

# A review of disease Covid-19 caused by Virus SARS-CoV-2

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**Abstract:** Virus are made of a strip of ribonucleic acid (RNA) inside a spherical protein capsule which has projected spikes. Those crown shaped spikes (prongs) sense, recognize and stick to ACE2 protein, which is found on the outer surface of human cells. This is its first step towards an infection in the host cell. The contours of SARS-CoV-2 are remarkably complementary to shape of ACE2 protein. The spikes of Coronavirus family consist of two connected halves. The virus can penetrate a host cell if the spikes activate. The spikes activate when two halves are separated. The ease with which separation of halves occur is crucial in coronavirus infection. In SARS-classic, this separation happens with rather greater difficulty. But in SARS-CoV-2, the separation of halves and thus activation of spikes is much easier due to presence of an enzyme available in human tissues. The bridge that connects the two halves of SARS-CoV-2 virus, can be easily eaten by an enzyme called furin, which is made by human cells and incidentally is found across many tissues. Reactivity with furin is probably reason for many of the really unusual behavior seen in this virus. Starting symptom in Wuhan appear to be sore throat and a dry cough. The virus then crawls downward the bronchial tubes and reach to lungs. In mild viral loading, the immune system fights back and attacks the virus resulting into inflammation and fever. But in case of excess loading, the immune system goes berserk, causing more damage to itself than the actual virus. The virus seems quite stable as it is found that there are only 4 to 10 genetic differences between the strains circulating in the US and the original virus that was isolated from Wuhan patients. This suggests that if an effective vaccine is found it should continue to work for some time. Several candidate vaccines based on traditional technology involving a weakened virus are proposed and some are on trial already. Besides, few companies are working on vaccines based upon newer technologies as well involving proteins and mRNA.

## 1. Introduction

Virus is an infectious biological agent of minute size and of naive biochemical composition that can multiply only in living cells of animals, plants or bacteria. The name has its genesis from a Latin word meaning slimy liquid or poison.

Viruses have a unique taxonomic position as they are not plants, animals, or Prokaryotic bacteria ( a single-cell organisms without a well defined nuclei), and they are generally placed in their own kingdom. Viruses, in the strictest sense, should not be considered organisms, because they are not free-living. Like a free-living, they cannot reproduce and undergo metabolic processes without communicating with a distinct host cell.

Discovery of viruses trace back to 1892 to 1898 in studies of Russian scientist Dmitry I. Ivanovsky and Dutch scientist Martinus W. Beijerinck. Beijerinck first suggested that the virus under study was a new kind of infectious agent, and he designated this agent as *contagium vivum fluidum*, which means that it was a live, reproducing organism that differed from other organism. It was found during these two studies that tobacco mosaic virus causes disease to tobacco plants and this virus will not grow on an artificial medium and was not visible under the light microscope.

For a deeper understanding and classification of viruses, a challenge of finding a susceptible animal host was needed. During the year 1933, British scientists Wilson Smith, Christopher H. Andrewes, and Patrick P. Laidlaw were able to transmit influenza virus to ferrets, and the influenza virus later adapted to mice.

A dramatic advancement in study of viruses was achieved when American scientists John Enders, Thomas Weller, and Frederick Robbins in 1949 developed the technique of culturing cells on glass surfaces. Cells could then be infected with the viruses that cause diseases like polio. Before this, virus could be grown only in organs of an animal host for example polio virus could be grown in the brains of chimpanzees or the spinal cords of monkeys. This made it possible that viral diseases could be identified by their effects on cells called cytopathogenic effect and by the presence of antibodies to relevant viruses in the blood. It was the Cell culture that led to the development and production of vaccines used to develop immunity against a disease caused by virus. Almost at the same time the development of the electron microscope made it possible to visualise individual virus particles resulting into meaningful classification of viruses and greater insight into structure of the viruses [1-2].

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Studies were conducted on how a virus use its host cells for synthesizing viral nucleic acids and proteins. Monoclonal antibodies were guided to particular antigenic sites on proteins to get deeper understanding of structure and function of viral proteins.

The infective extracellular form of a virus is called the Virion. It contains at least one unique protein synthesized by specific genes in the nucleic acid of that virus. In all viruses it is observed that at least one of these proteins forms a shell called a capsid around the nucleic acid. Disease-causing virus like organisms that contain only nucleic acid and have no structural proteins are called Viroids.

A virus is not an independent biological creature. mRNA in short, which is a complementary copy of the nucleic acid of the nucleus that associates with ribosomes and directs protein synthesis) into proteins. Viruses must use the ribosomes of their host cells to translate viral mRNA into viral proteins.

## 2. Classification of viruses

Logically, viruses can be classified on the basis of the host they infect. This is justified in many cases but it is not universal, and thus host range and distribution of viruses are only traditional and one criterion for their classification. Broadly viruses can be grouped into three categories of those that infect plants, animals, or bacteria.

Certain viruses are restricted in their host range to the various orders of vertebrate. Some viruses seem to be adapted for growth only in ectothermic vertebrates (cold-blooded, such as fishes and reptiles), possibly because they can reproduce only at low temperatures. Other viruses are restricted in their host range to endothermic vertebrates (warm-blooded, such as mammals).

There are techno friendly viruses too. For example, a benign bacterial virus can be used to improve the performance of lithium-oxygen storage batteries according to a study of Massachusetts Institute of Technology.

### 2.1 Coronavirus family

The SARS-CoV-2, the cause of currently pervading pandemic belongs to a completely different and distinct family of viruses. This family, the coronaviruses, includes totally six other members that infect humans. Four of them OC43, HKU1, NL63, and 229E have been mildly perturbing humans for more than a century, causing a third of common colds. The other two, MERS and SARS (or "SARS-classic," as some virologists have designated it) both cause far more severe disease than the previous four. But it was this seventh coronavirus that went to the extent to become a pandemic. Our knowledge about coronaviruses becomes a matter of concern after the pandemic.

Coronaviruses (CoVs) are important pathogens for humans and animals, usually associated to respiratory and gastro-intestinal infections. CoVs are spherical enveloped viruses with a diameter of 100–160 nm. Each particle contains a positive-sense single-stranded RNA genome of 27–32 kb in stretch that interacts with the nucleoprotein. Viral envelope of the virus includes three different proteins namely, Membrane protein (M protein), Envelope protein (E protein) and Spike protein (S protein). M protein binds nucleocapsid and is vital in assembly and budding of the virus. E protein is responsible for viral morphogenesis and release and also for viral pathogenesis. The last one, S protein creates crown shaped spikes (projected prongs) that recognize the receptor in the host cell initiating infectious viral entry into the target host cell [3].

Physical structure of this virus provides one clue about its unprecedented success among family members. In appearance, it's essentially a spiky sphere. Those spikes or prongs sense, recognize and stick to ACE2 protein, which is found on the outer surface of human cells. This is its first step towards an infection. The contours of SARS-CoV-2 are remarkably complementary to shape of ACE2 protein. The exact contours of SARS-CoV-2's spikes enable it to bind far more strongly to ACE2 proteins of humans than SARS-classic virus could do, and most likely it is really crucially responsible for inter personal transmission. It is a common observation that, the tighter the bond the less number of virus is required to start an infection.

The spikes of Coronavirus family consist of two connected halves. The virus can penetrate a host cell if the spikes activate. The spikes activate when two halves are separated. The ease with which separation of halves occur is crucial in coronavirus infection. In SARS-classic, this separation happens with rather greater difficulty. But in SARS-CoV-2, the separation of halves and thus activation of spikes is much easier due to presence of an enzyme available in human tissues. The bridge that connects the two halves of SARS-CoV-2 virus, can be easily eaten by an enzyme called furin, which is made by human cells and incidentally is found across many tissues. Reactivity with furin is probably reason for many of the really unusual behavior seen in this virus.

This virus exists within and infects a person but initially exhibits no symptoms. Severe symptoms are exhibited later. Therefore virus can spread between people before symptoms show up. This characteristics has made it difficult to control its spread. It can exploit the universally present furin, so it can infect in many parts.

Most respiratory viruses tend to infect either the upper or lower airways. More often, upper-respiratory infection spreads more easily, but tends to be milder and lower-respiratory infection is harder to transmit, but is more severe. SARS-CoV-2 seems to infect both upper and lower airways, perhaps because it can exploit the ubiquitous furin.

## 2.2 Evolving coronavirus family

The novel virus SARS-CoV-2 have certainly shown capabilities of being effective at infecting humans, despite its animal origins. The closest wild relative of this novel corona virus is found in bats, which suggests it originated in a bat, then jumped to humans either directly or through another species. One more coronavirus found in wild pangolins also resembles SARS-CoV-2, but only in the small part of the spike that recognizes ACE2, dissimilar otherwise and therefore pangolins are rejected to be the original reservoir of the new virus. The coronavirus family seems evolving. There are millions or billions of these viruses that are prevailing there in nature and unbelievable events happen in nature such as perfect matching profiles of coronavirus spikes and ACE2 proteins by coincidence. Moreover, The sensitivity of SARS-CoV-2 virus with an enzyme called furin, which is produced in human cell across tissues, is probably reason for its sarcastic behavior in infecting human being. It may exist in humans without showing symptoms and is capable of infecting several parts of humans.

## 2.3 Mutation

The novel coronavirus started its journey from Wuhan, in China. From there it has traveled to nearly 200 countries. The virus found at other sites are studied comparatively with the virus found at Wuhan and other locations in order to find changes it has undergone. It is observed that, Since the start at Wuhan, the virus has not changed in any obvious and substantial ways. It's mutating in the usual way that all viruses do. None of the mutations have been risen to dominance, insinuating none is noticeably important. It is spreading around the world right now easily without evolutionary pressure to transmit better. The virus has been remarkably stable.

## 2.4 Virulence

About the fact that some coronaviruses are deadly and some are not, there is no clear explanation available yet. There's really no understanding at all of why SARS or SARS-CoV-2 are so deadly but OC43 just gives us a runny nose. A change in sequence of genes of a virus might suggest about its virulence. At the late stages of epidemic, it was observed that a stretch of genes disappeared from SARS-classic. It may be imagined that the change was responsible for making the original virus less virulent. A few SARS-CoV-2 viruses that were sampled from COVID-19 patients are missing a stretch of genes that also disappeared from SARS-classic during the late stages of its epidemic. But it will be far too early to establish that it will lessen the virulence of SARS-CoV-2 also.

## 3. Modus Operandi

### 3.1 Spread

Scientists and clinicians have learned much of coronavirus disease 2019 (COVID-19), and its pathogenesis, which can be broadly summarized as-

(a) Not all people exposed to SARS-CoV-2 are infected and not all infected patients develop severe respiratory illness. Accordingly, SARS-CoV-2 infection can be roughly divided into three stages; stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load

(b) From the point of view of prevention, individuals at stage I, the stealth carriers, are the least manageable because, at least on some occasions, they spread the virus unknowingly

(c) The role of asymptomatic SARS-CoV-2 infected individuals in disseminating the disease remains to be defined [4].

The virus is spread through droplets transmitted into the air from coughing or sneezing, which people nearby can take in through their nose, mouth or eyes. The viral particles in these droplets travel quickly to the back of your nasal passages and to the mucous membranes in the back of your throat, attaching to a particular receptor in cells. Coronavirus particles have spiked proteins sticking out from their surfaces, and these spikes hook onto cell membranes that contain ACE2 protein, allowing the virus's genetic material to enter the human cell. Viral attack may be understood as virus taking control of cell metabolism and cell stops functioning for itself. It starts working precisely to multiply virus before it is dead eventually. ACE2-bearing cells line our airways so the virus is able to attack it. Dying cells slough away, filling the airways with junk and carrying the virus deeper into the body, down toward the lungs. As the infection progresses, the lungs clog with dead cells and fluid, making breathing more difficult. The virus has special affinity to ACE2 bearing cells and might also be able to infect ACE2-bearing cells in other organs, including the gut and blood vessels. The virus may also spread indirectly because it has an estimated life of about 14 days on materials such as plastics, wood and metal though its life may vary material to material. Once an object is infected, it becomes source of infection if a person come in touch with it.

### 3.2 Mechanism

In mild viral loading, the immune system fights back and attacks the virus resulting into inflammation and fever. But in case of excess loading, the immune system goes berserk, causing more damage to itself than the actual virus. For example, blood vessels might open up

to allow defensive cells to reach the site of an infection, but the lungs fill with fluid to a harming level. These self damaging overreactions are called cytokine storms. Cytokine storms were historically responsible for many deaths during the 1918 flu pandemic, H5N1 bird flu outbreaks, and the 2003 SARS outbreak. They are most likely behind the most severe cases of COVID-19. These viruses need time to adapt to a human host, and they tend to elicit berserk responses from human immune system.

During a cytokine storm, the immune system is not just going berserk but it loses its ability to locate right targets. When this happens, people become more susceptible to infectious bacteria. If a COVID-19 patient has history of chronic diseases, cytokine storm induces complications in other organs and causes secondary infections. The response of a person infected with SARS-CoV-2 depends upon immune system, amount of virus they're exposed to (viral loading), other microbes in their bodies and ability to control cytokine storm.

No much attention has been given towards studying about numbers of people get normal coronaviruses every year neither we have any surveillance system for coronaviruses to trace their seasonal activity through out year. therefore it is yet to be known how these viruses mutate year on year.

Starting symptom in Wuhan appear to be sore throat and a dry cough. The virus then crawls downward the bronchial tubes and reach to lungs. The inflammation can damage the alveoli or lung sacs and they have to work harder to carry out their function of supplying oxygen to the blood that circulates throughout our body and removing carbon dioxide from the blood so that it can be exhaled. The swelling and the impaired flow of oxygen can cause those areas in the lungs to fill with fluid, pus and dead cells. Pneumonia, an infection in the lung, can occur. Some people get trouble in breathing and in worst case develop Acute Respiratory Distress Syndrome. Pathology reports indicate that the virus appears to start in peripheral areas on both sides of the lung and can take a while to reach the upper respiratory tract, the trachea and other central airways. Infection in the peripheral lungs were not detected in early cases. CT scans are normal in early stage of disease and as the disease progresses, CT scans show ground glass opacities, a kind of hazy veil in parts of the lung that are evident in many types of viral respiratory infections. The opaque areas can scatter and thicken in places as the illness worsens creating "crazy paving" pattern on CT scan. The illness resembles SARS in many respects and has elements in common with influenza and pneumonia. Seemingly Virus is able to infect cells in the gastrointestinal system and can also get into the bloodstream. Bone marrow and organs like the liver can become inflamed too. It may also land on organs like the heart, the kidney, the liver, and may cause some direct damage to those organs but impact of coronavirus is not yet fully understood.

### 3.3 Understanding virus Strategy

Researchers created a 3D map of the 'spike' protein used to latch on to cells to throw light on critical biological mechanism that seemingly help the coronavirus to infect humans and spread rapidly throughout globe. An analysis of the virus's structure shows that the club-like "spikes" that it uses to establish infections hook on to human cells about four times more strongly than those on the related Sars coronavirus responsible for 2002 epidemic. The finding suggests that coronavirus particles that are inhaled through the nose or mouth have a high chance of attaching to cells in the upper respiratory tract, meaning that relatively few are needed for an infection to gain a foothold.

The 3D structure shows that compared to the virus that caused the 2002-2003 Sars outbreak, the new coronavirus has evolved new strategies to bind to its human receptor, resulting in tighter binding. The tight binding to the human receptor helps this virus infect human cells and spread among humans more easily. The map of the virus will help in finding effective drugs that can neutralise the virus before duplication multiplies and the infection makes its baston. Potential antibody drug may, by binding to those sites on the virus more strongly than the receptor, block the virus out of cells. The map may

also guide work on vaccines to prevent future infections. But because the study only used fragments of the virus spike and host ACE-2 protein, conclusions are theoretical yet.

### 3.4 Clinical suggestions from patient's symptoms and observations

People of all ages can be infected by the new coronavirus.

The evidence so far indicates the virus can be transmitted in all weather conditions and weather changes alone won't necessarily reduce the number of cases.

Those who are already critically ill, are more likely to develop severe complications, if infected by coronavirus.

### 3.5 Testing

Antibody testing for all is on the horizon. Cheap, reliable antibody tests that reveal whether someone has previously had Covid-19 are viewed as crucial for managing the next phase of the pandemic. Population-level screening can gauge the overall level of immunity and can allow people to incrementally return to work. Various teams around the world are already using lab-based antibody testing, but this is challenging to scale up, partly because the tests need to be performed a few weeks after infection. In parallel, companies have been working on home-testing kits that work something like a pregnancy test.

## 4. Coronavirus Vaccine

The containment strategies such as lockdown and personal distancing have only slowed the spread of the respiratory disease Covid-19. This was prime reason that World Health Organization finally declared it a pandemic. The need of the moment is a vaccine, because only a vaccine can prevent the spread. About 35 companies and academic institutions are making efforts to find a vaccine, at least four of which already have formulations, which have been tested in animals. Boston based biotech firm Moderna will start human trials at the earliest.

Coronaviruses have caused two other recent epidemics – Severe acute respiratory syndrome (Sars) in China in 2002-04, and Middle East respiratory syndrome (Mers), which started in Saudi Arabia in 2012. Several companies did start work on vaccines for Sars and Mers but later stopped when the outbreaks were contained. Sars-CoV-2 shares between 80% and 90% of its genetic material with the virus that caused Sars, hence its name. Both consist of a strip of ribonucleic acid (RNA) inside a spherical protein capsule that is covered in spikes. The spikes lock on to receptors on the surface of cells lining the human lung, the same type of receptor in both cases allowing the virus to break into the cell. Once inside, it captures the cell's reproductive machinery to produce more copies of itself, before breaking out of the cell again and killing it in the process. Therefore work on vaccines for Sars and Mers, could be furthered for development of vaccine for Sars-CoV-2. One such company Maryland-based Novavax has restarted working on those vaccines for Sars-CoV-2, and announced it has several candidates ready to enter human trials. Another company Moderna announced about vaccine for Sars-CoV-2 based on earlier work on the Mers virus. This is also speeded by Chinese efforts to share the sequence of the genetic material of Sars-CoV-2, the virus that causes Covid-19 allowing researchers to grow the live virus and study how it prevails human cells.

### 4.1 Conventional Vaccines

All vaccines work according to the same basic principle. Part or all of the pathogen is injected into the human immune system at a low dose, to let the system to produce antibodies to the pathogen. Antibodies are a kind of immune memory which, having been produced once, can be remobilised again if the person is exposed to the virus. Conventionally, immunisation has been achieved using live, weakened forms of the virus, or part or whole of the virus after it has been inactivated by heat or chemicals. These methods have drawbacks. The live form can continue to evolve in the host, for example, potentially recapturing some of its virulence and making the

recipient sick, while higher or repeat doses of the inactivated virus are required to achieve the necessary degree of protection. Some of the Covid-19 vaccine projects are using these tried-and-tested approaches.

Meanwhile, among several antiviral medicines which are seen as effective medication in race, Remdesivir (manufactured by Gilead Sciences, USA), chloroquine and HCQ seems to lead as per literary survey. Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV5) infection in cultured cells, mice and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection. Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination. Our time-of-addition assay showed remdesivir functioned at a stage post virus entry, which is in agreement with its putative anti-viral mechanism as a nucleotide analogue. Warren et al. showed that in NHP model, intravenous administration of 10 mg/kg dose of remdesivir resulted in concomitant persistent levels of its active form in the blood (10  $\mu$ M) and conferred 100% protection against Ebola virus infection. Our data showed that EC90 value of remdesivir against 2019-nCoV in Vero E6 cells was 1.76  $\mu$ M, suggesting its working concentration is likely to be achieved in NHP. Our preliminary data showed that remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV. Chloroquine, a widely-used anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV. Our time-of-addition assay demonstrated that chloroquine functioned at both entry, and at post entry stages of the 2019-nCoV infection in Vero E6 cells. Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo. Chloroquine is widely distributed in the whole body, including lung, after oral administration [5].

Clinical trials take place in three steps. The first step involves few volunteers to test the vaccine for safety, and adversary effects. The second step ropes in hundreds of people affected by disease to find efficacy of the vaccine. The third step involves trials on several thousand people. The process has a high rate of rejection. Approval of vaccines based on newer technology is more time taking as it will be unprecedented and will attract due diligence and extra caution.

A traditional vaccine was developed in the 1960s against respiratory syncytial virus, that causes cold-like symptoms in children. In clinical trials, this vaccine was produced to aggravate those symptoms in infants who went on to catch the virus. An experimental Sars vaccine during trials on animals reflected similar effect. Though vaccine was modified to eliminate that unwanted effect. If those vaccines are repurposed for Sars-CoV-2, special stringent safety testing is needed to eliminate the risk of enhanced disease. It is for these reasons that making a vaccine candidate go all the way to regulatory approval on average takes a decade or more. So it is unlikely that an approved vaccine for Sars-CoV-2 will surface on reality before a year. Next challenge will be up sizing the production facility for the specific vaccine to meet the vast demand. The virus seems quite stable as it is found that only 4 to 10 genetic differences between the strains circulating in the US and the original virus that was isolated from Wuhan patients. This suggests that if an effective vaccine is found it should continue to work for some time.

So far experiments are carried on small number of patients (about 100). it is observed that An HIV pill, marketed by AbbVie as Kaletra, that combines the chemicals lopinavir and ritonavir didn't improve the condition of severe Covid-19 patients. Fujifilm's favipiravir, or avigan improved chest symptoms shown on CT scans. Hydroxychloroquine, a malaria drug that President Donald Trump has promoted as a potential treatment for coronavirus, was found to

be no more effective than conventional care. In latest developments, plasma therapy is also been seen as cure to the virus. Plasma therapy uses plasma of those who recovered from covid-19 as agent to fortify immune system, on assumption that patients recover due to antigens developed in blood by their immune system.

#### 4.2 Vaccine based on Newer Technologies

There are newer technologies. Novavax is using one new technology based on protein spike on the surface of Sars-CoV-2. This involves extracting the genetic code for the protein spike on the surface of Sars-CoV-2 and pasting it into the genome of a bacterium or yeast forcing these microorganisms to churn out large quantities of the protein. Still more advanced approach is to bypass the protein and build vaccines from the genetic instruction itself. Moderna and Cure Vaccination both boston based, are building Covid-19 vaccines based on messenger RNA. A vaccine based on newer technology will take at least 12 to 18 months to be ready.

The use of convalescent plasma was recommended as an empirical treatment during outbreaks of Ebola virus 2014 And a protocol for treatment of Middle East respiratory syndrome coronavirus with convalescent plasma was established in 2015. This approach with other viral infections such as SARS-CoV, H5N1 avian influenza and H1N1 influenza also suggested that transfusion of convalescent plasma was effective [6].

Ventilator are being purchased in large quantities by governments as it is also being seen life saver for those who are severely infected in lungs by viral loading. A ventilator or respirator is a machine that supports breathing in patients. Ventilators will get oxygen into the lungs, remove carbon dioxide from the body and help patients to breathe easily. A ventilator is often used during surgery when patients are under general anesthesia or during treatment for a serious lung disease or other condition that affects normal breathing.

#### 5. Exit Strategy and Conclusions

In absence of any universally acceptable medication, lockdown measures and personal distancing are only strategy in sight which need to remain in place for ample duration to have their intended effect because despite all measures the disease is in third stage in most societies. Testing of suspected and testing of large sample, then isolating the tested positive patients is being implemented universally and symptomatic suggestive medication being practiced in every hospital in the world. Hospitals are depending upon respective national policy or their knowledge of local antiviral drugs which have been used in past and have record of no harmful side effects and such drugs are being prescribed. Ventilators are being used more and more for critical patients who suffer from acute respiratory distress syndrome caused by this virus. The disease covid-19 is not yet understood completely as most of the observations are based on few patients, which requires immediate attention. After the disease is overcome, long lockdowns would have dented severely the global economy and particularly economics of severely affected countries. The next challenge of the pandemic will be to absorb the pecuniary dents of the society.

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