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REVIEW ARTICLE

Novel SARS-CoV-2 outbreak and COVID19 disease; a systemic review on the global pandemic

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Abstract Since the beginning of the 21st century, several viral outbreaks have threatened humankind and posed a new challenge to the modern healthcare system. The recent outbreak in Wuhan (December 2019), China, represents a beta coronavirus classified as novel Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) which belongs to the Coronaviridae family. Novel SARS-CoV-2 represents a significant similarity with previous coronaviruses such as SARS-CoV in 2002, China and MERS-CoV in 2015, Middle East. However, preliminary research investigations have shown the novel SARS-CoV-2 evolved with several mutations and developed the capacity to cross the species, i.e., animal to human. The initial findings have shown that spike proteins are vital molecules target hACE2 receptor for its attachment and entry into cells. After successful entry virus primarily focuses on respiratory airway cell lines and triggers a massive immune response leading to mucus generation. In severe conditions, the virus is capable of forcing viral pneumonia leading to the collapse of the respiratory system, i.e., COVID19. So far, there is a lack of immunity against the virus in humans. At the same in the absence of therapeutic interventions, many countries experienced high mortality, such as the United States, European countries, i.e., Italy, Spain, France, and the United Kingdom. The vaccine development is underway and experiencing challenges, as many reports demonstrated genetic variations in viral genome and proteins as well. The present study provides a complete comprehensive overview of the novel SARS-CoV-2 outbreak, human transmission, and global spread.

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Introduction and overview of coronaviruses

Coronaviruses are a large group of animal viruses from Coronaviridae family cause disease to human and birds. These viruses are had a long history and remain associated with viral outbreaks in the past. In 1930 the first coronavirus was discovered, i.e., infectious bronchitis virus (IBV) caused the acute respiratory infection to chickens. In subsequent years during 1940, two more animal coronaviruses were isolated and characterized as mouse hepatitis virus (MHV) and transmissible gastroenteritis virus (TGEV), which were isolated.[1] The first human coronavirus was isolated in 1960 from humans as human coronavirus 229E and human coronavirus OC43. The most recent human coronaviruses caused viral outbreak and disease are SARS-CoV in 2003, HCoV NL63 in 2004, HKU1 in 2005, MERS-CoV in 2012, and SARS-CoV-2 in 2019.[2] Coronaviridae family is a large group of animal viruses and was further classified into four subgroups as alpha, beta, delta, and gamma coronaviruses. Based on scientific findings and available works of literature, all coronaviruses that emerged as a viral outbreak caused the disease to humans belongs to the beta group. The coronaviruses primarily infect birds are classified under delta and gamma subgroups.[3] It has been postulated wild animals are the natural reservoir of coronaviruses; however, several species of coronaviruses also habit in domestic and commercial animals. Beta coronaviruses infecting humans primarily cause disease to the upper respiratory airway in acute and lower respiratory tract infections in chronic cases. As a result, Severe Acute Respiratory Syndrome (SARS) is a common terminology used in corona viruses infecting a human.[4] These coronaviruses infect the human respiratory tract as a higher affinity of spike proteins of the virus with hACE2 receptor. The differential expression of hACE2 in children, adults, and the elderly defines the severity of diseases as well. The ACE2 expression is not limited to respiratory airway other tissues as well get infected with SARS-CoV such as gastrointestinal tract, kidney, heart, and liver. The rate and extent of infection also depend on the nature of viruses, i.e., wild type versus mutant.[5]

Coronaviruses outbreak and human health

In the last two decades, the world had witnessed several viral outbreaks associated with the loss of human lives worldwide. Based on scientific research investigations, these animal viruses gained the capacity to cross-species and infected humans.[6] The first SARS-CoV outbreak started in 2002 in China, linked with seafood marker and wild animals. Similarly, in 2012, the MERS-CoV outbreak in the Middle East finds a similar pattern of infection. The researchers are keen to understand the nexus between the animal and human in the viral outbreak. In both cases, i.e., SARS-CoV and MERS-CoV virus acquired genetic changes enabling a species jump and find a new host. So far, we do not have any precise medicine and vaccine for earlier coronaviruses and not novel SARS-CoV-2 posed a new threat to our healthcare system. The researchers believe that human nexus with animal life and habitat might be a significant risk factor in spreading animal viruses into new hosts, including humans. A similar case was reported in 2009 in the case of H1N1, where a cross-connection between animal viruses between pig, bird, and human triggered an influenza outbreak.[7] In context with the novel, SARS-CoV-2 researchers believe a close artificial habitat of various wildlife animals abundant in several coronaviruses allowed to cross-react and get mutated in more complex and pathogen serotype.[8] However, the exact mechanism of novel SARS-CoV-2 outbreak from animal to human not yet explored, and researchers are working to understand factors driven such spices migration.

Novel SARS-CoV-2 outbreak

In December 2019, in the City of Wuhan, China, several cases were first reported with mysterious viral pneumonia. The preliminary findings showed all these cases had H1N1, like flu symptoms. The virus novel SARS-CoV-2 spread across the world within three months result in pandemic posed a devastating threat to human health.[9] There are ongoing research efforts to understand the mechanism of SARS-CoV-2 entry into the host cell and the role of the receptor binding domain (RBD) of spike protein10. The pandemic caused by novel SARS-CoV-2 has made human life to a halt and posing a serious global public health. Considering the global map, COVID 19 has a cost more than 3, 46, 000 lives globally (infection more than 5 million) as per the recent report from the CDC and WHO updated on May 26, 2020 (https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm). The novel SARS-CoV-2 outbreak and epicenter remain to change over time. The worst affected countries outside China are the United States, Italy, and Spain. At present rapid rise in novel SARS-CoV-2 cases reported in Brazil, Russia and India The infection and mortality reported higher in the United States and Europe compare to Asian and the Middle East countries. At present, the United States is the epicenter for COVID19 disease, and New York City hit the most. The research finding underway to understand the origin of the viral outbreak in Wuhan, China, and recent findings have demonstrated a natural mechanism of SARS-CoV to cross the species and also reported mutations in receptor binding domains (RBDs). The preliminary studies have shown genetic variations in the SARS-CoV-2 strain worldwide. These variations may alter the rate of infections and death as well. On the contrary, such changes are a challenge in vaccine and therapeutic development. The receptor-binding domains in spike proteins of SARS-CoV-2 had shown promising opportunities for drug and vaccine development.[11]

Human to human transmission

To understand human to human transmission of novel SARS-CoV-2 took several weeks during an outbreak in Wuhan, China. Now, as per WHO and CDC guidelines, the human to human transmission occurs primarily via droplets (both oral and nasal) and aerosols generate during sneezing, coughing, and talk.[12] There are other means of transmission as well, including physical contact with COVID19 patients, various surfaces, and a share of household stuff. The viability and infection of novel SARS-CoV-2 differ on

multiple surfaces. There are several other sources of novel SARS-CoV-2 infection, such as stool and sputum. The recent findings have demonstrated that intensive care units in COVID hospitals may increase the risk of infection in the lack of proper pressure ventilation systems. There are growing research findings suggested the viability of novel SARS-CoV-2 in air, hospital environment, personal protective equipment, etc. may further increase the risk of infection.[13] Considering scientific literature available on NCBI, the massive rate of novel SARS-CoV-2 infection is due to asymptomatic patients. The novel SARS-CoV-2 titer also defines the rate of infection and severity of disease as well. Despite the fact that all modern protective gears in ICU medical and paramedical staffs get a higher rate of infection and prone to mortality, which is due to higher viral titer value. Nearly half of the novel SARS-CoV-2 infection remains asymptomatic and poses a risk to others as a potential carrier of the virus.[6] These asymptomatic infections also bypass rapid tests such as serum antibody tests.

COVID19

The novel SARS-CoV-2 infection primarily affects the respiratory airway and binds hACE2 receptor present on mucosal cells. The binding of RBDs of spike proteins with hACE2 results in several pathological outcomes differs in patients. Now, considering current research findings and clinical outcomes, the infection may lead to the symptoms according to the severity of disease i.e., mild, moderate, and severe.[10] The novel SARS-CoV-2 infection leading to the onset of COVID19 remains associated with the following;

- **Mild illness/non-symptomatic**: Patients' uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea, and vomiting
- **Pneumonia:** Prevalent in large population where infected patients with pneumonia however lack of severe pneumonia symptoms but require oxygen support.
- **Acute respiratory distress syndrome (ARDS):** The most crucial phase of infection of novel SARS-CoV-2 and diseases COVID19 can be seen within one week of infection, patient may develop ARDS, which is characterized by bilateral opacities, lobar or lung collapse, or nodules on CXR or CT scan.

Looking into the Coronaviridae family is always known for causing mild respiratory and enteric infections in animals. However, the first outbreak of coronavirus in humans reported in 2002—2003 when severe acute respiratory coronavirus (SARS-CoV) jumped to humans from animal and Middle East respiratory coronavirus (MERS-CoV) in 2012. The studies have demonstrated that both coronaviruses belong to beta genera of the Coronaviridae family remain associated with the outbreak and causing the disease to humans via species migration.[2] On the contrary, other alpha, gamma, and delta of this family are mainly using wild animals as there reservoirs and not associated with any human disease to date.[14] Furthermore, existing research finding show key symptoms in COVID 19 patients include fever (87.9%), cough (67.7%) and, fatigue (38.1%); with lower occurrences of symptomatic diarrhea (3.7%) and vomiting (5.0%).[15] At the same, based on individual immune capacity and pathophysiology, patients remain asymptomatic for several days, acting as a potential carrier for SARS-CoV-2. The research findings also demonstrate a large percentage of COVID 19 patients are characterized by lymphopenia (82%) and thrombocytopenia (36%). The laboratory findings have shown that most of the COVID-19 patients remain associated with elevated levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and creatinine kinase (CK). Looking into more clinical findings although a large percentage of COVID-19 infections develop the only mild or uncomplicated illness, approximately 14% develop the severe disease that requires hospitalization and oxygen support, and out of this 5% require admission to an intensive care unit due to acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi-organ failure, including acute kidney injury and cardiac injury. The higher risk of multiple organ failure in the case of novel SARS infection is largely due to a high affinity of viral proteins with host receptors in various tissues.[16] Risk factors for admission to ICU and death are older age (Age $>$ 60 years) and co-morbid diseases like pre-existing cardiovascular disease, chronic kidney disease, diabetes mellitus, hypertension, chronic respiratory disease, and immunocompromised states.

Global spread and pandemic

Overview of the global spread of novel SARS-CoV-2

The global spread of the novel SARS-CoV-2 started in December 2019 from Wuhan, China, site for the outbreak. The massive and frequent air travel between China, Europe, the United States, and another part of the world carried novel SARS-CoV-2. In December 2019 and early January 2020, there was significantly less surveillance, and monitoring arrangements at the airport failed to contain the virus.[17] Research findings have demonstrated that it is a novel SARS-CoV-2 infected and asymptomatic population that carried more than 80% of infections from Wuhan, China, to the rest of the world. The R0 value of novel SARS-CoV-2 is 2—3, and in lack of precautionary measures, infection remains rising to lead to a pandemic outbreak. Many countries gain success in reducing infection load and flatten novel SARS-CoV-2 disease curve.[18] The rapid diagnosis, robust tracking system, quarantine facility, and providing enough education about novel SARS-CoV-2 remain critical factors in reducing infections in South Korea, Taiwan, Australia, New Zeeland, and Japan. These preventive measures were ruled out in many countries, including Europe and the United States result in a massive outbreak of novel SARS-CoV-2. WHO, CDC, and epidemiologist across the globe recommend social distancing as a vital tool in reducing infections. Social distancing can be achieved voluntarily and or by putting restrictions as a lockdown.[19]

Pathophysiology of novel SARS-CoV-2

The infection primarily occurs via droplets and aerosol carry novel SARS-CoV-2 and gets attached to the respiratory airway (upper). The spike proteins of novel SARS-CoV-2 are key molecules to connect with the hACE2 receptor and allow viral entry to the host cell. The novel SARS-CoV-2 is an ssRNA virus that captures cellular machinery for the RNA replication process. The RNA dependent RNA polymerase is a crucial enzyme for replication of the viral genome, and then it gets assembled into new viral particles utilizing cellular protein synthesis mechanism.[20] The novel SARS-CoV-2 infection requires a minimum of four days to show symptoms. However, in an ideal setup, 4—14 days are needed period for novel SARS-CoV-2 incubation. In most cases, symptoms are mild (80%), and very few cases require medical care (20%). The severely ill patients need intensive care unit (ICU) and other health support, i.e., oxygen supply (ventilator etc). The recovery of COVID19 patients depends on many factors such as age, viral infection load, and morbidity risk factors, etc.[21] The severe infection of novel SARS-CoV-2 leads to trigger into the immune response as a protective measure. The cytokine storm as a response against novel SARS-CoV-2 infection leads to the accumulation of a large volume of mucous and fluid in the alveoli tissue of the lung, resulting collapse of the respiratory system. So far, there is a lack of immunity against novel SARS-CoV-2 infection, and COVID19 remains a chronic respiratory syndrome with a higher percentage of respiratory failure.[22]

The risk factors associated with novel SARS-CoV-2 infection

There are significant variations in the rate of infections and death associated with novel SARS-CoV-2 worldwide. Considering the current database on COVID19 developed by John Hopkins University (https://coronavirus.jhu.edu/map.html), the United States and Europe had the most severe Ro values. However, Germany remains slightly different in causalities compare to other European countries. So far, China and other Asian countries have shown the least Ro value and human casualties. Considering given databases from the WHO, CDC, and John Hopkins University, age is the most crucial factor in the case of new SARS-CoV-2 infection.[23] In most cases, the age group more than 60 plus are at higher risk compare to another age group. However, there is a slight variation in different populations on age-related novel SARS-CoV 2 infection and casualties. Second, co-morbidity conditions such as diabetes, cardiovascular diseases, chronic renal disease, cancer, and inflammatory diseases may trigger high risk for novel SARS-CoV-2 infection and disease as well.[24] The differential expression of the hACE2 receptor is the deciding factor in novel SARS-CoV-2 infection, and the population gains a higher risk in the case of chronic obstructive pulmonary diseases (COPD) and Asthma conditions. Malnutrition and lack of immunity may have an indirect rise in COVID19 cases reported in many parts of the world, especially in low-income nations.[25] However, there is a lack of scientific data behind malnutrition and the rise of novel SARS-CoV-2 infection cases. These statements are based on patterns reported in various populations infected with novel SARS-CoV-2. It is believed that viruses effectively alter the host immune system and regulate selective expression of gene/s useful for viral infection and suppression of the host immune system.[26]

Morbidity and mortality statistics

According to COVID19 data at the CDC and WHO, the mortality rate ranges between 0.3 and 10.0% in different populations across the globe. The mortality rate is also linked with Ro value, and as per recent findings, Italy had the highest mortality rate, nearly 10%.[27] The rate of mortality in China and other Asian countries range between 2.5 and 4.0%. In the United States and Iran (Middle East), the rate of mortality rate remains high and compare to Asian countries.[28] The difference in mortality rate in various populations around the globe is the function of risk factors, i.e., morbidity conditions.[29] According to the American Heart Association (AHA) report 2018, more than 60% of Native Americans are on the risk of cardiovascular diseases (CVD), obesity, and metabolic syndromes. These morbid conditions act as crucial risk factors for novel SARS-CoV-2 infections and COVID19 disease.[30] Italy reported the highest mortality in the case of COVID19, and as per data from the CDC, more than 85% of deaths are age group for more than 75 years. Italy is the second-largest home for the aged population after Japan. The average age in Italy is 75 years with a higher risk for COVID19.[31] Similarly, China has a large population of the age group and remains at a higher risk of COVID19 mortality. However, these findings are based on initial investigations, and a more accurate statement on COVID19 mortality can only be made after substantial research work. The rise in mortality of novel SARS-CoV-2 infection is probably due to an effective virulence system of viruses. Though the novel SARS-CoV-2 genome is 30 kb, but enzyme and proteins are highly effective in infection and causing diseases. This is a natural phenomenon in microbes and viruses to have robust and effective proteins/enzymes performing multiple tasks.[32,33]

Genome and proteome of novel SARS-CoV-2

Genome sequencing of SARS-CoV-2

The first genome sequence information was released on January 11, 2020, from Wuhan China. Based on the sequence information genome of novel SARS-CoV-2 is ssRNA consist of 30 kb.[34] Later more novel SARS-CoV-2 sequence made available with a slight change in genetic information in the United States, Italy, and India. Based on the initial findings of four different novel SARS-CoV-2 genome sequences, it is evident that the virus genome remains intact with slight modifications.[35,36] Research finding has shown that novel SARS-CoV-2 reported in Italy and the United States had three distinct mutations in RBDs of Spike protein while two variations in China and one in Indian novel SARS-CoV-2 strain. Epidemiologists and researchers worldwide

started connecting dots of novel SARS-CoV-2 genome sequence and infection rate along with mortality.[37] However, these findings need more clinical data and repeated sequencing for validation.

Proteome of SARS-CoV-2

Proteins are critical structural units for any virus and hence novel SARS-CoV-2. The novel SARS-CoV-2 genome is ssRNA made up of 29891 nucleotides, encoding for 9860 amino acids. Four structural proteins, including spike(S), envelope (E), membrane (M), and nucleocapsid (N) proteins, constructed the functional coronavirus. Among these, spike proteins (S) play a crucial role in the viral invasion into the host cell.[38] The S proteins find an affinity with ACE2 and allow entry into the host cell where the virus takes control of cellular machinery for new viral particle replications. Evidence demonstrates that the virus primarily infects mucosa cells in the respiratory tract and result in viral pneumonia.[11] Tai and colleagues (2020), characterized the receptor-binding domain (RBDs) of novel SARS-CoV-2, as an ideal target for drug design and vaccine development.[39] The initial studies have shown that the SARS-CoV genome contains six open reading frames encoding all essential structural and enzyme proteins.[18] It was reported a frequent frameshift between ORF1a and ORF1b drive synthesis of pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps). There are other ORF as well apart from ORF1a and ORF1b help encoding for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins and accessory proteic chains. Different CoVs present unique structural and accessory proteins translated by dedicated sgRNAs.[37]

Wang and colleagues (2020) further carried out a meta-analysis based on pre-existing research that availed no significant changes in the SARS-CoV-2 genetic makeup and receptor binding proteins.[40] Additionally, a close resemblance between the novel SARS-CoV-2 strains (reported in clinical isolates from Wuhan China) and SARS coronavirus from pangolin was established by the study. Based on macro-genomic sequencing, molecular biological detection, and electron microscopic analysis, novel SARS-CoV-2 from clinical isolates in Wuhan had more than 99% similarity with SARS coronavirus from pangolin.[18] These findings demonstrate how SARS-CoV-2 that emerged in Wuhan spread across the globe and precipitated the global COVID-19 pandemic. Research is yet underdeveloped, but based on preliminary reports, the transmission of novel SARS-CoV-2 from a mother to developing her fetus proved to be a risk factor. Based on global findings, old age and population associated with several chronic diseases, including CVD, diabetes, and inflammation were more likely at risk of SARS-CoV-2 infection and COVID-19 disease.[18,24] On the contrary, children demonstrated significantly lower chances of contracting novel SARS-CoV-2 infection and preliminary findings. There are contradictory studies about the transmission of novel SARS-CoV-2 infection during pregnancy from mother to growing fetus.[37]

Preventive and therapeutic measures

As for now, there is no cure for COVID19 diseases, and hence prevention of novel SARS-CoV-2 infection seems more useful rather than depending on non-specific therapeutics.[40] It is evident that during the novel SARS-CoV-2 in 2019—2020, many countries achieve initial success in flattening disease curve by giving much emphasis on prevention rather than cure. Countries such as South Korea, Taiwan, Australia, and New Zeeland have given the focus on isolating individuals by quarantine, so break the viral spread.[41] On the contrary, the United States and major countries in Europe (all major countries including Italy, Spain, the United Kingdom, France, and Switzerland, etc.) delayed in opting for preventive measures and hence experienced a higher rate of infection along with death as well. As per the recent report from the WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019) and the CDC (https://www.cdc.gov/coronavirus/2019-ncov/index.html) the pattern of novel SARS-CoV-2 remains similar; however, preventive measures can primarily reduce the level of infection. The effect of preventive measures, i.e., lockdown, contact tracing, quarantine, and isolation on novel SARS-CoV-2 and COVID19 disease, were first implemented in Wuhan, China, and reported effective as per the John Hopkins coronavirus map and live tracking system (https://coronavirus.jhu.edu/map.html).

Diagnosis of novel SARS-CoV-2

Reverse transcriptase Polymerase Chain Reaction (RT-PCR)

The diagnosis of the presence of novel SARS-CoV-2 infections and associated diseases i.e., COVID19 utilizes two significant approaches; one RNA bases diagnosis using quantitative reverse transcriptase Polymerase Chain Reaction (RT-PCR) and second serological assay i.e. for plasma antibodies.[42] The full genome of novel SARS-CoV-2 is available on NCBI, and other biological databases provide ease in quantitative RT-PCR.[43] Based on genome information WHO and CDC made available guidelines; Universal primers and protocols for RT-PCR test for novel SARS-Co-2. The RT-PCR test is based on the collection of throat and nose swab containing SARS-CoV-2 for its genetic material, i.e., ssRNA. The viral RNA is here use as a template for reverse transcription and converting into DNA. The converted DNA allows PCR for the amplification of genetic material (equivalent to viral load) using the recommended primers. The RT-PCR based diagnostic test for SARS-CoV-2 is the most useful and robust method for now and the widely accepted globe.[22] The advantage of RT-PCR based diagnostic tests for SARS-CoV-2 is the early detection of viral infection. The technique (RT-PCR) is efficient and capable of diagnosing the presence of a few copies of novel SARS-CoV-2 genetic transcripts (ssRNA). The recent finding has shown a slight genetic variation in novel SARS-CoV-2 in a different part of the world; however, it does not have much impact on RT-PCR as primers designed for the highly conserved region in the viral genome. However, even in the

case of genetic variations, it is the only primer to get change, and the rest of the protocol remains the same.[44] The extensive tests have shown that RT-PCR had the least false-negative result compare to other tests/diagnostic approaches.[45] The RT-PCR also provides a quantitative analysis of viral load in the infected patient/sample. RT-PCR based diagnosis remains associated with limitations such as slow and requires a laboratory setup, i.e., Real-Time PCR, BSL3 facility, and protective gear in handling samples. A detailed overview of various rapid test kits developed for the diagnosis of the second largest population, i.e. India, is given below in Table 1.

Serology/antibody-based SARS-CoV-2 diagnosis

Serology or antibody-based diagnosis is relatively fast methods for any diagnostics, including viruses. The serology testing allows diagnosis based on antibodies produced against antigens, i.e., novel SARS-CoV-2. Though the antibody-based testing is efficient, require less time, and provide instant result but remain associated with several issues, including a high rate of a false negative. There are several reports demonstrated antibody production against novel SARS-CoV-2 infections differs in a population. The key factors associated with the differential antigenic response of novel SARS-CoV-2 and hence antibody productions are age, sex, diet, native immunity, morbidity conditions, and the human race. The current serological testing kits provide only qualitative analysis of infection. In a recent finding, Zang et al, 2020 reported two serum antibodies IgM and IgG are directly associated with novel SARS-CoV-2 infection and disease COVID19.[46] The study also reported a rise in the level of both the antibodies in COVID19 patients to compare to healthy. There are growing scientific evidence shown immunogenic response of SARS-CoV-2 to human is due to a highly conserved region in the viral genome, i.e., the coding region for RBD of spike proteins. For commercial and clinical diagnosis of COVID19 serological tests utilizes IgM and IgG for an ELISA based analysis in the laboratory.[22] Ready to use antibody-based diagnostic test kits are based on sample principle; however, the fluorescent probe remains attached with the substrate, i.e., antigen on the test kit. A drop of blood from suspected patients allows the chemical reaction between antigen and antibody (if present) and shows fluorescence as a positive result. The rapid novel SARS-CoV-2 test kits are designed with single (IgG or IgM) and or multiple antigens (for both antibody IgG and IgM). The commercially available rapid novel SARS-CoV-2 test kits can be shown two fluorescent lines defines positive for (IgG and IgM) and one fluorescent line (IgG or IgM) with the control line.[18] These tests are useful in accessing the spread of disease in a large population to ensure other protective measures for infection containment.

Treatment options of COVID19

So for there is no selective and effective cure for COVID19, and all therapeutic interventions depend on the severity of disease and patients' pathophysiology. The novel SARS-CoV-2 infection primarily targets hACE2 and infects respiratory airway leading to viral pneumonia. The use of several antiviral drugs had shown a differential effect on case to case. At same time use of the antiviral drug in the case of novel SARS-CoV-2 infection is not universal, and as per the result available so far, no single antiviral drug had shown complete cure of COVID19.[47,48] As per a report from WHO, 2020 several antiviral medicines, an anti-malarial drug, and

Table 1 The details of the significant commercial diagnostic test for novel SARS-CoV-2 diagnosis in India approved by ICMR in April 2020.

S No	Diagnostic Test	Characteristics	Manufacturer
1	Real Star SARS CoV2 RT PCT Kit	RT PCR based Test for novel SARS-CoV-2, Ready to use	Altona Diagnostics
2	Patho Detect	RT PCR Based diagnostic test for novel SARS-CoV-2	MY LAB
3	SARS-CoV-2 RT PCT kit	RT qPCR based qualitative and quantitative analysis, Effective and robust	Krishgen Biosystem
4	Light Mix Modular SARS and Wuhan CoV E gene	Effective for SARS-CoV-2 with envelop protein based testing	Roche
5	Light Mix Modular SARS and Wuhan CoV N gene	Effective for SARS-CoV-2 with nuclear protein based testing	Roche
6	Light Mix Modular Wuhan RdRp gene	RNA dependent RNA polymerase based testing	Roche
7	Hi PCR CoV Probe PCR Kit	Probe based Rea time detection	HiMedia
8	SYBR green based one step qRT PCR test	Probe based (SYBR green) quantitative Real time detection	IIT Delhi
9	COVID19 Detection kit	RT PCR Based diagnostic test for novel SARS-CoV-2	Biogenomics
10	nCoV Real Time Detection Kit	Effective, RT PCR Based diagnostic test for novel SARS-CoV-2	SD Biosensor

immune modulators have been tested clinically to combat COVID19. The use of hydroxychloroquine (HCQ) and 4-aminoquinolines chloroquine (CQ) for COVID19 management remains in doubt as growing toxicological outcomes. However, many countries had allowed the use of HCQ and CQ for severely ill COVID19 patients and medical professionals working in high-risk areas as heme polymerase inhibitor both HCQ and CQ offer some extent of relief in viral replication.[49] Actemra (Tocilizumab) an anti-inflammatory recently approved drug being used for COVID19 management. Several antiviral drugs such as Remdesivir, a nucleotide analog is being tested for COVID19 (Table 2). Favipiravir, an RNA polymerase inhibitor, could be a potential drug for COVID19.[50] Apart from therapeutic intervention COVID19 patient recovery rate also depends on essential and critical medical care (intensive Care Unit-ICU). Immune booster and immune modulators are essential remedies in the case of COVID19 management.

Drug development

Drug development is a complicated and time-consuming process that requires a massive effort in research, clinical studies, and regulatory processes.[51] Considering the case of the novel SARS-CoV-2 pandemic, much emphasis is given on repurposing of existing drugs tested earlier, such as in the case of the SARS-CoV outbreak in 2002—03 and MERS-CoV outbreak in 2014—2015. As novel SARS-CoV-2 possesses a significant resemblance with SARS-CoV and MERS-CoV, hence there is increasing possibility in reevaluating therapeutics tested before.[52] The second approach is to develop a new class of drug by targeting the virus at different stages. As it is well established that viral attachment and entry to human cells occur via ACE2 receptor by developing an affinity with viral spike proteins; hence the emphasis is given to find inhibitors to restrict affinity between RBDs of spike proteins and hACE2. So far, there is no single drug or inhibitor to limit the affinity of RBDs of spike protein and hACE2. The next approach is to allow the use of nucleotide analog results in the arrest of viral replication events.[53] Remdesevir that is under clinical and experimental investigation is a nucleotide structural analog that could be a potential drug in the future for COVID19 management. The most important and effective means of viral replication control is inhibition of RNA dependent RNA polymerase, a viral enzyme responsible for making copies of the viral genome. Favipiravir is under clinical studies for its safety and efficacy as an RNA polymerase inhibitor. Several protease inhibitors might help in reducing cellular viral load by disabling enzyme activity. Kaletra (Lopinavir/ritonavir) combination is being tested in context with COVID19 as a protease inhibitor.[46]

These are a rise in the test for anti-inflammatory drugs such as Kevzara and Actemra (Fig. 1). Based on current findings, it seems the search for a cure and effective drug to combat COVID19 remains underway for a long time. The system biology approaches and computer-aided drug design (CADD) offer a promising area in the modern drug development process. It does allow finding the affinity of drug molecules towards various receptors in the host and selecting the best molecular target.[54] Several plant-based drugs were examined using different concentrations to inhibit the replication of novel SARS-CoV-2. Anti SARS-CoV plant products such as lycorine had shown preliminary positive results in reducing the inflammatory response. Recently several phytophenols were tested for antiviral properties and anti-SARS-CoV as well. The plant-derived phytophenol and active ingredients in tea had shown the source of anti-SARS-CoV compounds. In the subsequent study, Mizoribine and Ribavirin have shown an inhibitory effect on novel SARS-CoV-2 replication validated on plaque assay. However, these plant products require testing in clinical setup.[55,56] Apart from antiviral and immunomodulatory drugs for COVID19 management, the studies have shown the use of vitamins and other nutrients are crucial in the fast recovery of patients. The clinical studies have shown that the massive use of vitamin C and E are essential to COVID management. The use of specialized pro-resolving mediators (SPMs) was hypothesized to regulate inflammatory cascade during cytokine storm.[57,58] However, there is no clinical evidence in the case of COVID 19 about the role of SPMs in downregulating inflammation.

Vaccine development

For any contagious disease, the vaccine remains an ultimate solution to control disease spread and provide immunity to fight against infection. The genetic sequence of novel SARS-CoV2 published on January 11, 2020, open Research Avenue for vaccine designs. There is the race for a vaccine against novel SARS-CoV-2 and several are under clinical trial studies. As of early April 2020, there are 78 active projects worldwide on vaccine development.[59] Among that, nearly 73 are in the preclinical setting, and few are under clinical trials such as mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, and LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute (https://clinicaltrials.gov/ct2/results?cond=COVID-19). In the course

Table 2 The table summarizes major therapeutics available/tested/under trials for COVID19 management.

S No	Therapeutics	Category/Uses	Mechanism
1	Chloroquine	Anti Malarial Drug	Heme Pol Inhibitor
2	Kaletra	HIV Management	Protease Inhibitor
3	INF α-2b	Hepatitis C Management	Immune modulator
4	Remdesivir	Antiviral/Anticancer	Nucleotide analog
5	Favipiravir	Influenza Management	RNA Pol Inhibitor
6	Actemra	For Rheumatoid Arthritis	Anti Inflammatory
7	Kevzara	For Rheumatoid Arthritis	Anti Inflammatory

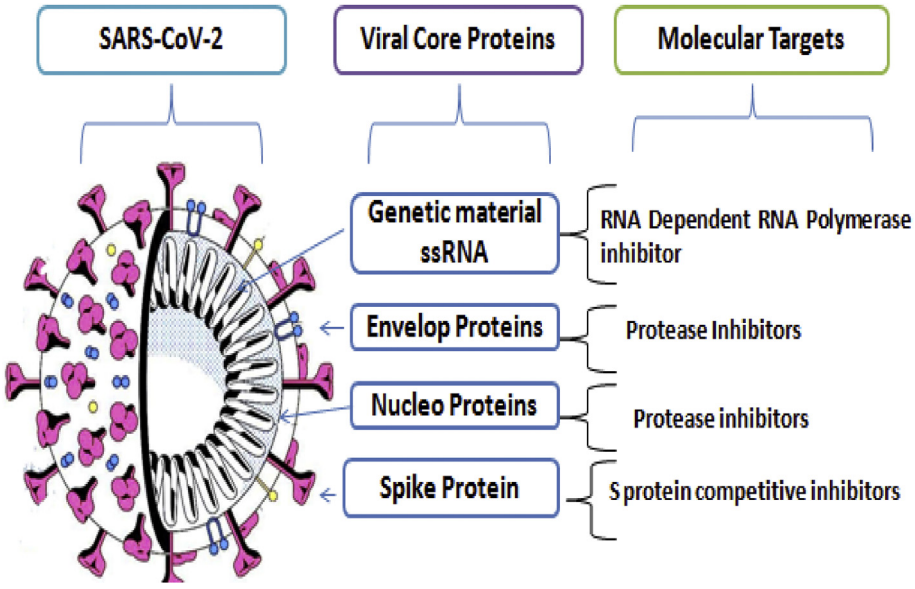

Figure 1 The figure demonstrates here various targets in novel SARS-CoV-2 for drug discovery.

Table 3 The table summarized roadmap and current state of vaccine development worldwide against COVID 19.

Research Institute/Industry	Type of Vaccine	Present status	Characteristics
Moderna/National Institute of Allergy and Infectious Disease (NIAID)	LNP-encapsulated mRNA	Phase II	Here, microRNA based vaccine development is underway
University of Oxford/AstraZeneca/ Serum Institute of India	ChAdOx1-S	Phase II	Non replicated viral vector
CanSino Biological Inc./Beijing Institute of Biotechnology	Adenovirus Type 5 Vector	Phase I/II	Here, a non replicating adenovirus is used for vaccine development
Wuhan Institute of Biological Products/Sinopharm	Inactivated	Phase I/II	An inactivated viral vaccine
Beijing Institute of Biological Products/Sinopharm	Inactivated	Phase I/II	An inactivated viral vaccine

of vaccine development against novel SARS-CoV2 multiple antigenic/immunogenic triggers are being used, such as attenuated virus, inactive virus, non replicating viral vectors, replicating viral vectors, recombinant proteins, peptides based vaccine and genetic material, etc.[60] There is rapid growth in vaccine development around the globe where the United States, China, Europe, Australia, and Asian countries are vital stakeholders. The development of vaccines requires a minimum of 18 months provided ease in regulatory processes; however, at the present scenario where novel SARS-CoV-2 remains as a pandemic, the timeline could differ from routine one.[61] Table 3 summarizes the recent update and development of vaccines on COVID 19. There are few studies have demonstrated that genetic variations in novel SARS-CoV-2 could be a risk factor in the race of vaccine development. Additionally, finding a universal vaccine is also critical to tackling the global pandemic.[62,63]

Conclusion

The outbreak of the novel SARS-CoV-2 pandemic has threatened the world with increasing infection and massive casualties. In December 2019, Wuhan, China, reported a rise in viral pneumonia cases caused by known agents. Later clinical findings and genome sequence analysis confirmed an outbreak of novel coronaviruses named nCoV or novel SARS-CoV-2. The reported virus does possess a higher similarity with SARS-CoV reported in 2002. Later in January 2020, a global spread of virus results in a pandemic state. The most affected region from the novel SARS-CoV-2 is Europe and the United States so far. As per the recent report from WHO and CDC, more than 5 million infections with 0.35 million death reported so far. The novel SARS-CoV-2 does belong to the beta coronavirus group contains SARS-CoV (2002—2003 outbreaks) and MERS-CoV (2014—2015 outbreaks). At present world is struggling in the containment of viruses and reducing the spread of disease, and few countries gained initial success, including South Korea, Taiwan, Australia, and New Zeeland. At present social distancing is the most effective parameter in reducing infection and spread. The rate of infection and mortality associated with novel SARS-CoV-2 remains linked with several risk factors, including age, sex, and morbidity conditions such as CVD, diabetes, and cancer. It is RBD of spike proteins of novel SARS-CoV-2 that remain a key target

for the therapeutic development process. There is a massive research effort in understanding the etiology of the outbreak and disease COVID 19. The drug design and vaccine development are underway and may require time before available for clinical uses. As for now, we are middle of a viral pandemic, and the non-therapeutic approach emerged as effective measures to reduce disease spread. These methods include social distancing, contact tracing, and quarantine of suspect. As per recent data at the clinical trials portal several vaccines completed phase I and entering into phase II. The fight against novel SARS-CoV-2 is not going to end soon as new scientific reports demonstrated a genetic variation in the viral genome posed a new challenge in drug and vaccine design.

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Conflict of interest

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Abbreviations

MHV	Mouse hepatitis virus
TGEV	Transmissible gastroenteritis virus
MERS-CoV	Middle East Respiratory Syndrome Corona Virus
SARS-CoV	Severe Acute Respiratory Syndrome Corona Virus
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
CDC	Centre for Disease Control
WHO	World Health Organization
RBDs	Receptor Binding Domains
ACE2	Human Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
CRP	C-reactive protein
LDH	lactate dehydrogenase
CK	creatinine kinase
COVID19	Corona Virus Disease 2019
AHA	American Heart Association
ICU	Intensive Care Unit
RT-PCR	Reverse Transcription Polymerase Chain Reaction
BSL	Bio Safety Level
RNA	Ribonucleic Acid
ssRNA	single Strand RNA

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