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Original Research Article

Covid-19 Disease Outbreak: A Vital & Healthy Review

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Abstract:

Background: Coronaviruses are RNA viruses that are phenotypically and genotypically myriad. In this Review, we light on the basic virological concept of SARS-CoV-2, including genomic attributes and receptor use, highlighting its role key variance from previously known coronaviruses. The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which is also called, as the 2019 novel coronavirus (2019-nCoV) was rapidly spreaded from its origin in Wuhan City of Hubei Province of China to all parts and became a cosmopolitan problem for world. Around 704,539,018 cases of coronavirus disease 2019 (COVID-19), 7,008,958 deaths and 675,395,611 have been reported till 31/ 03/2024 in the world. India has reported 45,034,136 cases, and 533,547 deaths till 31/ 03/2024. But the future course of this virus is unknown. Coronaviruses are known to be associated with a variety of diseases in humans and domestic animals. It has been postulated that the proximity of humans to wild animals might have led to animal pathogens jumping across species from animals to humans, and become the causative pathogen in the latter. It is important to determine whether there is an animal reservoir, as breaking transmission of the virus may be more difficult and a recurrence of the disease is more likely. The clinical manifestations of COVID-19 are found myraid, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. Common characteristics wasclude fever, cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα. This finding suggests that receptor usage may not be the only factor that determines the severity of HCoV infection. Dipeptidyl peptidase 4 (DPP4, also known as CD26), the receptor for MERS-CoV, is a multifunctional cell surface protein widely expressed on epithelial cells in kidney, small intestine, liver and prostate and on activated leukocytes. DPP4 is expressed in the upper respiratory tract epithelium of camels. In the human respiratory tract, DPP4 is mainly expressed in alveoli rather than the nasal cavity or conducting airways. DPP4 is a key factor in the activation of T cells and immune response costimulatory signals in T cells, which could indicate a possible manipulation of the host immune system. Human aminopeptidase N (CD13), a cell-surface metalloprotease on intestinal, lung and kidney epithelial cells, has been identified as the receptor for hCoV229E. The receptor for HCoV-OC43 is 9-O-acetylated sialic acid. Currently, the receptor for HCoV-HKU1 has not been identified.

Aim: This article may try to gives a blue eye view about this new virus. Since knowledge about this virus is rapidly updating and evolving, readers are urged to update themselves regularly.

Discussion: Current understanding of the pathogenesis of HCoVs infection is still limited. However, several significant differences in the pathogenesis exist among SARS-CoV, MERS-CoV and the other HCoVs. Cell entry and receptors. The critical first step for HCoV infection is entry into the susceptible host cells by combining with a specific receptor. Spike proteins (S proteins) of HCoVs are a surface-located trimeric glycoprotein consisting of two subunits: the N-terminal S1 subunit and the C-terminal S2 subunit. The S1 subunit specializes in recognizing and binding to the host cell receptor while the S2 region is responsible for membrane fusion. To date, a wide range of diverse cellular receptors specifically recognized by the S1 domains have been identified for all HCoVs except HCoV-HKU1. ACE2, the receptor for SARS-CoV and HCoVNL63 is a surface molecule localized on arterial and venous endothelial cells, arterial smooth muscle cells, epithelia of the small intestine and the respiratory tract. In the respiratory tract, ACE2 is expressed on the epithelial cells of alveoli, trachea, and bronchi, bronchial serous glands, and alveolar monocytes and macrophages.

Conclusion: The 2019 novel coronavirus (2019-nCoV) outbreak is a major challenge for clinicians, and social, economic & public health prosperity to almost whole world. In India the economic progress and prosperity sturdily challenged and affected. The clinical course of patients remains to be fully characterized, little data are available that describe the disease pathogenesis, and no pharmacological therapies of proven efficacy yet exist.

Keywords: Covid, SARS, MERS, Monocyte, Alveoli, Human, Virus.

Introduction

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which is also called, as the 2019 novel coronavirus (2019-nCoV) was rapidly spreaded from its origin in Wuhan City of Hubei Province of China to all parts and became a cosmopolitan problem for world [1]. Around 704,539,018 cases of coronavirus disease 2019 (COVID-19), 7,008,958 deaths and 675,395,611 have been reported till 31/ 03/2024 in the world. India has reported 45,034,136 cases and 533,547 deaths till 31 / 03/2024 [2]. But the future course of this virus is unknown. This article may try to gives a blue eye view about this new virus. Since knowledge about this virus is rapidly updating and evolving, readers are urged to update themselves regularly.

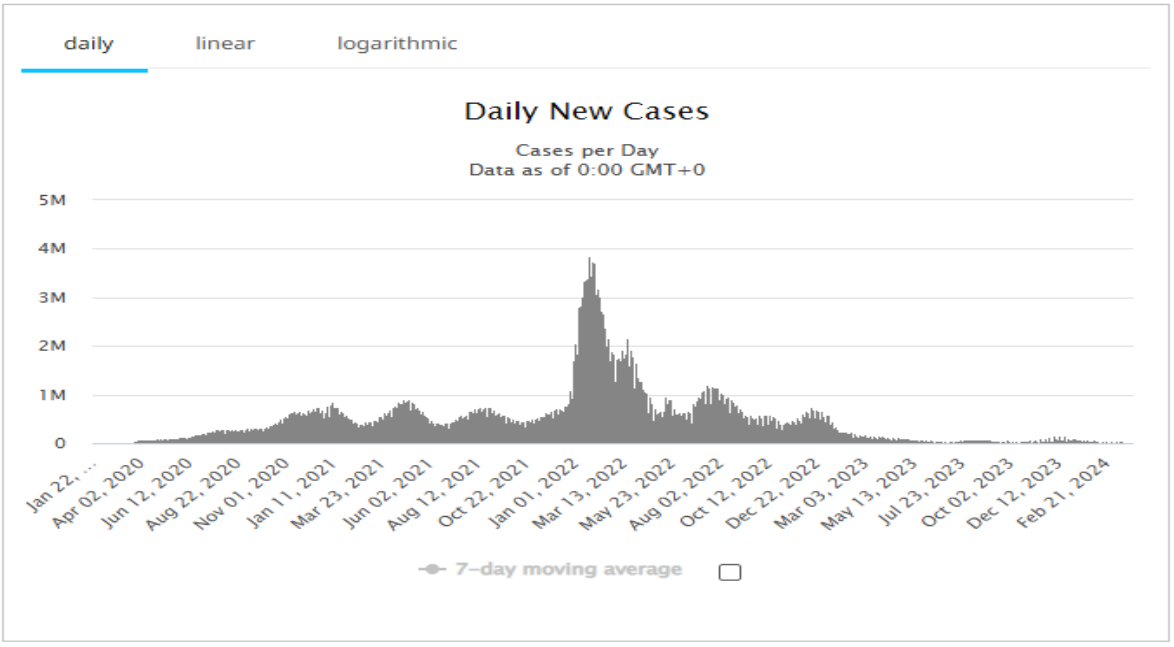

Figure 1: Showing daily new cases rise world wide

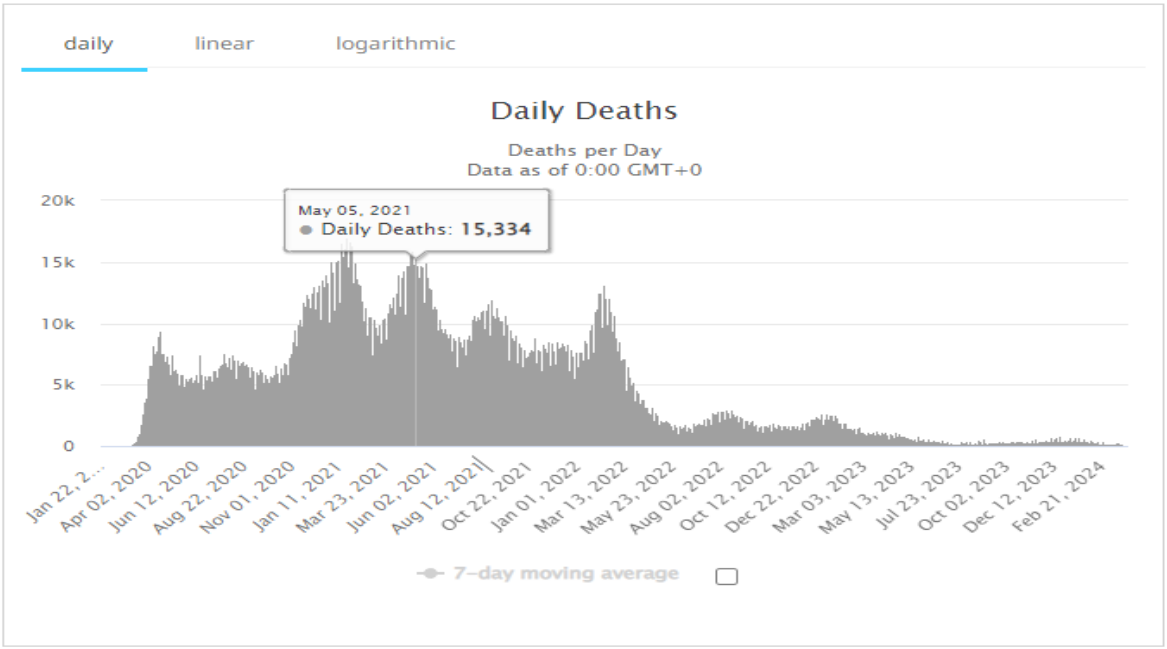

Figure 2: Showing daily deaths worldwide

The disease caused by the SARS-CoV-2 coronavirus. It usually spreads between people in close contact. COVID-19 vaccines provide strong protection against severe illness and death.

Although a person can still get COVID-19 after vaccination, they are more likely to have mild or no symptoms. Anyone can get sick with COVID-19 and become seriously ill or die, but most people will recover without treatment.People over age 60 and those with existing medical conditions have a higher risk of getting seriously ill. These conditions include high blood pressure, diabetes, and obesity, immunosuppression including HIV, cancer and pregnancy.

Unvaccinated people also have a higher risk of severe symptoms. Since knowledge about this virus is rapidly updating and evolving, readers are urged to update themselves regularly [3].

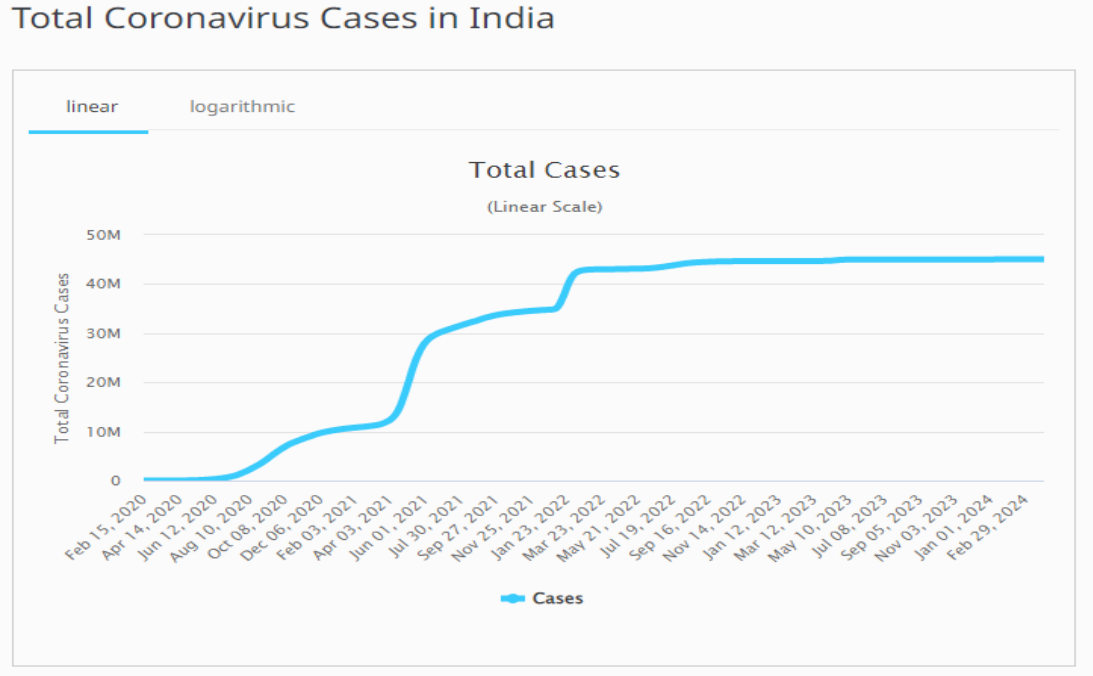

Figure 3: Showing total corona cases in India

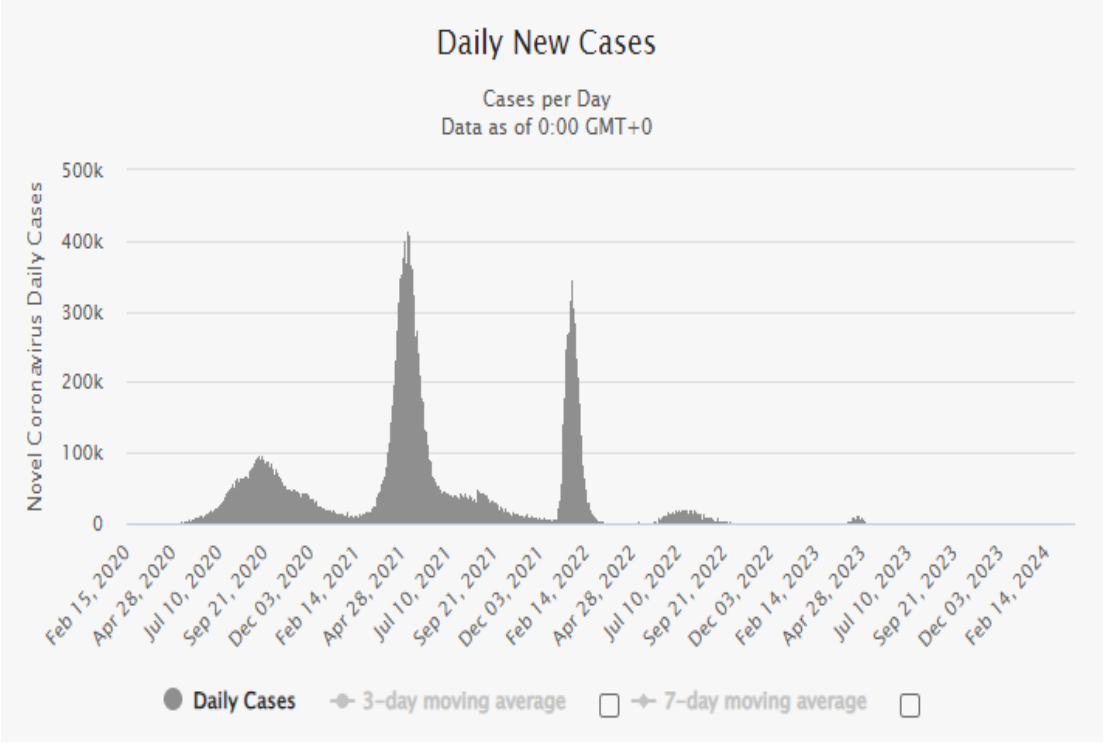

Figure 4: Showing daily new cases in India

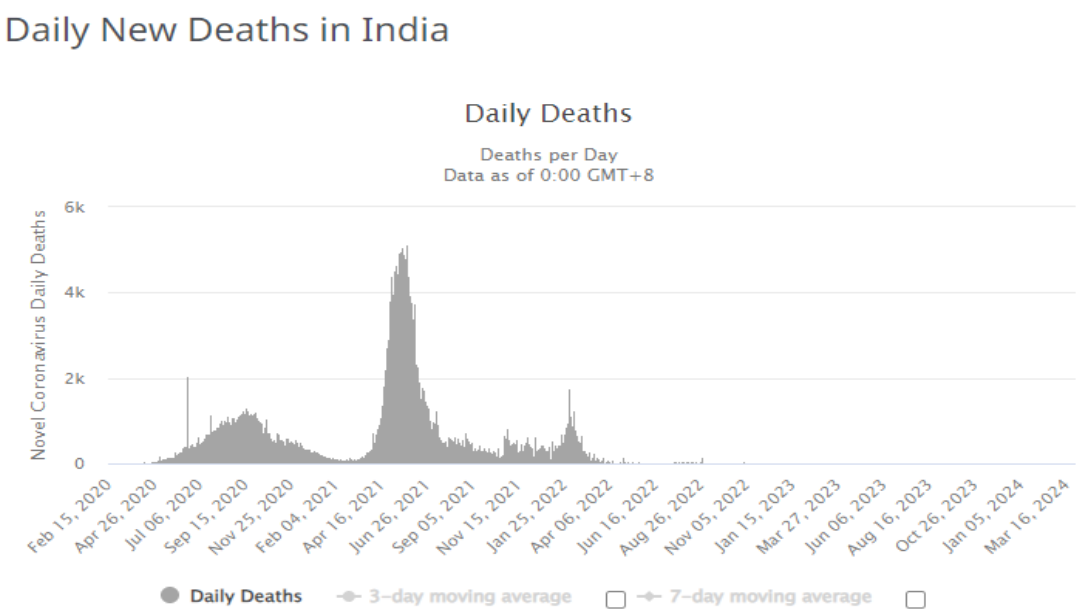

Figure 5: Showing daily new deaths in India

History of covid-19

Under the electronic microscope coronaviruses are enveloped positive sense RNA viruses with a diameter ranging from 60 nm to 140 nm along with spike like projections on its surface giving it a crown like appearance; hence for this reason they are known as coronavirus [3]. The corona viruses namely HKU1, NL63, 229E and OC43 have been identified yet in circulation in humans, and generally cause mild respiratory disease. In 21th century two previous coronavirus outbreaks had been reported. The clinical features of 2019-nCoV, in comparison with SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, are slightly changeable. The ongoing 2019-nCoV outbreak has undoubtedly caused the memories of the SARS-CoV outbreak starting 17 years ago to resurface in many people. In November, 2002, clusters of pneumonia of unknown cause were reported in Guangdong province, China, now known as the SARS-CoV outbreak [4].

The international spread of SARS-CoV in 2003 was attributed to its strong transmission ability under specific circumstances and the insufficient preparedness and implementation of infection control practices.

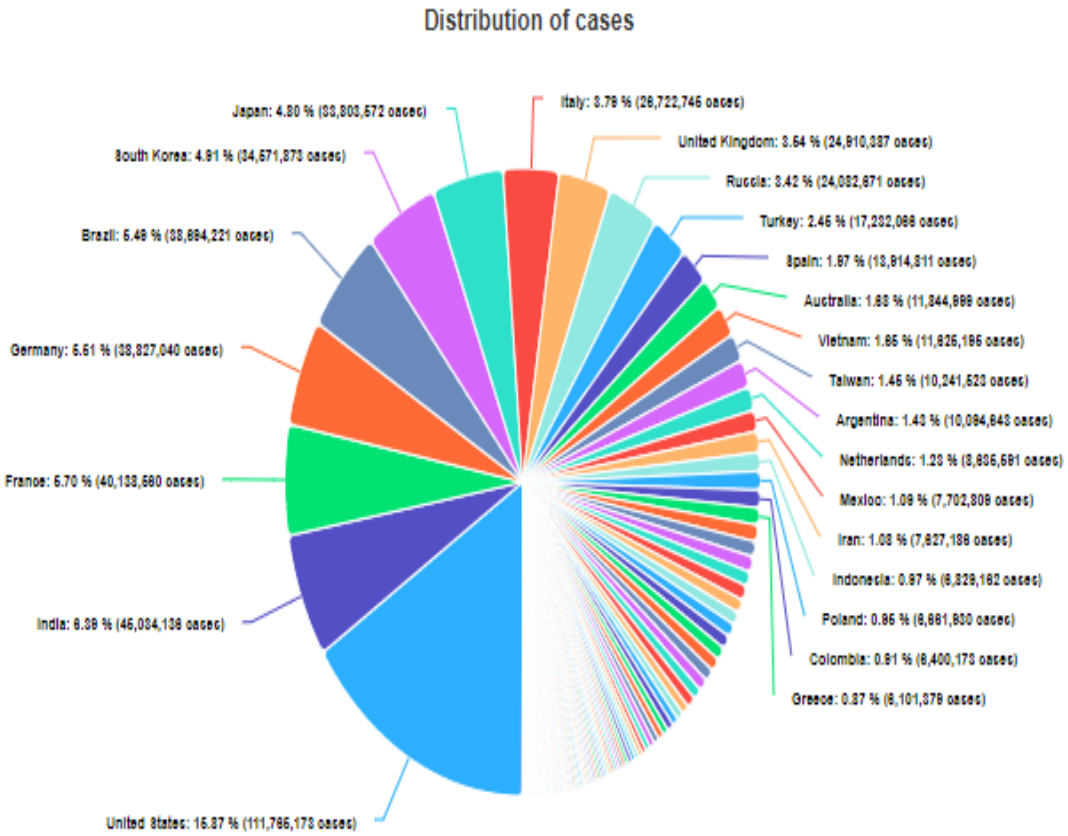

Figure 6: Showing distribution of cases worldwide:

Chinese public health and scientific capabilities have been greatly transformed since 2003. An efficient system is ready for monitoring and responding to infectious disease outbreaks and the 2019-nCoV pneumonia has been quickly added to the Notifiable Communicable Disease [4]. Consequently, the 2019-nCoV outbreak has led to implementation of extraordinary public health measures to reduce further spread of the virus within China and elsewhere [5]. Although WHO has not recommended any international travelling restrictions so far, the local government in Wuhan announced on Jan 23, 2020, the suspension of public transportation, with closure of airports, railway stations, and highways in the city, to prevent further disease transmission [6].

Pathogenesis

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occurs from asymptomatic people and before onset of symptoms. The virus can remain viable on surfaces for days in favorable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them or then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/ feco oral route is also hypothesized. Studies have identified angiotensin receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa. The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modelling studies. In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009 [7].

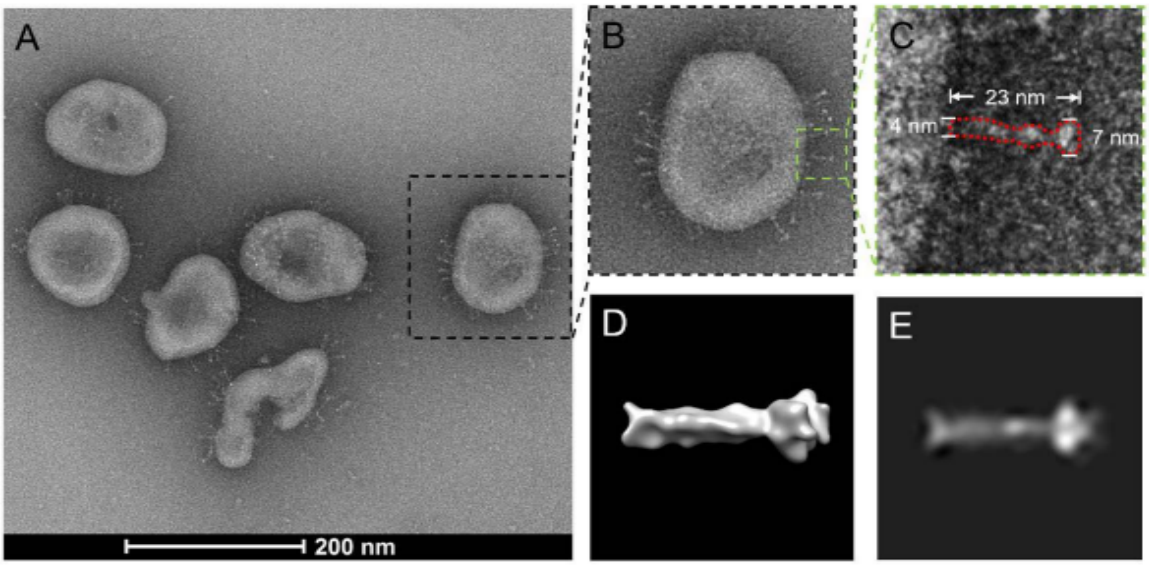

Figure 7: Negative stain EM results of SARS-CoV-2. (A). Image of negative stained SARS-CoV-2. Nail-like spikes can be clearly seen. (B). Enlarged view of virion boxed in (A). (C) Zoom-in view of a spike boxed in (B). The shape is depicted by red dot line. Length, the diameter of stem and spike's head is 23nm, 4nm and 7nm, respectively. (D). Three-dimensional surface of post-fusion state S2 protein (EMDB code: 9597) [15]. (E). Projection of post-fusion state S2 protein.

Coronaviruses are known to be associated with a variety of diseases in humans and domestic animals. It has been postulated that the proximity of humans to wild animals might have led to animal pathogens jumping across species from animals to humans, and become the causative pathogen in the latter.

It is important to determine whether there is an animal reservoir, as breaking transmission of the virus may be more difficult and a recurrence of the disease is more likely. While some investigators suggested that the virus mutates rapidly, as the strain responsible for the Amoy Gardens outbreak appeared to cause a more serious disease with diarrhea as a prominent feature, scientists in Singapore found that the virus is rather stable[8].

Preliminary studies of samples from patients using reverse transcriptase polymerase chain reaction (RTPCR) technique have demonstrated the presence of the RNA of SARS-virus in nasopharyngeal aspirate (NPA) in 31% on day 2, 43% on day 3–5, and 60% of patients from 6 to 8 days to 2 weeks after onset of the illness and in stool samples in almost 100% of patients at the end of 2 weeks [9]. It is unknown at present whether asymptomatic carriers are infectious or not, a factor important for disease control. Moreover, it is not known how long a patient can remain infectious as virus has been found in stool samples as long as one month after the onset of illness. The virus is transmitted from human to human by droplets generated by coughing and sneezing and by direct inoculation. Contact with infected droplets on a surface can be a source of infection.

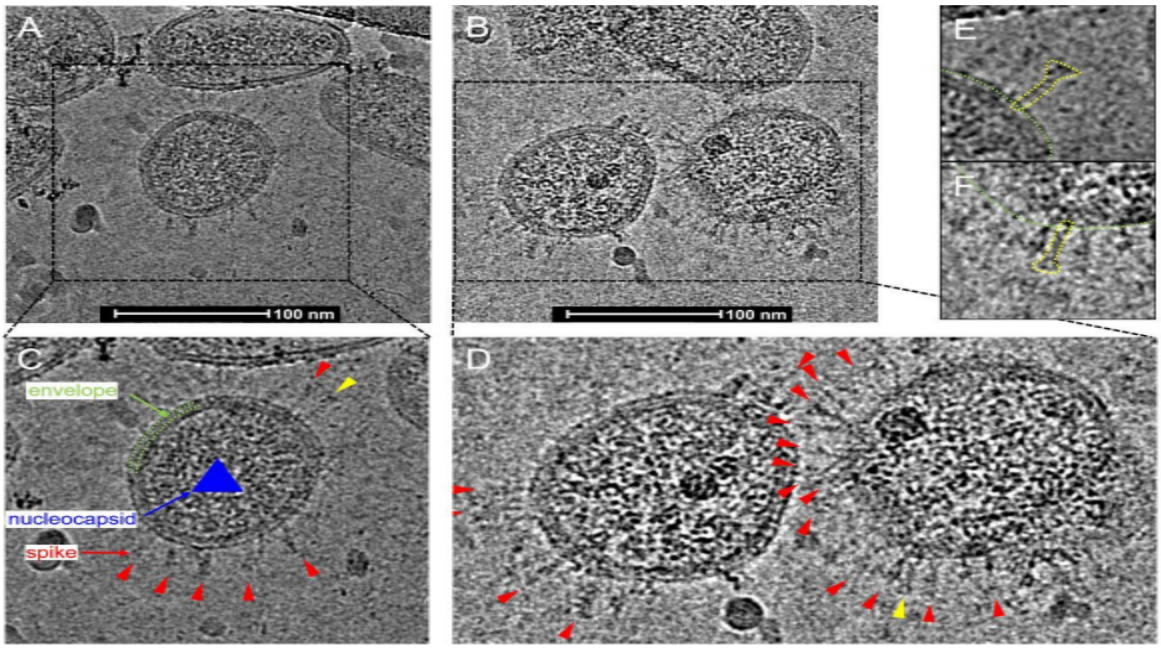

Figure 8: Cryo-EM results of SARS-CoV-2. (A) and (B). Cryo-EM images of SARSCoV-2. (C). Zoom-in view of the virion showed in (A). Envelope and nucleocapsid are indicated by green and blue respectively, remarkable spikes are indicated by red triangles. (D). Zoom-in views of the two virions showed in (B), remarkable spikes are indicated by red triangles. (E). Zoom-in view of the spike indicated by yellow triangle in (C). The shape is depicted by yellow dot lines. (F). Zoom-in view of the spike indicated by yellow triangle in (D). The shape is depicted by yellow dot lines.

Fortunately, the virus loses its infectivity after exposure to several commonly used disinfectants such as Clorox, 75% ethanol and fixatives such as formaldehyde and paraformaldehyde. The large number of residents in Amoy Gardens developing disease within a short period of time raised the suspicion that other modes of transmission such as airborne or oral-fecal route may be responsible. Investigation conducted by the Department of Health, Hong Kong concluded that the virus was carried by droplets into people's bathrooms as a result of contamination of waste drainage pipes and failure of the U-shaped water-seal. The contamination could be traced to a patient who had loose stools when he visited his brother in one of the flats in E Block of Amoy Gardens. The report excluded airborne transmission, but clear evidence has yet to be provided [10].

Clinical findings

The clinical manifestations of COVID-19 are found myraid, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. Common characteristics wasclude fever, cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα [11]. The median time from onset of symptoms to dyspnea was 5 day, hospitalization 7 d and acute respiratory distress syndrome (ARDS) 8 d. The need for intensive care admission was in 25–30% of affected patients in published series. Complications witnessed included acute lung injury, ARDS, shock and acute kidney injury. Recovery started in the 2nd or 3rd week. The median duration of hospital stay in those who recovered was 10 days. Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50–75% of fatal cases). Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range between 2 and 3% . Interestingly, disease in patients outside Hubei province has been reported to be milder than those from Wuhan [12]. Disease in neonates, infants and children has been also reported to be significantly milder than their adult counterparts. In a series of 34 children admitted to a hospital in Shenzhen, China between January 19th and February 7th, there were 14 males and 20 females. The median age was 8 y 11 months and in 28 children the infection was linked to a family member and 26 children had history of travel/residence to Hubei province in China. All the patients were either asymptomatic (9%) or had mild disease. No severe or critical cases were seen. The most common symptoms were fever (50%) and cough (38%). All patients recovered with symptomatic therapy and there were no deaths. One case of severe

pneumonia and multiorgan dysfunction in a child has also been reported [13].

Discussion

Current understanding of the pathogenesis of HCoVs infection is still limited. However, several significant differences in the pathogenesis exist among SARS-CoV, MERS-CoV and the other HCoVs. Cell entry and receptors The critical first step for HCoV infection is entry into the susceptible host cells by combining with a specific receptor. Spike proteins (S proteins) of HCoVs are a surface-located trimeric glycoprotein consisting of two subunits: the N-terminal S1 subunit and the C-terminal S2 subunit.

The S1 subunit specializes in recognizing and binding to the host cell receptor while the S2 region is responsible for membrane fusion [14] To date, a wide range of diverse cellular receptors specifically recognized by the S1 domains have been identified for all HCoVs except HCoV-HKU1. ACE2, the receptor for SARS-CoV and HCoVNL63 [15,16] is a surface molecule localized on arterial and venous endothelial cells, arterial smooth muscle cells, epithelia of the small intestine and the respiratory tract. In the respiratory tract, ACE2 is expressed on the epithelial cells of alveoli, trachea, and bronchi, bronchial serous glands, and alveolar monocytes and macrophages. ACE2 is a homologue of the ACE protein, and both are key enzymes of the renin–angiotensin system [17] ACE2 plays a protective role in lung failure and its counterpart ACE promoting lung oedema and impaired lung function [18].

Down regulation of ACE2, as occurs during SARS-CoV infection, is believed to contribute to pathological changes in the lung. This form of lung damage can be attenuated by blocking the renin–angiotensin pathway [19] interestingly; HCoV-NL63 also employs the SARS receptor for cellular entry, despite their markedly different pathogenicity and disease courses. This finding suggests that receptor usage may not be the only factor that determines the severity of HCoV infection. Dipeptidyl peptidase 4 (DPP4, also known as CD26), the receptor for MERS-CoV,[18] is a multifunctional cellsurface protein widely expressed on epithelial cells in kidney, small intestine, liver and prostate and on activated leukocytes. DPP4 is expressed in the upper respiratory tract epithelium of camels. In the human respiratory tract, DPP4 is mainly expressed in alveoli rather than the nasal cavity or conducting airways [21]. DPP4 is a key factor in the activation of T cells and immune response costimulatory signals in T cells, which could indicate a possible manipulation of the host immune system. Human aminopeptidase N (CD13), a cell-surface metalloprotease on intestinal, lung and kidney epithelial cells, has been identified as the receptor for hCoV229E. The receptor for HCoV-OC43 is 9-O-acetylated sialic acid. Currently, the receptor for HCoV-HKU1 has not been identified [22].

Treatment for COVID-19

To date, there are no generally proven effective therapies for COVID-19 or antivirals against SARS-CoV-2, although some treatments have shown some benefits in certain subpopulations of patients or for certain end points. In vitro experiments showed that it has activity against SARS- CoV-2, and current clinical data revealed it may be more effective than lopinavir and ritonavir in treating COVID-19. However, other clinical studies showed umifenovir might not improve the prognosis of or accelerate SARS- CoV-2 clearance in patients with mild to moderate COVID-19. Yet some ongoing clinical trials are evaluating its efficacy for COVID-19 treatment. Camostat mesylate is approved in Japan for the treatment of pancreatitis and postoperative reflux oesophagitis. Previous studies showed that it can prevent SARS-CoV from entering cells by blocking TMPRSS2 activity and protect mice from lethal infection with SARS-CoV in a pathogenic mouse model (wild type mice infected with a mouse- adapted SARS-CoV strain). Recently, a study revealed that camostat mesylate blocks the entry of SARS- CoV-2 into human lung cells [23]. Thus, it can be a potential antiviral drug against SARS- CoV-2 infection, although so far there are not sufficient clinical data to support its efficacy.

Chloroquine and hydroxychloroquine are other potential but controversial drugs that interfere with the entry of SARS- CoV-2. They have been used in the prevention and treatment of malaria and autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. They can inhibit the glycosylation of cellular receptors and interfere with virus-host receptor binding, as well as increase the endosomal pH and inhibit membrane fusion. Currently, no scientific consensus has been reached for their efficacy in the treatment of COVID-19. Some studies showed they can inhibit SARSCoV-2 infection in vitro, but the clinical data are insufficient.

Two clinical studies indicated no association with death rates in patients receiving chloroquine or hydroxychloroquine compared with those not receiving the drug and even suggest it may increase the risk of dying as a higher risk of cardiac arrest was found in the treated patients [24].

The safety and efficacy of these strategies need to be assessed in future clinical trials. Virus Replication Inhibition: Replication inhibitors include remdesivir (GS-5734), favilavir (T-705), ribavirin, lopinavir and ritonavir.

Except for lopinavir and ritonavir, which inhibit 3CLpro, the other three all target. Remdesivir has shown activity against SARS-CoV-2 in vitro and in vivo.

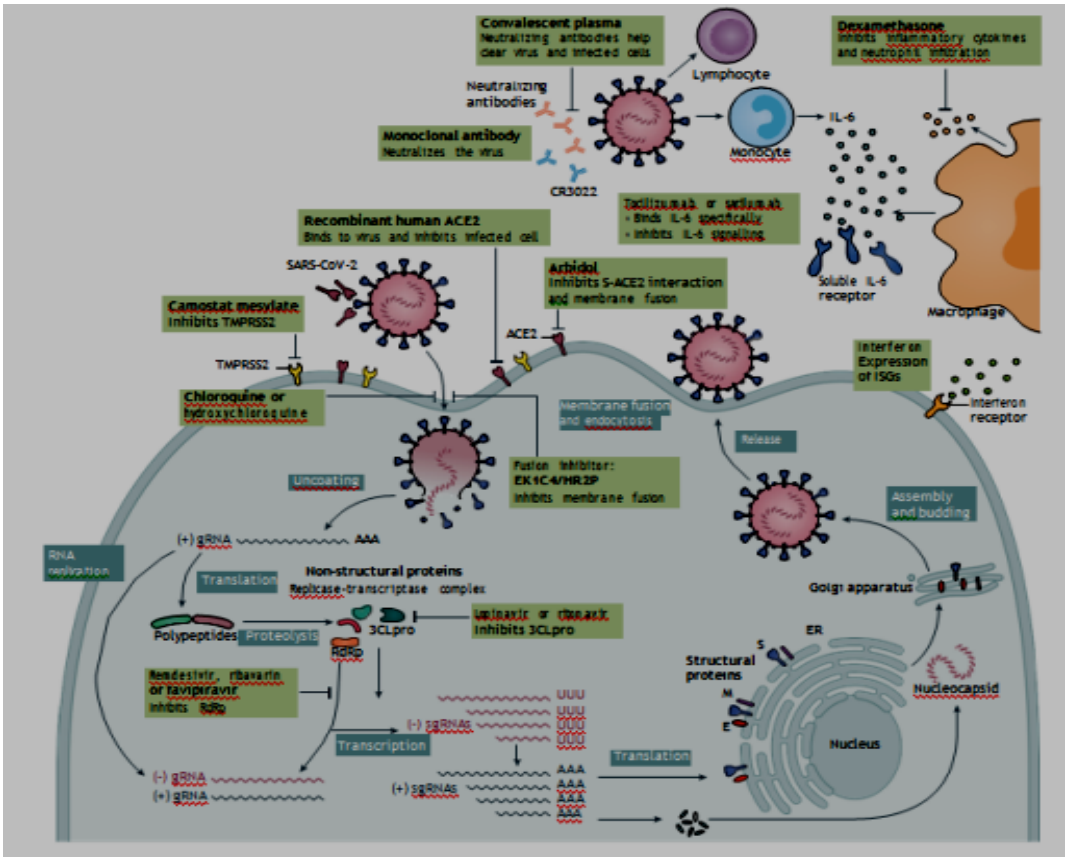

Figure 7: Replication and Potential Therapeutic Targets for SARS-CoV-2: Potential antivirals target the different steps of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication, ranging from receptor binding, entry and fusion to replication

Furthermore, immunoglobulin-based and immunomodulatory drugs are potential therapeutics as well. Note that robust data on clinical efficacy are lacking for most of these treatments so far. 3CLpro, 3C-like protease; ACE2, angiotensin-converting enzyme 2; CR3022, a SARS-CoV-specific human monoclonal antibody; E, envelope protein; EK1C4, lipopeptide derived from EK1 which is a pan-coronavirus fusion inhibitor targeting the HR1 domain of the spike protein; ER, endoplasmic reticulum; gRNA, genomic RNA; HR2P, heptad repeat 2-derived peptides of SARS-CoV-2 spike protein; IL-6, interleukin-6; ISG, interferon stimulated gene; M, membrane protein; RdRp, RNA-dependent RNA polymerases; sgRNA, subgenomic RNA; S, spike protein; TMPRSS2, transmembrane protease serine protease 2.A clinical study revealed a lower need for oxygen support in patients with COVID-19.

Preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT) clinical trial by the National Institute of Allergy and Infectious Diseases (NIAID) reported that remdesivir can shorten the recovery time in hospitalized adults with COVID-19 by a couple days compared with placebo, but the difference in mortality was not statistically significant.

The FDA has issued an emergency use authorization for remdesivir for the treatment of hospitalized patients with severe COVID-19. Favilavir (T-705), which is an antiviral drug developed in Japan to treat influenza, has been approved in China, Russia and India for the treatment of COVID-19. A clinical study in China showed that favilavir significantly reduced the signs of improved disease signs on chest imaging and shortened the time to viral clearance. A preliminary report in Japan showed rates of clinical improvement of 73.8% and 87.8% from the start of favilavir therapy in patients with mild COVID-19 at 7 and 14 days, respectively, and 40.1% and 60.3% in patients with severe COVID-19 at 7 and 14 days, respectively [25].

Lopinavir and ritonavir were reported to have in vitro inhibitory activity against SARS-CoV and MERS-CoV. Alone, the combination of lopinavir and ritonavir had little therapeutic benefit in patients with COVID-19, but appeared more effective when used in combination with other

drugs, including ribavirin and interferon beta-1b143.

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, a national clinical trial programme in the UK, has stopped treatment with lopinavir and ritonavir as no significant beneficial effect was observed in a randomized trial established in March 2020 with a total of 1,596 patients. Nevertheless, other clinical trials in different phases are still ongoing elsewhere [26]

Prevention

Right now there is no valuable and appreciated or approved treatments for this infection, prevention is critical. Several properties of this virus make prevention difficult namely, non-specific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery.

People should get vaccinated as soon as it's their turn. They should follow local guidance on vaccination and ways to protect themselves against COVID-19. COVID-19 vaccines provide strong protection against serious illness, hospitalization and death.

To prevent the spread of COVID-19: Pople should avoid crowds and keep a safe distance from others, even if they don't appear to be sick; should wear a properly fitted mask if you feel sick, have been close to people who are sick, if you are at high-risk, or in crowded or poorly ventilated areas; should clean your hands frequently with alcohol-based hand rub or soap and water; should cover your mouth and nose with a bent elbow or tissue when you cough or sneeze; dispose of used tissues right away and clean your hands; and if you develop symptoms or test positive for COVID-19, self-isolate until you recover [27]. Vaccination against COVID-19 is based on priority groups such as people aged 60 years and over, and those with underlying medical problems such as high blood pressure, diabetes, chronic health problems, immunosuppression (including HIV), obesity, cancer, pregnant persons, and unvaccinated people. In March 2023, WHO updated its recommendations on primary series vaccination (two doses of any vaccine) as well as the need for booster doses.

These recommendations are time-limited and can change at any time depending on how the SARS-CoV-2 virus is circulating in your area or country. It is important to stay up to date with local guidelines and recommendations provided by your local health authority. Since its introduction, COVID-19 vaccines have saved millions of lives across the world by providing protection against severe disease, hospitalization, and death. Even though vaccines protect against severe disease and death, it is still possible to spread SARS-CoV-2 to others after being vaccinated [28].

Conclusion

The 2019 novel coronavirus (2019-nCoV) outbreak is a major challenge for clinicians, and social, economic & public health prosperity to almost whole world. In India the economic progress and prosperity sturdily challenged and affected. The clinical course of patients remains to be fully characterized, little data are available that describe the disease pathogenesis, and no pharmacological therapies of proven efficacy yet exist.

The first line and advances in prevention and effective management of COVID-19 will require basic and clinical investigation and public health and clinical interventions. Corticosteroids were widely used during the past outbreaks and are being used in patients with 2019-nCoV in addition to other therapeutics. However, current interim guidance from WHO on clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected.

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