclusion of these drugs in the COVID treatment regimen by certain state governments. The cow is considered sacrosanct in Hinduism. Cow urine is being touted as a panacea for the disease by certain leaders with mass appeal but no scientific logic. The greatest irony is that when they themselves contracted the disease, they turned to allopathy for refuge.

The anaesthesiologists armed with the knowledge of respiratory dynamics and expertise in oxygen therapy, management of mechanical ventilation in day-in and day-out practice have assumed a lead role in the management of COVID-19 patients and have been bearing the brunt of the sickest of all in most of the hospitals. The ABC of resuscitation,<sup>[22]</sup> basics of securing the airway,<sup>[23]</sup> all have been challenged and modified. While it was felt that the tracheas were intubated too early in the first wave leading to increased mortality, have we delayed intubation in this wave with the more pathogenic variant? While a group of researchers is interested in finding out the optimal time for tracheal intubation,<sup>[24]</sup> another group of researchers backed by retrospective observations opine not to

hurry intubation.<sup>[25]</sup> To intubate, or not to intubate the trachea? A question that still remains unanswered as the second and one of the most deadliest waves turns over the peak. Most vulnerable to the generation of aerosols, anaesthesiologists devised ways and means to protect themselves.<sup>[26-28]</sup> This included the use of video laryngoscopes, aerosol boxes, plastic spread sheets and many others.<sup>[29-32]</sup> Wagh *et al.*<sup>[33]</sup> present a method to prevent aerosolisation during a tracheostomy in this issue. While some methods have stood the test of time, others have faded as valiant attempts.

It is said that all battles demand sacrifice. A press release from the Indian Medical Association (IMA) website indicates that 864 doctors sacrificed their lives in the line of duty battling the ongoing COVID-19 pandemic.<sup>[34]</sup> Many continued to serve whilst they lost near and dear ones. That is what we would say is a true homage to the Hippocratic Oath.

The challenge is not over with the treatment of the disease itself. Apart from the thrombotic complications mentioned earlier, there have been cases with spontaneous pneumomediastinum as discussed by Cherian *et al.*<sup>[35]</sup> and rarer still like haemolytic anaemia by Renganathan *et al.*<sup>[36]</sup> in this issue of the IJA.

But this is not the end. A beginning of the end, perhaps. There may be many more facets of the disease which are evolving, and it is the quest of the curious mind which will unfold how this disease pans out in the near future.

With limited treatment options, COVID appropriate behaviour and vaccination remain the mainstay of controlling the disease. The research community is still struggling to provide answers to few issues related to the usefulness of vaccines in terms of nature and the duration of the protective immune response to SARS-CoV-2. A major issue regarding vaccine efficacy is the reported mutation in the spike glycoprotein and its possible effect on T-cell immunity. Nevertheless, one should not forget that large-scale immunisation will leave fewer susceptible individuals and lesser opportunity for SARS-CoV-2 to spread and mutate.<sup>[37]</sup> Currently, Covishield and Covaxin are the vaccines being administered in India. The gap between the two doses of the Covishield vaccine has been revised and widened by the COVID-19 Working Group, from the initial 6–8 weeks to 12–16 weeks based on published data.<sup>[38]</sup> As no such data is available for Covaxin, the

inter-dose gap for Covaxin has been left unchanged at 28 days. It may be several years before we know about the overall effectiveness of the vaccines in preventing COVID-19 symptoms, severe disease or deaths, but the need of the hour is to ramp up large-scale immunisation by addressing the vaccine shortage and micromanagement of vaccination programme at the ground level. We all have the collective responsibility for an effective vaccination programme in India because vaccination not only protects the vaccinated community but also indirectly protects the community with a compromised immune system that cannot be vaccinated. With the research in COVID progressing the way it is, all we can do is to hope for an effective vaccine and a curative drug with minimal side effects...

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