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Emergence of the Coronavirus (SARS-CoV-2) as a Pandemic

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Abstract: ***Before the emergence of severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) in 2003, only 12 other animal or human coronaviruses were known. The discovery of this virus was soon followed by the discovery of the civet and bat SARS-CoV and the human coronaviruses NL63 and HKU1. Surveillance of coronaviruses in many animal species has increased the number on the list of coronaviruses to at least 36. The explosive nature of the first SARS epidemic, the high mortality, its transient reemergence a year later, and economic disruptions led to a rush on research of the epidemiological, clinical, pathological, immunological, virological, and other basic scientific aspects of the virus and the disease. This research resulted in over 4,000 publications, only some of the most representative works of which could be reviewed in this article. The marked increase in the understanding of the virus and the disease within such a short time has allowed the development of diagnostic tests, animal models, antivirals, vaccines, and epidemiological and infection control measures, which could prove to be useful in randomized control trials if SARS should return. The findings that horseshoe bats are the natural reservoir for SARS-CoV-like virus and that civets are the amplification host highlight the importance of wildlife and biosecurity in farms and wet markets, which can serve as the source and amplification centers for emerging infections. [1]***

Keywords: SARS-CoV, MERS-CoV, SARS-CoV-2, COVID-19, RaTG13-2013, 2019-nCoV

1. Background

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV). In general, SARS begins with a high fever (temperature greater than 38.0ºC). Other symptoms may include headache, feeling of discomfort, and body aches. Some people might also have mild respiratory symptoms in the beginning. About 10 to 20 % of patients also complain of loose stools/ diarrhea. After 2 to 7 days, SARS patients may develop a dry cough. Majority of the patients develop pneumonia. The case- fatality rate among humans with SARS is approximately 10- 15% [2].

The main mode of the spread of SARS is by close person-to-person contact. The virus that causes SARS is said to be transmitted by respiratory droplets (droplet spread) produced when an infected person coughs or sneezes in public. Droplet spread when the droplets from the cough or sneeze of an infected person are propelled a short distance (Up to an area of 3 feet) through the air and deposited on the mucous membranes of the mouth, nose, or eyes of persons who are within this area. (3 feet) The virus also can spread when a person touches a surface or object contaminated with these infectious droplets and then touches his mouth, nose, or eye(s). In addition, it is possible that the SARS virus might spread more broadly through the air (airborne spread) or by other ways that are not known yet.

As of now, there is no known effective treatment against SARS. [3]

2. Introduction

Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) is a novel virus that caused the first major pandemic of the new millennium. It was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia. According to the World Health Organization (WHO), during the SARS outbreak of 2003, a total of 8,098 people worldwide became sick with SARS. [4] Public health officials worldwide commonly used isolation and quarantine measures to control the outbreak.

The rapid economic growth in China has led to an increasing demand for animal proteins including those from exotic animal food such as civets, bats, etc. Large numbers and varieties of the animal food in overcrowded cages and the lack of biosecurity measures in wet markets has allowed the transition of the virus and micro-organisms from animals to human. Its capacity for human-to-human transmission, the lack of awareness in hospital infection control, and international air travel facilitated the rapid global distribution of these agents. A large population are affected, with a crude fatality rate.

The recurrence of SARS related diseases after the resumption of wildlife food market with the recent discovery of a similar virus in horseshoe bats, bat SARS-CoV, suggested that SARS can return if conditions are fit for the introduction, mutation, amplification, and transmission of such dangerous virus.

According to published scientific articles, Severe Acute Respiratory Syndrome (SARS)-like virus has been isolated from the Viverridae family, apprehended from the areas

originating in China where the 2002-2003 SARS outbreakswere found. Shipments of civets are being imported into the United States and further distributed. CDC is banning the importation of all civets immediately and until further notice. CDC is taking this action to prevent the importation and spread of SARS, a communicable disease.

Chinese health authorities have also been taking health measures since the 2004 non- laboratory-acquired case was reported include interventions on civets in the animal market based upon an accumulating but as yet unpublished body of evidence linking them with SARS-CoV infection. [5] To this date, scientists have not been able to confirm the origin of SARs in humans. Some public health officials hypothesize that SARS-CoV was transmitted from an animal to human thereby sparking the 2003 outbreak.

Until the very end of 2019, there were six coronaviruses known to cause disease in humans. Four of these result in little more than a common cold and are endemic around the world. The viruses known as human coronavirus (hCoV)-229E, hCoV-HKU1, hCoV-NL63, and hCoV-OC43 are of little concern at a global public health level. The other two, however, have caused more widespread concern. In 2002, severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in the human population. In a matter of months, this virus from a bat that transmitted via a palm civet to infect a human in the Guangdong province of China infected over 8,000 people, killing roughly 10%. In 2003, SARS-CoV infections stopped, and the virus has not been seen since.

A second epidemic coronavirus, known as Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in 2012. Like the SARS-CoV outbreak, MERS-CoV started with a patient suffering pneumonia and came from a zoonotic event. (This time from a bat via a camel to a human) [6] However, MERS-CoV has shown far more limited human-to-human transmission than SARS-CoV. Since 2012, there have been roughly 2,500 cases of MERS-CoV, mostly confined to regions of the Middle East. While case numbers are low for MERS-CoV, there is a high case fatality ratio (CFR) of approximately 35%, making this virus one of the deadliest human pathogens.

Coronaviruses that infect humans all appear to have respiratory transmission, making them pathogens of pandemic potential. The end of 2019 saw the emergence of a novel human coronavirus (SARS-CoV-2) that is rapidly spreading around the global and has a higher degree of lethality than the endemic coronaviruses, though not to the level of SARS-CoV or MERS-CoV. The virus was initially named 2019-nCoV but is now termed SARS-CoV-2 and causes the disease COVID-19 (coronavirus disease 2019). At the time of writing this article, there have been over 3,260 active,99 deaths and 229 removed cases in India, and around 1,213,192 cases worldwide with over 65,600deaths and 253,597 recovered. [7]

The rapid spread of this virus across the world in only 3 months highlights the transmissibility of this family of viruses and the significant morbidity and mortality that they can cause [8]

The first case of COVID-19 was reported to the WHO by Chinese authorities on 31 December 2019 as a result of a patient suffering pneumonia in Wuhan City, Hubei Province, China. Over the following days, more patients were suspected to be suffering the same disease, and by 9 January, a novel coronavirus had been detected and the sequence was published online shortly thereafter [9]

Over 100 other countries have reported cases. Most cases outside China have been associated with travel to that country, but more clusters of cases are now being detected without travel history.

2.1 SARS-CoV-2 virology

SARS-CoV is one of 36 coronaviruses in the family Coronaviridae within the order Nidovirales. Members of the Coronaviridae are known to cause respiratory or intestinal infections in humans and other animals

The novel virus SARS-CoV-2 therefore shares common features of this family. Coronaviruses have large (30-kb) single stranded, positive-sense RNA genomes. The genome can be roughly divided into a 5' two-thirds and a 3' third. The first two-thirds of the genome code for two large polyproteins (pp1a and pp1ab from ORF1a and ORF1b) which are proteolytically cleaved into the nonstructural proteins (nsp1 to -16) that are essential for production of new viral genetic material. The remainder of the genome codes for the structural proteins and carries the accessory genes that produce virions and alter the host response, respectively. [10]

The newly emerged coronavirus is closely related to SARS-CoV, sharing roughly 80% identity at a nucleotide level. The closest relative of SARS-CoV-2 appears to be a virus found in bats known as RaTG13-2013 (96% identity), suggesting that, similarly to SARS-CoV, the virus entered the human population from a spillover event either directly from a bat or through an animal intermediate. [11]

Studies on SARS-CoV-2 have shown further similarities with its namesake virus in that the spike protein utilizes ACE2 as its cell surface receptor. [12] ACE2 is found on ciliated epithelial cells of the human lungs, and this receptor utilization influences the tropism of these viruses. Despite these similarity with the genome sequence of SARS-CoV and SARS-like CoVs, It has been identified that a peculiar furin-like cleavage site in the Spike protein of the 2019-nCoV, that lacks in the other SARS-like CoVs.

2.2 Spreading Rate of the virus

The virus is tentatively associated with a seafood market in Wuhan, China, where the sale of wild animals may be the source of zoonotic infection. Although bats are likely reservoir hosts for 2019-nCoV, the identity of any intermediate host facilitating transfer to humans is unknown.

Compared to the two other highly pathogenic coronaviruses that have emerged in the 21st century, SARS-CoV-2 appears to spread very fast in the human population. SARS-CoV and SARS-CoV-2 appear to use the same cell receptor of ACE2,

suggesting a similar tropism, yet the novel coronavirus appears to spread much more efficiently simply based on the number of cases and the speed at which they have emerged. Whether proteolytic cleavage sites, such as a furin site in the spike protein of SARS-CoV-2. [13] influence this will be important to determine for this outbreak and for the next. There are many other coronaviruses that have been found in bats that have potential for spread in the human population. [14] Developing an understanding of the difference in the dynamics of spread between SARS-CoV-2 and the other coronaviruses will provide insights to understand which viruses may pose the most threat for zoonotic transmission and mass spread in the human population.

2.3 Animal reservoir/intermediate host

Bat virus termed RaTG13- 2013 is said to be the reservoir to the spread. It has 96% identity with SARS-CoV-2, strongly pointing toward a shared common ancestor and suggesting that the novel human pathogen originated in bats. When the zoonoses first occurred remains an interesting question. Both SARS-CoV and MERS-CoV also have common ancestry with viruses found in bats. Both of these viruses had an intermediate host for transmission into humans, these being palm civets and camels for SARS- and MERS-CoV, respectively. There has been a suggestion that pangolins might be the intermediate host for SARS-CoV-2, but same has still not been established. Knowing the intermediate host is an important step for understanding how SARS-CoV-2 became a human virus and how to potentially curtail further spillover events. As knowing intermediate host allows for measures to be taken to limit human contact with the animal and transmission in humans. This allows the development of a vaccine to potentially limit spread to humans. As obtaining approval for novel vaccines in animal hosts is far easier than in approvals in humans. Moreover, knowing the intermediate host allows for measures to be taken to limit human contact with the animal (e.g., bynot selling meat from these animals in wet food markets), which can again help reduce the chances of future spillover events.

2.4 Comorbidities associated with the disease outcome

Most severe cases and mortality is associated with underlying health conditions. The most common associated comorbidities are pulmonary disease, diabetes, and old age. [15] SARS and MERS were associated with diabetes and other underlying health conditions, diabetes itself can impact the immune response to infection, leading to increased pathogenesis. [16] It is interesting to see whether SARS-CoV-2 infection is similarly impacted. Most of the known human coronaviruses are endemic and have cause little more than the common cold. Currently, SARS-CoV-2 is a global pandemic. The outbreak may be contained, and the virus never seen again, like SARS-CoV. Alternatively, the virus may become an endemic virus with seasonality like influenza and the other human coronaviruses. However, it is too early to know whether SARS-CoV-2 spread will be affected by changing weather conditions. It is believed that the cases might decrease as temperatures increase in the Northern Hemisphere, as is case of other influenza but, same remains to be seen.

2.5 Clinical Features of the disease

Clinical presentation of all known SARS is that of viral pneumonia with rapid respiratory deterioration Fever (99%), chills, myalgia (44%), malaise (70%), and nonproductive cough (60%), Shortness of breath, persistent pain or pressure in the chest, drowsiness, and gastroenteritisare the major presenting symptoms, whereas headache, dizziness, diarrhoea, nausea, vomiting, rhinorrhea and sore throat are less frequently seen. In severe cases Pharyngeal pain, Dyspnea, Pneumonia and kidney failure is seen. He infection may also effect the Liver, heart valves and other vital organs.

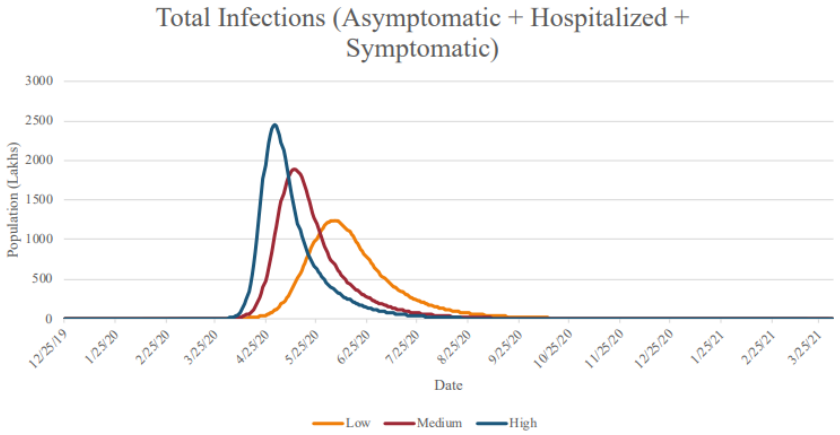
The most common laboratory abnormalities among patients hospitalized with COVID-19 are marked lymphopenia, prolonged prothrombin time, elevated lactate dehydrogenase and elevated D-dimer. These laboratory abnormalities are similar to the ones seen in SARS-CoV and MERS-CoV infections. Bilateral patchy shadows and ground-glass opacities are seen on chest imaging. The most common complications of COVID-19 are acute respiratory distress syndrome, arrhythmias, acute cardiac injury, shock and acute kidney injury. [17-18] The in-hospital transmission of the virus is very high with rates as high as 40 per cent. Of the hospitalized patients, the mortality rate is around 4-5 per cent. [19]. There is adequate descriptive evidence in the published literature to develop a complete clinical picture of the disease. However, there is a need for planned constructions for providing multidisciplinary care in an integrated, single-service area. Further, designing and building these isolation wards, using humane and helpful esthetics, is also an essential step in empowering health systems to mount an adequate response to the surge in cases.

Treatment of COVID-19 is mostly supportive based on the organ systems affected. The setting of patient management, i.e., intensive care unit or high dependency unit versus general wards, should be decided early on in the course of the disease, considering the high mortality rate among hospitalized patients and the facilities available for containment of infection.

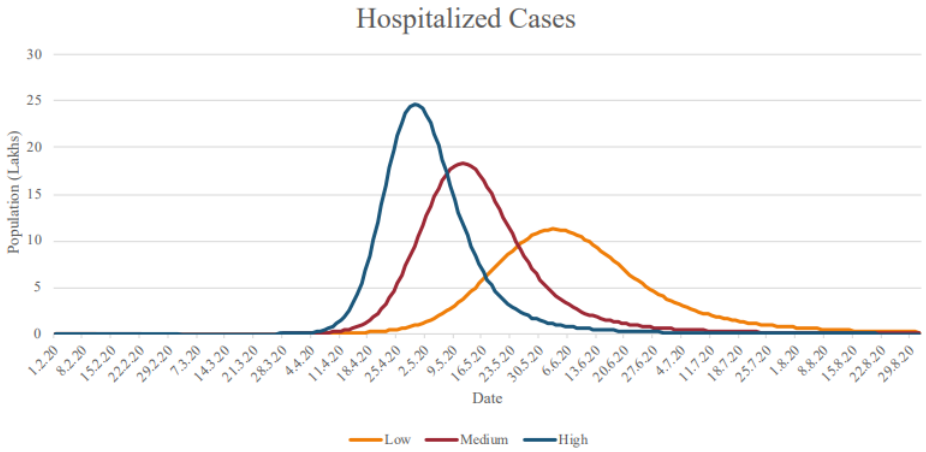
3. Infection Scenarios in India

Community transmission of COVID-19 in India most likely started in early March. [20] National containment is no longer an option in India. However, state or local (temporary) containment and mitigation is the best option. At baseline (without interventions), between 300 and 400 million Indians are likely to be infected by July. Most of these cases will be mild with a peak, somewhere between April and May 2020. 100 million individuals will be infected. Of these, approximately 10 million will be severe and about 2-4 million will require hospitalization. This is the most critical period. Generalized social distancing can, in theory, reduce this peak load by as much as 75%, although this may be difficult to enforce in India. Hospital outbreaks of COVID-19 induced by the admission of infected patients into hospitals could also be a major issue. Thus, there is a need for large, temporary hospitals to handle this patient load over the next three-month period. Secondary, hospital-based transmission fuels the epidemic. [21]

Predicted Infections from COVID-19 in India



Predicted Hospitalizations from COVID-19 in India



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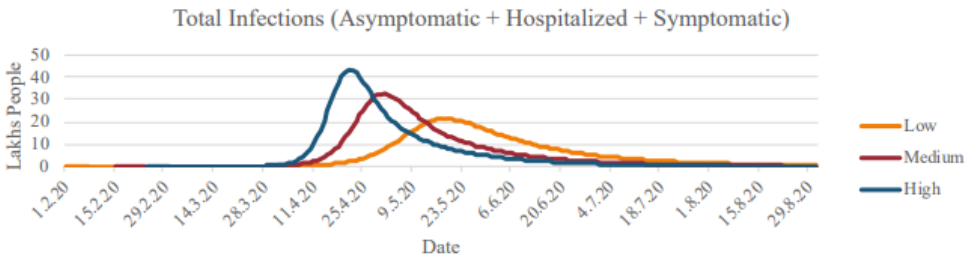
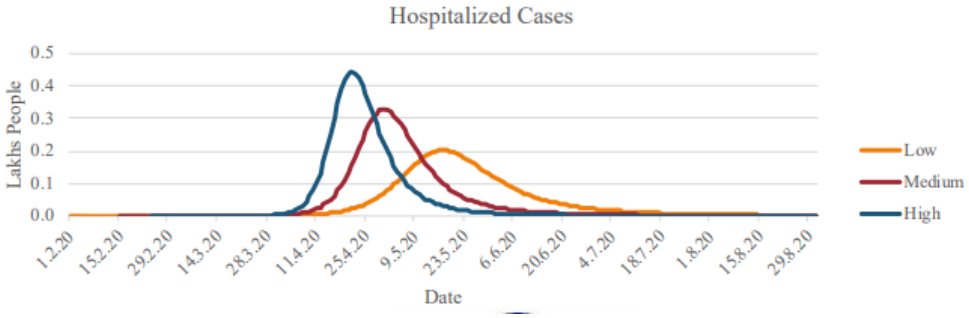
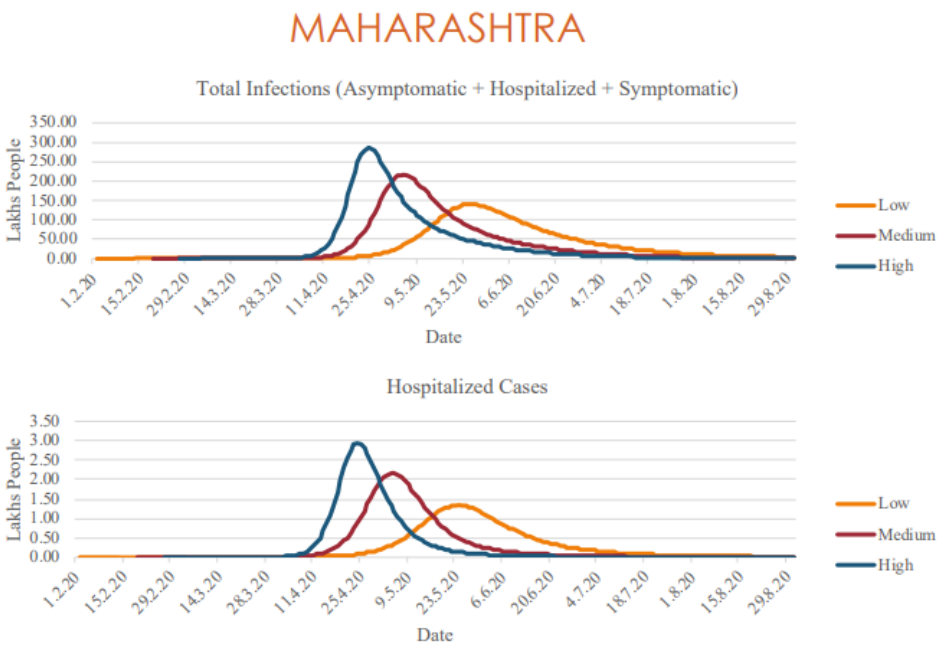


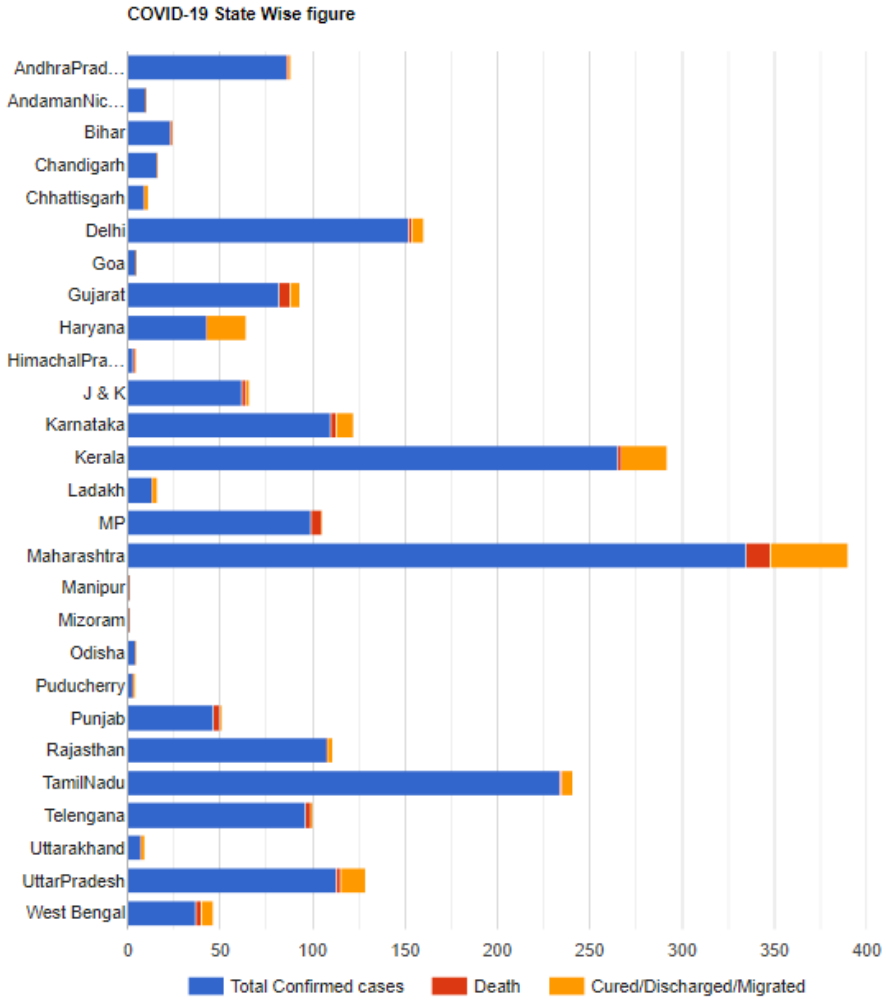




4. Recommendations

Immediate social distancing, focused on the elderly population is essential. Anyone above the age of 65 should essentially shelter in place, while everyone else should practice significant social distancing. A three-week period of complete isolation for the elderly. The longer this period, the more we can delay infections into the post-July period. An assumed high compliance with non-elderly social distancing is recommended to all. Even if moderate, this may be the most useful option given where we are in the epidemic, in order to contain the peak.

A state wise chart shows the number of infected, recovered, and death [22] (*Data as of 5th April 2020*)



5. Research Work

Early studies on SARS-CoV-2 determined that the cellular receptor for the virus is ACE2, similarly to SARS-CoV [23]. This knowledge helps to develop an understanding of susceptibility of certain in vitro cell lines to infection with the novel virus. The likelihood is that if cells were not permissive for growth of SARS-CoV, they probably will not support growth of SARS-CoV-2. As more labs around the world are researching on this new virus, a better understanding of the permissive cell lines will be developed, an important step to testing therapeutic options and developing a better understanding of basic aspects of SARS-CoV-2 virology. The more challenging aspect of lab-based research on the novel human coronavirus will be developing small-animal models. The early research on receptor usage suggests the virus is not able to infect cells expressing mouse ACE2 [24], thus making a mouse model potentially challenging. Whether expression of human ACE2 in mouse lungs using adenovirus or mouse adaptation of SARSCoV-2 can develop appropriate models, as was done for SARS-CoV [25], is a pressing question. Whether other small-animal models can be used also needs to be investigated. These models will be essential for thoroughly testing therapeutic candidates and vaccine strategies and understanding the pathology of disease.

As the case count and death toll of the epidemic continue to increase, it becomes imperative to identify therapeutic options for COVID-19. Once in vitro and in vivo systems have been established, these tests can proceed. Drug repurposing may prove to be the best strategy for quick development of novel therapeutic options. A novel therapeutic being tested is Remdesivir, [26] which in combination with chloroquine has been found to inhibit SARS-CoV-2 growth in vitro. [27] It was recently announced by the NIH that Remdesivir would be entering phase 3 clinical trials in humans. Chloroquine has also been reported to be effective in patients in China [28]. A combination of Lopinavir and Ritonavir is also under investigation in human cases of COVID-19. Many more people will need to be treated with these drugs to determine true efficacy, but they are promising leads.

There are several platforms being used to develop vaccines against SARS-CoV-2, including spike subunit, DNA, RNA, whole-virion, and nanoparticle vaccines. Future testing in cells and animal models will determine which is most likely to be successful in humans. [29] The vaccine studies for CoV-2 are currently in the preclinical phase.

6. Conclusion

Past 18 years have seen the emergence of three novel coronaviruses that have caused significant morbidity and mortality in the human population. The year 2020 has started with a rapid, global epidemic of the virus SARS-CoV-2, causing the disease COVID-19. The virus appears to have transmitted to humans in a zoonotic event from bats. There are many questions to investigate regarding all aspects of SARS-CoV-2 virology and epidemiology. These questions range from how the virus emerged to how it spreads and how the disease manifests. But most pressingly as the global outbreak continues to grow, can we develop effective vaccine and therapeutic strategies to treat not only this epidemic but any future coronavirus spillover events.

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Conflicts of Interest: None.

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