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An extensive literature review on COVID-19 challenges, its phylogeny and the advantages of COVID-19 modeling while intercepting its different variants

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Abstract: The novel coronavirus caused by the Severe Acute Respiratory Syndrome Coronavirus 2 was originated in the Chinese city of Wuhan in 2019. Firstly, identified as an outbreak, as it was related to the original coronavirus that caused severe acute respiratory syndrome, but SARS-CoV-2 spreads faster and farther than the others. This is likely because of how easily it transmitted from person to person, even from asymptomatic carriers of the virus. But with due course of time, the genetic material of the virus has gone through innumerable changes and mutations and gradually swept into the globe affecting each and every sphere of human life like social, economic and physical as well as the mental wellbeing of any person. Majority of experts have agreed to the fact that unlike the previous pandemics in human history, the corona virus is of zoonotic origin i.e., the virus spreads between animals and the people. Although numerous ideas, including a number of conspiracy theories, have been put forward regarding the virus's origin but the lack of evidence for this explanation makes it considerably less credible. In this study, we compared the many elements that contributed to the corona virus's spread. It was observed that many socio-economic and geographic elements were present along with these characteristics. By observing the alterations and the onset of symptoms, we were able to determine how COVID-19 differed from the ordinary flu. Studying these contrasts gave us a better understanding of how modeling COVID-19 with various models may be highly beneficial in combating the virus. In order to comprehend this, data and information from research publications that dealt with the issues and obstacles experienced by different people, communities etc. were taken into consideration.
Keywords: Keywords boldfacedCOVID-19 outbreak, pharmaceutical and non-pharmaceutical interventions, covid-19 modeling, gaps and complexities in modeling.

Introduction: Background of the outbreak
On 31st December 2019, in Hubei province of the Republic of China, Wuhan health commission notified to National Health Commission, China Centre of Disease Control and

Prevention (CDC) and the World Health Organization (WHO) that a cluster of 27 pneumonia cases of unknown etiology have been discovered where a variety of symptoms, including fever, dyspnea, dry cough were prevalent and radiological results revealed glassy opacities in both the lungs.[1] Meanwhile, the public health office tracked and linked each case to the Hunan Seafood Wholesale Market, which deals in live bat, snake, pangolin, and badger species. Soon Wuhan became the pandemic's hotspot due to a number of intrinsic factors that accelerated early transmission dynamics. Due to its vast population and proximity to a market where live animals were sold, Wuhan became the epicenter of the human-animal interface. Also due to some intrinsic factors, like the inability to trace its origin accurately and also unavailability of any containment zones for the early cases there was a rapid acceleration in transmission dynamics.

The Coronavirus disease 2019 (CoVid-19) created an outbreak in the whole world creating havoc among the people with its rapid spread causing disruptions along with higher mortality rates.[2]The root cause was found to be the novel corona virus which causes acute respiratory syndrome (SARS) that brought up lot of critical challenges for the health, research and medical communities.[3]

The China CDC discovered the novel coronavirus 2019 (2019-nCOV), which was commonly known as the "Wuhan Coronavirus" on January 7, 2020. In order to de-stigmatize the virus's affiliation with any nation or region, the WHO renamed it to SARS-CoV-2 and linked it to the virus's symptamology [3]. The SARS-CoV-2 was found to be the root cause and having genetic traits of novel corona virus which causes Severe Acute Respiratory Syndrome (SARS) in 2002 that brought up lot of critical challenges for the health, research and medical communities.[2]

Interestingly, the Bat-CoV and Bat-CoV RaTG13 viral genomes in Rhinolophus affinis species of Yunnan province fit with the SARS-CoV-2 entire genome with 96% similarity.[3]When these coronaviruses find an animal reservoir that offers a suitable cellular environment for the virus to multiply and develop into a variety of beneficial mutations, the virus can become contagious. These modifications can subsequently make it possible for the virus to infect and proliferate inside human hosts[4]. Figure 1 shows the different coronavirus affecting humans through different intermediate hosts.
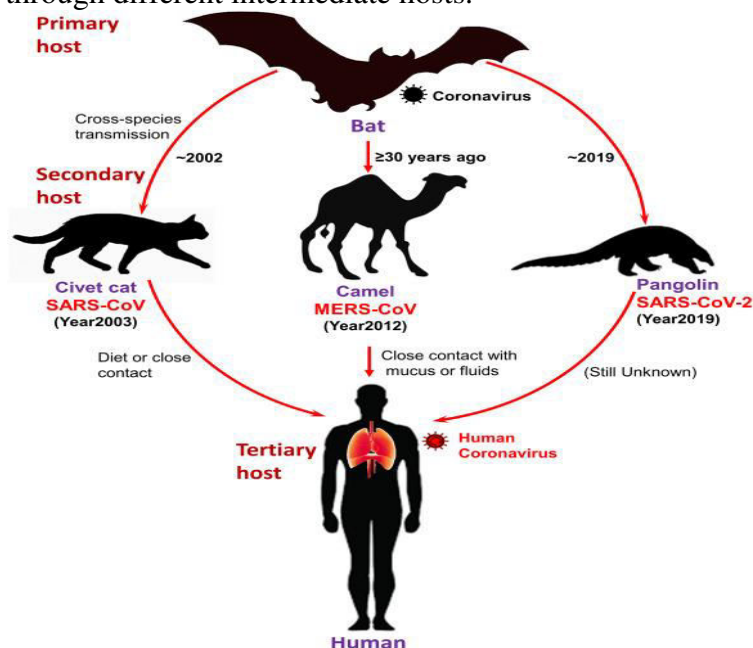
Figure 1. The origin of the virus affecting the target through different intermediate hosts.

Till date there has been more than 645 million cases reported over the world resulting to more than 6 million deaths.[4] The word 'corona', which is Latin for 'crown', refers to the structure that corona viruses take on as a result of the spike proteins that protrude from them. The biology of this virus depends on these spike proteins. These spike protein are what latches to a human cell to cause infection, enabling the virus to multiply inside the cell and spread to neighboring cells.[5]The vast family of viruses known as corona viruses is responsible for a variety of respiratory infections, from the common cold to serious diseases like the Middle East Respiratory Syndrome (MERS) outbreak in 2011 and the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak.[6] Due to the disruptions caused by the coronavirus in social as well as economic aspect of every human being, it was declared as a public health emergency of international concern on 30th January 2020 and characterized as a pandemic on 11th March, 2020 by the Director-General of World Health Organization (WHO) Dr. Tedros Adhanom Ghebreyesus.[7]

The ongoing iterative mutational infections of the virus have made it more difficult to reach the goal of herd immunity through different measures like containment, vaccines and other treatments.
COVID-19 as compared to the previous outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle-East Respiratory Syndrome (MERS), was found to be more complicated, uncertain, easily transmissible from human to human due to its strong mutation, which build it up as one of the continuous and still evolving one of all.[8]From the cases of the virus that were found to be either symptomatic or asymptomatic, the asymptomatic ones acted as the unseen cause of the inexplicable spread of the virus as its root cause, diagnosis and mitigation of COVID-19 was difficult to detect.[9]

Although detection of the virus's nature was difficult to recognize but the government has put forward some restrictions to handle the outbreak. Different non-pharmaceutical interventions (NPI) like social distancing, usage of masks and sanitizers, quarantine or home isolation, closure of any educational institutions, restrictions in gathering of people etc. taken up by different governments played an important role to tackle the spreading of the virus. This had a positive impact to a great extent but at the same time had a negative impact on business and trade, socio-economic wellness, public life, mental health etc. Departments like health care, society, government, economy etc. have faced a lot of challenges since the onset of the virus, which provided an opportunity for the research community to conduct any research for the better understanding of the virus.[10]
To combat the COVID-19 pandemic, the CDC (Centre for Disease Control) collaborated closely with state, tribal, municipal, and territory health departments as well as other public health partners. Predicting the expected effects of COVID-19 over time, forecasts of fatalities, hospitalizations and cases helps in informing public health decisions. Public health choices on pandemic planning, resource allocation, deployment of social distancing measures, and other interventions are informed by forecasts using mathematical modeling.
The primary objective of COVID-19 modeling is to quantitatively comprehend and characterize the virus, estimate and forecast COVID-19 transmission, detect and trends, determine the effectiveness of prevention strategies in terms of social, economic, psychological, and political aspects, etc. Modeling COVID-19 helps to understand the complex nature of the disease and how it has affected every aspect of human life to strive and survive the pandemic. Through the modeling techniques, the researchers has brought some light on the different techniques and interventions to create the awareness of the species of the virus, its variants, diagnosis, vaccines, impact etc.

Mode of transmission

The virus mostly spread through droplets transmission while having a conversation in close proximity, faecal-oral pathway, conjunctiva and fomites [11].Additionally, biological fluids from the patient, including as saliva, faeces, urine, and respiratory droplets, can be used to determine the source of local transmission [12].The virus particle is stabilized at lower temperatures, meaning that it can survive at 4°C longer than at 22°C. Throughout the clinical course, SARS-CoV-2 virions are shed. COVID-19 can disseminate the infection before symptoms show up, during the symptomatic phase, and when the clinical recovery period begins [12]. The mode of transmission of the virus through droplets, aerosols etc. can be shown by Figure 2.
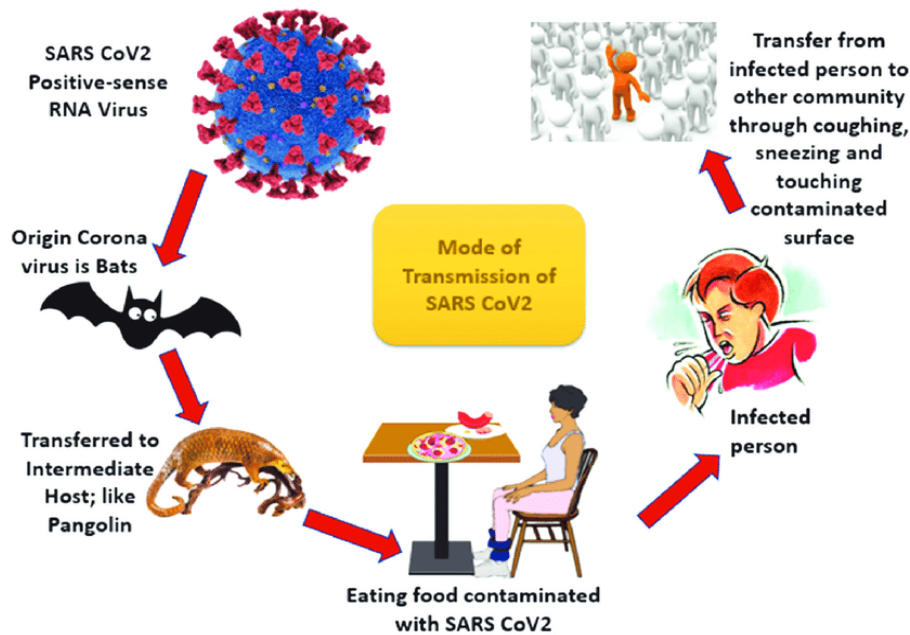

Figure 2. Mode of transmission of COVID-19 through different mediums

Differences between covid-19, common cold and flu

The common cold is caused by viruses mainly rhinoviruses. Both COVID-19 and common cold have a slow and moderate presentation of the symptoms unlike the flu, caused by various strains of influenza. One of the most common symptoms of COVID-19 and flu is raised body temperature also known as pyrexia. However, coryzal symptoms such as rhinorrhea (nasal cavity filled with mucus fluid), nasal congestion are dominant in common cold and are rare in flu and COVID-19[13].

Clinical manifestations of these disorders might range from mild pneumonia to severe pneumonia. The Basic Reproduction Number (R_o), another element that affects the pace at which any virus spreads, is important. The SARS-CoV-2 virus has a R_o of 2.3 compared to the influenza virus's R_o of 1.3. Therefore, compared to influenza patients, each COVID-19 patient can transfer the disease to 1.8 times more new contacts [14].

In contrast to SARS, which is caused by the SARS-CoV-1 virus, certain patients with Covid 19 (caused by the SARS-CoV-2 virus) may be contagious throughout the incubation period, even at the asymptomatic stage.The faster potential transmission of SARS-CoV-2 can be determined by the longer incubation for the emergence of COVID and being able to transmit infection during this time. These variations in the incubation period of COVID-19 and the common orthomyxovirus are shown in Table 1.

Virus family	Coronavirus			Orthomyxovirus	
Virus name (Disease)	SARS-CoV-2 (Covid-19)	SARS-CoV-1 (SARS)	MERS-CoV (MERS)	H1N1 Influenza A (Swine flu)	Influenza A (Seasonal flu)
Incubation period (in days)	2 to 14 days	2 to 7 days	5 days	1 to 4 days	2 days

Significance of COVID-19 modeling:

To combat the COVID-19 pandemic, the CDC (Centre for Disease Control) collaborated closely with state, tribal, municipal, and territory health departments as well as other public health partners. Predicting the expected effects of COVID-19 over time, forecasts of fatalities, hospitalizations and cases helps in informing public health decisions. Public health choices on pandemic planning, resource allocation, deployment of social distancing measures, and other interventions are informed by forecasts using mathematical modeling.
The primary objective of COVID-19 modeling is to quantitatively comprehend and characterize the virus, estimate and forecast COVID-19 transmission, detect and trends, determine the effectiveness of prevention strategies in terms of social, economic, psychological, and political aspects, etc. Modeling COVID-19 helps to understand the complex nature of the disease and how it has affected every aspect of human life to strive and survive the pandemic. Through the modeling techniques, the researchers has brought some light on the different techniques and interventions to create the awareness of the species of the virus, its variants, diagnosis, vaccines, impact etc.

The COVID-19 modeling plays a significant role to understand characteristics of the complex nature of the disease and how it has affected every aspect of human life to strive and survive the pandemic. Through the modeling techniques, the researchers have put some light on the awareness of the species of the virus, its variety, its diagnosis, vaccines, impact etc. on the human life.
All the national governments and the World Health Organization (WHO) have largely depended on modeling to determine the most effective COVID-19 impact mitigation techniques. These have mostly been epidemiological models for e.g., a baseline curve-fitting model, an extended SIR (eSIR) model, two extended SEIR models, and a semi-mechanistic Bayesian hierarchical model designed to comprehend the disease's spread and the effects of various therapies. It is suggested that the selection of the modeling framework is influenced by the requirements of the decision makers, the nature of the issue, and the complexity and properties of the system (Tako & Robinson, 2009, 2012; Borshchev& Filippov, 2004; Brennan et al., 2006; Chahal &Eldabi, 2010; McHaney et al., 2018).
An effective strategy for situational awareness and decision-support for policymakers is infectious disease modeling. The COVID-19 modeling attempts, however, ran into a number of difficulties, from bad data to shifting laws and people's behavior. Forecasting models can help situational awareness of the current and near future states of disease transmission and insights from the modeling can help people reduce their personal risks [15].
The strategies used in China and other nations to subdue the spread of the virus and flatten the infection curve were to adopt the most drastic measures to significantly minimize disease

transmission, increase herd immunity and effectively curb the epidemic at the expense of economic growth during the outbreak [16].

Though modeling COVID-19 by different researchers using different models have made them understand the epidemiology of the virus, but it has its own downside. One of them is that these researches carry some challenges, inaccuracy, biasedness etc. as the recording of the occurrences are not accurate due to unavailability of test kits, or delayed assistance of any medical help etc[17]. Another snag while modeling COVID-19 is that the data quality lowers to some level as the detection of the cases gets delayed due to numerous undiscovered and unreported cases along with the prolonged incubation period.

COVID -19 Modeling complexities:

The COVID-19 pandemic is essentially an open system with the complex interactions and relationships between diseases, environment and the nature; high degree of uncertainty of viruses, diseases, and their complexities; the significant emergence of effects and impacts on society in almost every region of the world. Thus, the limited data available, related to Covid-19 fails to describe the complexities and epidemiological characteristics in an explicit way for any research in modeling Covid-19.

Modeling goals with limited COVID-19 data becomes challenging due to the constraints in collecting the data available. This results in some limitations while testing the capacity of the hypothesis that is to be modeled. Due to the poor quality data limit, the scientists were restricted to only simple classic models instead of implementing complicated and parameterized models to get specific results. As a result, deep multidisciplinary collaboration involving computer science, bioinformatics, virology, sociology, and many other fields is necessary for modeling COVID-19. The inherent and complex character of COVID-19, as well as the unpredictability and dynamics of this pandemic, cannot be revealed by a single factor alone. The Table 2 shows the various objectives and factors while modeling Covid-19 in different years.

Objectives of the study	Methods and approaches taken	Factors under consideration	Year of study	References
Influence and its aftermath	Statistical analysis, questionnaire methods, age-structured SIER models, simulation models etc.	Social activities and mobility demographies, specialized knowledge and precautionary advice from authorities, quarantine and contingency plans and policies on groups and individuals, and related news, reports, social media discussions, and misfortune	2020-2021	[13], [14], [15], [16], [17], [18], [35]
Outbreak characteristics and its transmission	Regression, probabilistic compartmental models, time-age dependent compartmental	Newly infected cases, recovered cases, rate of transmission, morbidity and mortality rates	2020	[19], [20], [21], [22], [23], [24], [25], [26]

	models			
Identification, analysis and screening of the virus	Linear, statistical modeling, shallow and deep models, techniques for image retrieval and significant data, etc.	Clinical, pathological, and genomic information (symptoms, medical facilities, hospitalization records, medical history, respiratory signals, medical imaging, physical and chemical measurements, gene sequences, proteins), movement, and contacts, among other things.	2020	[27], [28], [29], [30], [31], [32], [33]
Non-pharmaceutical interventions and strategies	Regression, stochastic models, Bayesian hierarchical models etc.	Epidemiological causes, newly infected and recovered, infected and death case counts, time of reporting the cases, precautionary and mitigation measures and policies on communities and individuals etc.	2020-2021	[34], [35], [36], [37], [38], [39]
Medical interventions (Diagnosis, pathological and biomedical analysis)	Time-series methods, genome analysis, protein analysis deep neural network etc.	Clinical evaluations, hospitalization records, records of medical tests, pharmacological therapies, records of intensive care units, usage of ventilators, drug and vaccine info, immunization response etc.	2020-2021	[40], [41], [42], [43], [44], [45]
Re-emergence and variation of the virus	Compartmental models, simulation models, regression, epidemic renormalization group etc.	Newly-infected-recovered-death case counts, reporting time of the infected cases, quarantine and mitigation strategies on communities and individuals, social activities and movement, seasonal and environmental factors (e.g., season, geographical location, temperature, humidity and wind speed.)	2020	[46], [47], [48], 49]

Environmental factors and its effect on the incubation period	Stochastic theory mathematical models, Auto-regressive integrated moving average (ARIMA) models, Susceptible-exposed-infectious-removed (SIER) model, Bayesian model etc.	Impact of environmental factors, incubation period, impact of age, gender, weather variability, temperature and relative humidity (RH) using statistical methods including Response Surface Methodology (RSM)	2020-2023	[50], [51], [52], [53]

Discussion

We know very little about the SARS-CoV-2 virus and COVID-19, including their features, epidemiological traits and dynamics, socioeconomic influences, and viral mutations, among other things, because they are novel and distinctive. The modeling efforts and contributions are specifically constrained by our limited comprehension of the fundamental and complex pathogenic, biological, and epidemiological characteristics of the emerging SARS-CoV-2 and COVID-19 systems. As a result, without extensive information and thorough data about the system intricacies, our understanding of the virus and disease is still limited. To overcome these problems in modeling there is a need of thorough understanding of the nature of viruses and the core intricacies of COVID-19 complicated systems. We emphasize the following significant unanswered topics among the many to be investigated, which call for interdisciplinary scientific investigations combining medical research, virology, biomedicine, and data-driven discovery.

Nature of the virus: One of the causes for the virus's failure to be discovered was the difficulty to determine why it was interacting with both human and animal hosts. Another difficulty was the lack of information on the features of the virus that affected people in various contexts, such as demographic, community, weather, risk factors for infection and mortality, etc.

Unexplainable mutations of the virus: The mechanisms behind these differences are to be identified, as well as the genetic and pathogenic determinants that dictate how viruses change from one generation to the next. It is also important to understand why the genetic variations vary between populations and between geographical locations.

Influence of external factors in virus transmission: The virus has evolved under different contexts be it environmental, demographical etc. Detection of how and why these factors have affected the viruses transmission, how the viruses spread has been affected due to public activities, hygiene etc. is very important to study the nature of the virus.

Adaptation of the virus to vaccines and drugs: In due course of time the virus have gone through mutations while adapting to different weather conditions and external factors for which the effect of drugs have decreased to some extent. This is due to the inability of people dealing with researches, health care etc. to identify the relation among factors affecting the virus spread or some constraints. Even if different vaccines were discovered to stop the chain of reaction, but the increasing virus mutants and their contagious new strains and unpredictable resurgence have made it difficult for the researchers and the health care professionals for coming up with any solid cure for the virus.

Understanding their nature, as well as their system features and complexity, provides the most significant potential for unraveling the riddles of the COVID-19 virus. Extraction, representation, and distinction of latent components to explain the epidemiological, biological, and medical features, dynamic processes of the virus, its mutations, variations, etc. are some methods for describing the issue. Identifying and describing the external influences on the disease's progression and how they interact with them, detailing and modeling the many relationships and interactions between internal and external elements, large-scale simulation and quantification of the parasitism, interactions, adaptability, and evolution of viruses with human, animal, and live hosts may be some of the areas to be looked upon.

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