

REVIEW

Three months of COVID-19: A systematic review and meta-analysis

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Summary

The pandemic of 2019 novel coronavirus (SARS-CoV-2019), reminiscent of the 2002-SARS-CoV outbreak, has completely isolated countries, disrupted health systems and partially paralyzed international trade and travel. In order to be better equipped to anticipate transmission of this virus to new regions, it is imperative to track the progress of the virus over time. This review analyses information on progression of the pandemic in the past 3 months and systematically discusses the characteristics of SARS-CoV-2019 virus including its epidemiologic, pathophysiologic, and clinical manifestations. Furthermore, the review also encompasses some recently proposed conceptual models that estimate the spread of this disease based on the basic reproductive number for better prevention and control procedures. Finally, we shed light on how the virus has endangered the global economy, impacting it both from the supply and demand side.

KEYWORDS

ACE-2, COVID-19, pandemic, SARS-CoV, mathematical modeling

1 | INTRODUCTION

The initial outbreak of the novel coronavirus in December 2019 was centered in Wuhan, Hubei Province of the People's Republic of China.¹⁻⁵ It was initially named as 2019 novel coronavirus, soon after the International Committee of Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2,¹ because of the previously identified variant- severe acute respiratory syndrome coronavirus (SARS-CoV). The clinical illness it causes is termed as coronavirus disease 2019 (COVID-19).² While several other human coronaviruses such as HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1 cause mild respiratory disease, others like the zoonotic Middle East respiratory

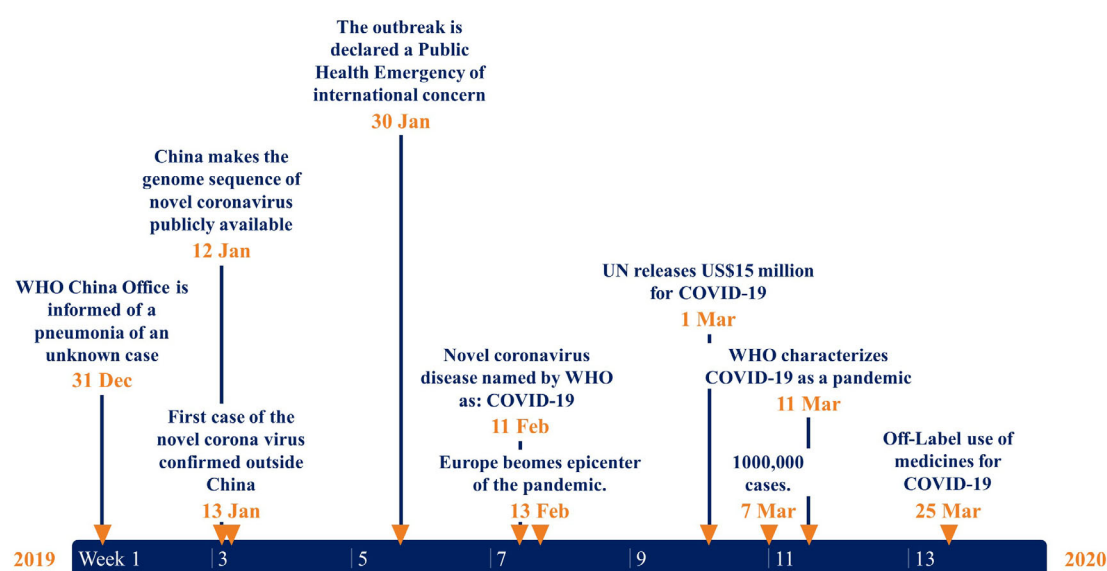
syndrome coronavirus (MERS-CoV) and SARS-CoV tend to have a higher fatality rate⁶ (summarized in Table 1).

SARS-CoV-2019 has rapidly transmitted from Wuhan to other parts of the world, resulting in more than 80 000 cases in mainland China, above 140 000 cases in US, and over 100 000 in Italy. The total global number of COVID-19 cases has surpassed 700 000, infecting at least 203 countries as on 31st March 2020, with number of infected people still growing significantly.⁷ High diffusion and global positive cases became important to both the medical and public sector, as well as the general population. This led the WHO Emergency Committee to declare a global emergency on January 30, 2020.⁷ Very recently, inertia in combating viral spread helped increase the number of cases outside China to about 13-fold in 2 weeks. This led the WHO chief Dr Tedros Adhanom Ghebreyesus to declare the novel coronavirus outbreak as a pandemic—"worldwide spread of a new disease" on March 11, 2020⁷ (Figure 1). The last time the WHO declared a pandemic was during the H1N1 outbreak in 2009, which infected nearly a quarter of the world's population.⁸

List of Abbreviations: ACE2, Angiotensin Converting Enzyme II; ARDS, Acute Respiratory Distress Syndrome; COVID-19, Coronavirus Disease 2019; ODE, Ordinary Differential Equation; PCR, Polymerase Chain Reaction; SEIR, Susceptible-Exposed-Infectious-Recovered; SARS-CoV-2019, 2019 Novel Coronavirus; TEN, Toxic Epidermal Necrolysis; TMSP, Transmembrane Serine Protease.

TABLE 1 Major respiratory outbreaks in last century

Outbreak	Most affected age groups	Area of emergence	Deaths	Fatality rate	Year
Spanish flu	Young adults, elderly and young children	Unclear	20-50 million	>2%	1918-1919
Asian flu	Children	Southern China	1-4 million	0.1%-0.2%	1957-1958
Hongkong flu	All age groups	Southern China	1-4 million	0.1%-0.2%	1968-1969
Serious acute respiratory syndrome (SARS)	Middle-aged adults (45-65)	China	774	<10%	2002-2003
Swine flu	Children, young adults and pregnant women	Mexico	18 000	<0.025%	2009-2010
Middle east respiratory syndrome (MERS)	Elderly (60+)	Middle East	861	>30%	2012
COVID-19	All age groups	China	36 000 and continuing	>2%	2019-2020

**FIGURE 1** A timeline of COVID-19

SARS (affecting people in 26 countries) and MERS were not considered pandemics.

2 | BIOLOGY OF SARS-COV-2

2.1 | Morphology and classification

Coronaviruses (Latin: corona = crown) are positive sense single-stranded, segmented, enveloped large RNA viruses that infect a wide range of animals, including humans. Morphologically spherical virions, they bear a core shell with surface projections that make them resemble a crown. They were first described by Tyrell and Bynoe in 1966, from patients with the common cold.⁹ Four subfamilies of coronaviruses have so far been discovered;

- Alpha: Originate from mammals, particularly bats, cause asymptomatic or mildly symptomatic infections

- Beta: Originate from mammals, particularly bats, can cause severe disease and fatalities. SARS-CoV-2 belongs to the beta-coronaviruses and is closely related to the SARS-CoV virus.^{10,11} SARS-CoV-2 is 96% identical to a bat coronavirus at the whole-genome level.¹¹
- Gamma and delta: Originate from pigs and birds

The genome size of coronaviruses varies between 26 and 32 kb with four major structural genes encoding the membrane glycoprotein (M), spike protein (S), nucleocapsid protein (N), and a small membrane protein (SM) (Figure 2). An additional membrane glycoprotein (HE) occurs in the HCoV-OC43 and HKU1 beta-coronaviruses.¹²

SARS-CoV-2019 has succeeded in transferring from bats to humans, presumably in the seafood market in Wuhan, China. However, potential intermediate hosts remain to be identified and the precise route of transmission urgently needs to be clarified. Because of the novelty of this virus, experts' understanding of exactly how it spreads is restricted.

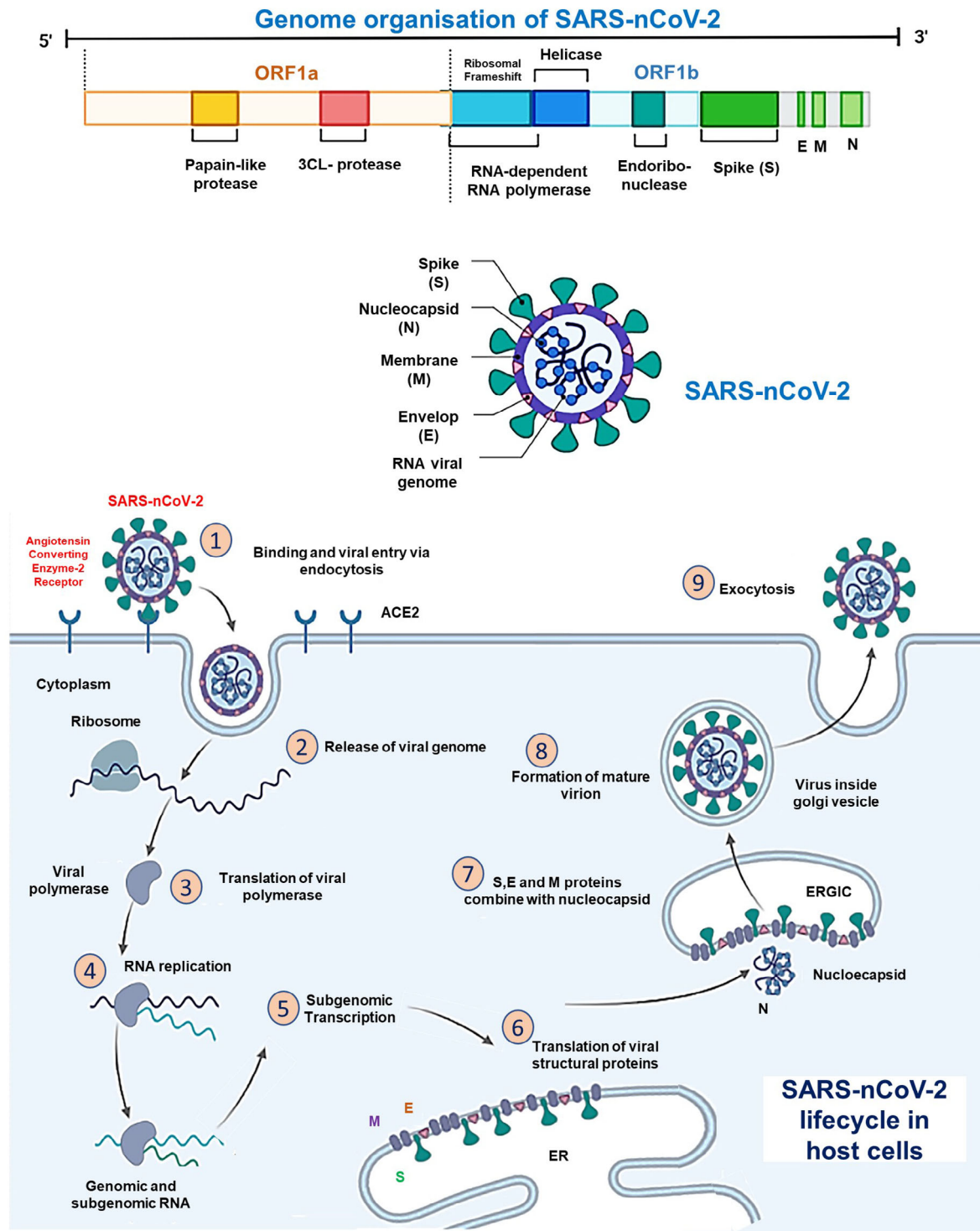


FIGURE 2 Genome organization and life-cycle of SARS-nCoV-2

2.2 | Mechanism of action

Research suggests that the cellular receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2),¹³ expressed normally on type I and II alveolar epithelial cells of human lung and intestinal epithelia.¹⁴ Eighty-three percent of Type II alveolar epithelial cells

express ACE2 receptor. The binding of SARS-CoV-2019 to ACE2 results in an augmented expression of ACE2, which can result in alveolar cell damage. This in turn triggers a cascade of systemic reactions. It has also been suggested that the receptor-binding ability of SARS-CoV-2 is 10-20 times stronger than that of SARS-CoV.¹⁵ Moreover, the virulence and transmission of SARS-CoV-2019 may shift over

time. Very recent study, however, suggests that SARS-CoV-2 has evolved in two different types designated as L (aggressive and more prevalent) and S (evolutionarily older and less aggressive), explaining the higher mortality of initial reports from Wuhan compared to series of recent cases.^{16,17}

2.3 | Pathophysiology

The primary pathology of COVID-19 is ARDS (Acute Respiratory Distress Syndrome), characterized by diffuse damage of alveolar cells and hyaline membranes. Direct invasion of the virus causes cytopathogenic changes in pneumocytes instead of a purely hyperinflammatory injury.¹⁸ Recent studies suggest that patients with severe conditions respond to COVID-19 with an exuberant “cytokine release storm” (that shows characteristics of hemophagocytic lymphohistiocytosis or bacterial sepsis). The condition may show clinical markers of enhanced levels of ferritin and C-reactive protein that may correspond with disease mortality and severity.¹⁹

2.4 | Stages of illness

The patients may move through different stages of illness:

- Replicative stage - The virus may take several days to replicate. Initially, it evokes the first line of defence, that is, innate immune response, but this fails to contain the virus resulting in fairly mild symptoms due to direct viral cytopathic effect.
- Adaptive immunity stage - The innate immune response is eventually followed by the adaptive immune response which tends to decrease the titer of the virus. Meanwhile, the inflammatory cytokines show augmented levels culminating in tissue damage and consequent clinical deterioration. This explains the sudden deterioration of the patients after being relatively fine for several days.²⁰

Potentially clinical inferences can be drawn:

- Preliminary clinical symptoms are not essentially prognostic of future outcome.
- Antiviral therapies need to be given during the replicative stage to work optimally.
- It is desirable to deploy any immunosuppressive therapies in the adaptive immune stage to blunt the immunopathologic response.

2.5 | Signs and symptoms

The initial clinical sign of the COVID-19 that allowed its case detection was pneumonia. While some reports suggest gastrointestinal symptoms associated with this disease, others describe asymptomatic

infections, particularly among young children.²¹ SARS-CoV-2019 may cause lower respiratory symptoms, upper respiratory symptoms, constitutional symptoms, and, less commonly, gastrointestinal symptoms. Most patients show lower respiratory symptoms and constitutional symptoms (eg, cough and fever).

- The incidence of fever is variable among studies (ranging from 43% to 98%). This may relate to different strains of virus or different levels of disease severity between several cohorts. Regardless of the frequency, absence of fever in a patient does not exclude COVID-19.
- About 80% of patients may have lymphopenia.^{22,23}
- Mild thrombocytopenia is very common (but only rarely do platelet counts decline below 100).
- Lower platelet count is a marker of poor prognosis.¹⁹
- Also, up to 10% of patients can initially show gastrointestinal symptoms (eg, nausea and diarrhea), followed by dyspnea.²⁴
- Some patients, especially the elderly, may have “silent hypoxemia” and respiratory failure without dyspnea.²⁵
- Approximately, 2% of patients may develop pharyngitis or tonsil enlargement.²²

3 | TRANSMISSION AND MANAGEMENT

3.1 | Large droplet transmission

Typical of respiratory viruses like influenza virus, SARS-CoV-2019 can spread through large droplets (with a transmission risk restricted to ~6 ft from the patient).²⁶ The droplet containing viral particles (saliva or mucous droplets) can be ejected during coughing, sneezing, laughing, singing, breathing, and talking. If these droplets do not encounter anything along the way, they typically land on the ground or the floor. This transmission via large droplet can be reduced by using a normal surgical-style mask.

3.2 | Airborne transmission

It is not yet clear whether SARS-CoV-2019 can spread through an airborne route. This would necessitate the use of N95 masks rather than standard surgical masks. However, the possibility of aerosol transmission is enhanced by a very recent study that established the capacity of the virus to remain in aerosols for hours.²⁷ Nevertheless, The World Health Organization and Canadian guidelines have recommended the use of only droplet precautions for routine care of COVID-19 patients. However, both of these guidelines endorse airborne protections for aerosol-generating procedures (eg, noninvasive ventilation, bag-mask ventilation, intubation, CPR prior to intubation, extubation, high-flow nasal cannula, tracheostomy, and bronchoscopy). On the other hand, The United States CDC first recommended the use of airborne precautions for managing COVID-19 patients but

recently stated that the use of surgical masks can be acceptable when N95 masks are no longer available.

3.3 | Contact transmission

This mode of transmission is usually overlooked, but it is very important. It works in four chains of reactions:

1. Infected person coughs or sneezes and emits large virus-loaded droplets. The droplets settle on surfaces of fomites (inanimate objects) to create a thin film of the virus.
2. Depending upon the type of the surface, the virus resides on fomites in the environment for hours or days.²⁷
3. The virus gets transferred from the contaminated surface to the hands of the person who touches the surface subsequently.
4. From their hands, the virus comes in contact with a mucous membrane (mouth, nose, or eyes) and subsequently transmits the infection.

This contact transmission can be blocked/disrupted in the following ways:

1. Hand hygiene: Washing hands with sanitizers containing a high concentration of ethanol can inactivate the virus.²⁸
2. Consistent cleaning of environmental surfaces (eg, using 0.5% sodium hypochlorite solutions or 70% ethanol).²⁸
3. Avoidance of touching the face: This would avoid contact with mucous membranes.

3.4 | Maternal–fetal transmission

There are currently no reports of intrauterine maternal–fetal transmission, but neonatal transmission can occur.²⁹

4 | DRUGS TO TREAT COVID-19

Research thus far has revealed more than 30 agents including natural products, western medicines, and traditional Chinese medicines with potential efficacy against COVID-19. Some promising results have been achieved which are summarized below and listed in Table 2, but formal randomized clinical trials will be required to prove efficacy and safety.

4.1 | Lopinavir/ritonavir

Lopinavir and ritonavir are protease inhibitors that work in conjunction to block viral replication. Ritonavir, being a CYP3A inhibitor, reduces the metabolism of lopinavir, thus boosting its levels. A 4 µg/mL

concentration of lopinavir was required for in vitro antiviral activity against SARS while 1 µg/mL of lopinavir was enough when used in combination with ribavirin.³⁰ Both protease inhibitors appear to function synergistically with ribavirin. Combination of all three drugs has been used previously on SARS and MERS.³⁰ Recently, the combination of lopinavir/ritonavir has not proven impressive, suggesting that a cocktail of ribavirin/lopinavir/ritonavir might be required for efficacy.²⁰ Nevertheless, lopinavir/ritonavir is advantageous over ribavirin because of its wide availability and an established toxicity profile.

4.2 | Remdesivir

Originally developed for Ebola, this drug was the most obvious fit for SARS-CoV-2019 as it has already been tried out for ssRNA viruses like SARS and MERS.³¹ Remdesivir is a prodrug whose phosphoramidate is cleaved off to leave the active compound GS-44-1524 with a 5'OH. The active compound is processed by the RNA polymerase and gets incorporated into viral RNA. This leads to RNA termination and inhibition of viral replication. Five clinical trials of this drug are underway including two open-label trials sponsored by Gilead, two phase-III trials at China-Japan Friendship Hospital in Hubei, and one adaptive-design Phase II trial by NIH in Nebraska. Unfortunately, Remdesivir is commercially unavailable. Remdesivir has been used for one of the earliest patients of COVID-19 in the United States on the basis of "compassionate use".^{32,33}

4.3 | Favipiravir

An RNA polymerase inhibitor, Favipiravir, from Toyama Chemical of Japan, is in a trial for experimental treatment of COVID-19 in China. Unfortunately, it is ineffective in in vitro tests. However, the human trials are still underway and have shown good clinical efficacy. The preliminary results from a study of 80 patients have shown that favipiravir had more effective antiviral action compared to lopinavir/ritonavir.³⁴

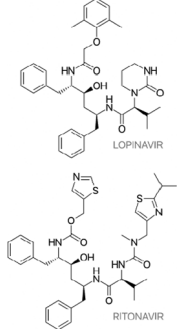
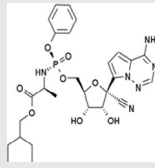
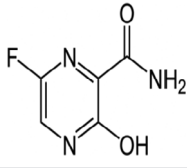
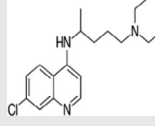
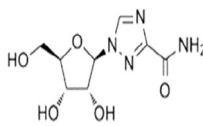
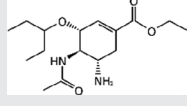
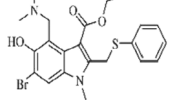
4.4 | Oseltamivir

Oseltamivir, a neuraminidase inhibitor, has previously been ineffective against SARS; however, it works well for patients with influenza pneumonia. It is presently used as a component of several drug cocktail trials as patients with viral pneumonia suffer more likely from influenza than from COVID-19.³⁵

4.5 | Arbidol

A recent study reported that arbidol can efficiently inhibit SARS-CoV-2 infection in vitro at a concentration of 10 to 30 µM.^{34,36}

TABLE 2 Major drugs in clinical development for treatment of COVID-19

Drug	Mechanism	Dosage and mode of administration	Side effects	Clinical trial
Lopinavir/ritonavir 	Protease inhibitors, that work together to block the viral replication	400 mg/100 mg, 2 times/d (Oral)	<ul style="list-style-type: none"> Hypersensitivity reaction, Pancreatitis, Angioedema, Toxic epidermal necrolysis, AV block, Renal failure Hyperglycaemia, Leukopenia, Hypertriglyceridemia, Neutropenia, Hepatotoxicity etc. 	11 trials (for instance NCT04307693, 3/13/20)
Remdesivir 	Gets incorporated into viral RNA leading to RNA termination trouble and inhibition of viral replication.	200 mg once for first day, followed by 100 mg/d (Intravenous)	<ul style="list-style-type: none"> Elevated liver enzymes, Nausea, Rectal bleeding, Vomiting etc. 	6 trials (eg, NCT04292899, 3/19/20)
Favipiravir 	RNA polymerase inhibitor	1600 mg twice for 1 day followed by 600 mg 2 times/d (Oral)	<ul style="list-style-type: none"> Neurological and psychiatric symptoms, Anaphylaxis, Hepatic dysfunction, Acute kidney injury, Toxic Epidermal Necrolysis (TEN), Colitis haemorrhage etc. 	At least three trials (eg, NCT04303299 3/12/2020)
Chloroquine 	Interferes with the cellular receptor ACE2 and also impairs the acidification of endosomes, thereby impeding the virus trafficking inside the cells	500 mg (300 mg for chloroquine) for 2 times/d (Oral)	<ul style="list-style-type: none"> Anaphylaxis or anaphylactoid reaction, Neuropsychiatric disorders, Neuromuscular impairment, Hepatitis thrombocytopenia, Pancytopenia, Neutropenia, aplastic anaemia etc. 	At least ten trials (eg, NCT04303507, 3/11/20; NCT04261517, 2/14/20)
Ribavirin 	Nucleoside analog of ribofuranose that inhibits viral RNA synthesis	500 mg for 2-3 times/d in combination with lopinavir/ritonavir or IFN- α (Intravenous)	<ul style="list-style-type: none"> Cardiac arrest, Pulmonary function deterioration, Headache, Fatigue, Abdominal cramps, Chronic obstructive lung disease, Chest soreness, Ventilator dependence, Conjunctivitis etc. 	At least 5 trials (NCT04254874, 2/5/20; ChiCTR2000029308, 1/23/20)
Oseltamivir 	Neuraminidase inhibitor	12.5 mL of oral suspension or 75 mg capsule 2 times/d (Oral)	<ul style="list-style-type: none"> Vomiting, Nausea, Headache, Mood or mental changes, Skin rashes, Pain etc. 	One trial (NCT04261270, 2/7/20)
Arbidol 	Blocks viral fusion	200 mg for 3 times/d (Oral)	<ul style="list-style-type: none"> Diarrhoea, Nausea, Dizziness, Elevated serum transaminase 	Two trials (NCT04260594, 2/7/20; NCT04286503, 2/27/20)

4.6 | Chloroquine

Chloroquine, generally used for amebiasis and malaria, is currently being considered for treating COVID-19 in view of its ability to interfere with the cellular receptor ACE2. It also impairs the acidification of endosomes, thereby impeding virus trafficking inside cells. Although chloroquine has been unsuccessful in treatment of SARS-infected mice,³⁷ recent reports from in vitro data show that chloroquine inhibits SARS-CoV-2 at a 50% inhibitory concentration of 1 μ M. This suggests the possibility of achieving therapeutic levels in humans.³⁸ It is worth mentioning that for SARS, the 50% inhibitory concentration of chloroquine is near to 9 μ M,³⁹ implying chloroquine is more potent against SARS-CoV-2 than SARS. Studies of chloroquine and hydroxychloroquine are underway.⁴⁰⁻⁴³ At the same time, it is important to establish its dosage as it has a number of liabilities, including sudden effects on blood glucose, seizures, retinopathy, and hearing damage.

4.7 | Other potential drugs

Several other potential drugs include BCR-ABL kinase inhibitor imatinib and Type-II transmembrane serine protease (TMSPSS2) inhibitors.⁴⁴ Imatinib inhibits the fusion of virions with the endosomal membrane and as such possesses anti-coronavirus activity.⁴⁵ A drug screening research team led by The Shanghai Tech University and Shanghai Institute of Materia Medica recently reported 30 agents with potential antiviral activity against SARS-CoV-2.⁴⁶ These agents include remdesivir, saquinavir, indinavir, ritonavir, lopinavir, darunavir, fosamprenavir, carfilzomib, presatovir, atazanavir, enzaplatovir, tipranavir, maribavir, abacavir, bortezomib, raltegravir, elvitegravir, deoxyrhapontin, montelukast, polydatin, disulfiram, chalcone, ebselen, tideglusib, carmofur, PX12, shikonin, TDZD-8, cinanserin, and cyclosporin A. Also, some Chinese herbal medicines such as Radix Sophorae Tonkinensis and Rhizoma Polygoni Cuspidati were found to possess activity against SARS-CoV-2.⁴⁶

5 | TESTS FOR DETECTION OF SARS-COV-2

5.1 | Real-time reverse transcription PCR

Specimens include nasopharyngeal swab, tracheal aspirate (if patient is intubated), broncho-alveolar lavage, or induced sputum. The SARS-CoV-2 RT-PCR test is a real-time reverse transcription polymerase chain reaction (rRT-PCR) test in which the RNA isolated from the specimen is reverse transcribed into cDNA and then subsequently amplified. It utilises one primer and probe set to detect human RNase P (RP) as a control and three primer and probe sets to detect three regions in the SARS-CoV-2 nucleocapsid (N) gene in a clinical sample.⁴⁷ The interpretation of the results is given in Table 3.

5.2 | Antigen detection test

The presence of SARS-CoV-2 viral proteins (antigens) in a sample from the respiratory tract of a person can also be detected within 30 minutes by rapid antigen detection test. If the sample contains a sufficient concentration (actively replicating titre) of viral proteins (target antigens), it will produce a visually detectable signal by binding to the specific antibodies immobilized on a paper strip. However, the sensitivity of the test varies between 34% and 80%, as it depends on the concentration of virus in the specimen, the time from onset of illness, and the quality of the specimen.⁴⁸ Also, there are high chances of false-positive results that are the reason WHO does not currently recommend its use for patient care.⁴⁹

5.3 | Host antibody detection

Another test marketed for the detection of SARS-CoV-2 relies on the presence of antibodies in the plasma of a person infected with SARS-CoV-2.⁵⁰⁻⁵³ However, the detection is possible only in the recovery phase when the patient will start developing antibody response. Till

TABLE 3 COVID-19 RT-PCR test results interpretation

SARS-CoV-2 N1	SARS-CoV-2 N2	SARS-CoV-2 N3	RNase P	Result interpretation	Report
+	+	+	+/-	SARS-CoV-2 detected	Positive
+	+	+/-	+/-	SARS-CoV-2 detected	Positive
+	-	+/-	+/-	SARS-CoV-2 detected	Positive
-	+	+/-	+/-	SARS-CoV-2 detected	Positive
-	-	+	+/-	Sample is again repeated. If the result remains the same, additional confirmatory testing is conducted	Presumptive positive
-	-	-	+	SARS-CoV-2 not detected	Negative
-	-	-	-	Sample is again repeated. If a second failure occurs, another sample is taken.	Invalid

then, the opportunities of disruption of disease transmission and clinical interventions might have already passed. Also, it suffers from drawbacks of cross reactivity with other pathogens and provides false-positive results. Till date, there is no evidence of prediction of patient's immunity for reinfection by antibody detection. WHO also does not recommend this diagnostic test for patient care.⁴⁹

6 | META-ANALYSIS AND COMPUTATIONAL MODELLING OF COVID-19

For the purpose of characterization of the epidemic of COVID-19, various mathematical models have been released that include the Returning Traveller Study (RTS) and the Bats-Hosts-Reservoir-People (BHRP) transmission network model.^{54,55} Among them, the deterministic "Susceptible-Exposed-Infectious-Recovered" (SEIR) compartmental model, that predicts the properties of COVID-19 spread, is the most important and is being used by many researchers. It is based on the epidemiological status of the individuals, clinical progression of the disease, and the intervention measures such as isolation, quarantine, and treatment. The SEIR model, as depicted in Figure 3, stratifies the populations as susceptible (S), quarantined susceptible (S_q), exposed (E), infectious and symptomatic (I), infectious but not yet symptomatic (pre-symptomatic) (A), hospitalized (H), recovered (R), and death (D) compartments.

Considering P as the total population, it is assumed that the susceptible population (S) is stably decreasing at a protection rate (α) and moving to compartment (S_q) that represents the quarantined individuals. Those who are not quarantined and come in contact with infected persons belong to the compartment exposed (E) depending upon the transmission rate (β). An exposed individual, if protected

from being infected (eg, by using protection of face mask or hand sanitizers) will move back to the susceptible (S) compartment at the safety rate (μ). The exposed individuals can get infected and move either to infectious and symptomatic (I) or infectious but not yet symptomatic/presymptomatic to (A) compartment depending upon the average latent time (γ_1^{-1}) and (γ_2^{-1}), respectively. The infected individuals can be detected and then hospitalized at a rate δ . From compartment (H), the patients can also move to the compartment recovery (R) at cure rate $\Lambda(t)$ or die at mortality rate $\kappa_1(t)$. However, the recovered persons are added back to the susceptible compartment (S) at a rate θ . It is important to mention that a percentage of people, though less, die in presymptomatic phase before being hospitalized. They also add to the death compartment at rate $\kappa_2(t)$.

The SEIR model described above can be modeled by a set of ordinary differential equations (ODEs) given as follows:

$$\frac{dS(t)}{dt} = -\frac{\beta S(t)I(t)}{P} - \alpha S(t) + \theta R(t) + \mu E(t),$$

$$\frac{dE(t)}{dt} = \frac{\beta S(t)I(t)}{P} - \gamma_1 E(t) - \gamma_2 E(t) - \mu E(t),$$

$$\frac{dI(t)}{dt} = \gamma_1 E(t) - \delta I(t),$$

$$\frac{dH(t)}{dt} = \delta I(t) - \Lambda(t)H(t) - \kappa_1(t)H(t), \quad (1)$$

$$\frac{dR(t)}{dt} = \Lambda(t)H(t) - \theta R(t),$$

$$\frac{dD(t)}{dt} = \kappa_1(t)H(t) + \kappa_2(t)A(t),$$

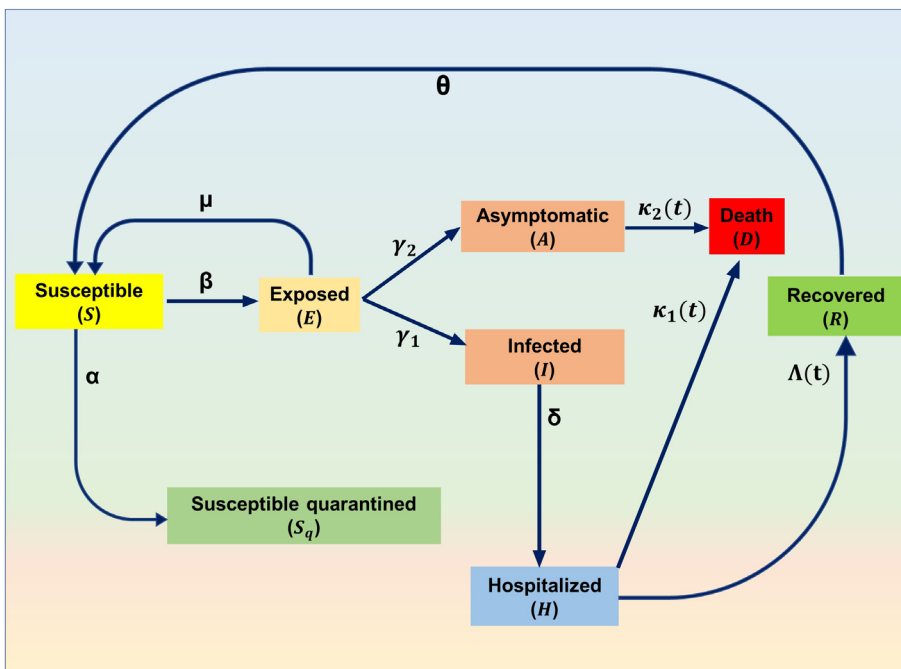


FIGURE 3 A conceptual SEIR model for COVID-19

$$\frac{dS_q(t)}{dt} = \alpha S(t),$$

$$\frac{dA(t)}{dt} = \gamma_2 E(t) - \kappa_2(t) A(t).$$

It follows that

$$P = S(t) + E(t) + I(t) + H(t) + R(t) + D(t) + S_q + A(t) \quad (2)$$

These nonlinear coupled ODEs can be solved using an explicit/implicit time stepping integrating scheme like the regular fourth-order Runge-Kutta scheme.⁵⁶

6.1 | Basic Reproductive number of COVID-19

In the past 3 months, various mathematical models have estimated the basic reproductive number (R_0) which describes the expected number of cases directly infected by a single case assuming that all the individuals in the population are susceptible to the infection. R_0 is affected by factors like behavior of the infected population and environmental conditions. $R_0 > 1$ marks the start of the spread of the infection, $R_0 < 1$ signifies the decline in the number of cases, and $R_0 = 1$ indicates that the disease is endemic. The key insights/highlights of these models are summarized as follows:

1. Shi Zhao, et al⁵⁷

- The authors in this study have advocated that the initial growth phase of COVID-19 follows an exponential growth pattern in China.
- The authors have used a maximum likelihood estimation to determine the number of unreported cases.
- The basic reproduction number (R_0) has been estimated to be 2.56 (95% CI, 2.49-2.63) as: $R_0 = \frac{1}{M(-\gamma)}$ where, γ is the intrinsic growth rate and $M(\cdot)$ is the moment generating function of the generation time distribution.

2. Biao Tang et al⁵⁸

- The study included collecting data for the cumulative diagnosis, quarantine, and released cases of mainland China.
- A deterministic SEIR model of the form in Equation (1) has been parametrized to estimate the basis reproduction number using likelihood-based and model-based approaches.
- An adaptive Metropolis-Hastings (M-H) algorithm was used to carry the Markov Chain Monte Carlo (MCMC) method to fit the model.
- The result showed the estimated mean control reproduction to be 6.47 (95% CI, 5.71-7.23), as compared to the SARS epidemics ($R_0 = 4.91$) in Beijing, China, in 2003 and ($R_0 = 3.5$ -6.7) in Jeddah, Kingdom of Saudi Arabia, in 2014.
- Later an updated estimation risk has been shown⁵⁹ that included calculating the time-dependent contact and diagnosis rates.

3. Ying Liu, et al⁶⁰

- The study provided an estimate of the average R_0 for COVID-19 from a period of January 1, 2020 to February 7, 2020.
- The authors have argued that the estimation of R_0 mainly depends on the estimation technique involved and the modeling assumptions used.
- Both deterministic and stochastic models were included in the study.
- The study showed an average base reproduction number (R_0) to be equal to 3.28 with a median of 2.79.

4. Liangrong Peng, et al⁶¹

- The study proposed a general SEIR model and estimated some key epidemic parameters such as latent time, cure rate, mortality rate, average contacts, severe condition rate, based on public data from Jan 20th to Feb 9th for Mainland, Hubei, Wuhan, Beijing, and Shanghai.
- The study included some predictions from the proposed model about the outbreak scenario in these provinces which are quite in agreement with the present situation.

5. Sheng Zhang, et al⁶²

- This study concerned the impact of COVID-19 on the Diamond Princess cruise ship.
- The study showed that the maximum-likelihood (ML) value of basic reproductive number (R_0) was 2.28 at an early stage on the ship for the COVID-19 outbreak.
- It was shown that if (R_0) value was reduced by 25% and 50%, the estimated total number of cumulative cases would be reduced from 1514 (1384-1656) to 1081 (981-1177) and 758 (697-817) as of February 26, 2020, respectively.

6. Tian-Mu Chen, et al⁶³

- In this research, a Bats-Hosts-Reservoir-People (BHRP) transmission network model for simulating transmission from bats to humans and a Reservoir-People (RP) transmission network model was developed.
- Berkeley Madonna 8.3.18 was employed for curve fitting.
- The value of (R_0) was estimated using the next-generation matrix approach which came out to be 2.30 for reservoir to person and 3.58 for person to person.

7. Jomar F. Rabajante, et al⁶⁴

- A detailed review about an early model-based estimation strategy of COVID-19 is presented in this study along with some useful insights from these models.
- Also, a Susceptible-Exposed-Infected (SEI) model framework was presented, and auxiliary strategies were described to prevent the COVID-19 outbreak. The study showed that exposure time plays a significant role in spreading the disease.

8. Tao Zhou, et al⁶⁵

- This study showed an R_0 value equal to 2.8 ~ 3.3 using real-time reports of infected cases of COVID-19 upto January 26, 2020.
- The study used an SEIR model for parameter estimation.

9. Qianying Lin, et al⁶⁶

- The authors in this study proposed a SEIR compartmental model to account for individual behavioral reaction (represented by α) and the governmental action (represented by κ) (eg, hospitalization, quarantine holiday extension, and travel restriction) in Wuhan, China. The estimates of these two key components were taken from the 1918 influenza pandemic that emerged in London, United Kingdom.
- The study involved simulating three different cases: i) a naive scenario (no individual reaction or governmental action) ii) with only individual reaction, and iii) with both individual reaction and governmental actions. The simulation results showed that the daily new infections fell dramatically as the governmental actions and individual reactions were increased. Furthermore, it has been specifically shown that for $\alpha = 0.9$ and $\kappa > 110$, the simulated data largely match the observed data. This model accurately fits the officially reported data from Wuhan, China, and can be used as starting point to carry forward numerical simulations of the disease spread to other countries.

10. Cleo Anastassopoulou, et al⁶⁷

- An epidemiological data of Hubei, China, was collected from January 11 to February 10, 2020.

- The data were used for estimation of basic reproduction number using a Susceptible Infected Recovered Dead (SIRD) framework.
- The estimated average value of R_0 was ~2.6 based on confirmed cases.

The plot for the estimated value of the (R_0) obtained by the above-mentioned studies is shown in Figure 4. The plot shows a high reproductive number at the beginning of the outbreak in China with the maximum peak in mid-January 2020. However, with passage of time, social distancing, self-quarantine, health care measures, and governmental actions had a substantial effect in containing the outbreak which is evident from the estimates of the (R_0) in the months of February and March, 2020.

It is pertinent to mention that the estimates of the basic reproductive number mentioned in the above studies can be poor due to insufficient data, and different estimation techniques can result in different forecasts. However, further collection of data with robust modeling can result in close estimates.

7 | IMPACT OF COVID-19 ON WORLD ECONOMY

Viral spread has borne out experts' downside fears, with consequences of possible containment measures, disrupted supply chains, and spill overs from the real economy to monetary markets.⁷⁵ Although the outbreak seems to have decelerated in China, COVID-19 has gone global. Infections are escalating in Europe, United States, Iran, South Korea, and elsewhere, with authorities instigating increasingly restrictive actions to contain the virus. Europe and Japan are already in

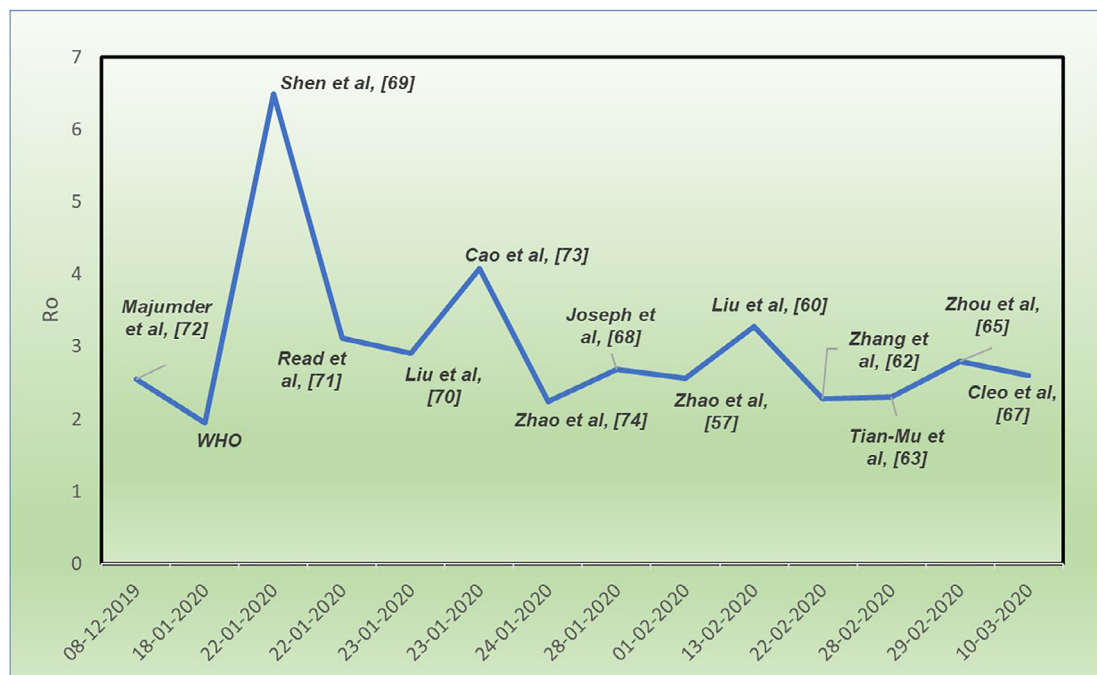


FIGURE 4 Timeline of R_0 for COVID-19

recession territory given their high reliance on trade and weak fourth quarter performance. The augmented uncertainty has resulted in volatility of the financial markets which is typically seen during a global financial crisis. While questions about governments' capacities to mount a coordinated and effective response linger, the UN's Trade and Development Agency, UNCTAD has envisaged COVID-19 to probably cost a slowdown of \$1 trillion to the global economy in 2020.⁷⁶ Bloomberg Economics has even warned that in a worst-case pandemic scenario, the full-year GDP growth might fall to zero. The extent of the damage, however, depends on the following factors:

1. Time taken to contain the virus
2. The steps taken by the authorities to contain it
3. Extent of economic support to be deployed by the government throughout the epidemic's immediate effect and aftermath

The COVID-19 outbreak has caused both supply and demand shocks reverberating across the global economy. As per OECD, the countries that are deeply interconnected to China are the ones that will forecast the largest downward growth revisions particularly Japan, South Korea, and Australia. Large-scale quarantines, social-distancing measures, and travel restriction measures have driven a sharp fall in consumer and business spending creating a recession.

At the sectoral level, the hardest hit industries would be:

1. Travel and tourism-related industries: As the authorities encourage "social distancing" and consumers stay indoors, the International Air Transport Association has envisaged that COVID-19 possibly would cost global air carriers between \$63 billion and \$113 billion in 2020.
2. The international film market: This industry could lose over \$5 billion in lower box office sales.
3. Hotel companies and restaurants: These have drastically plummeted in the past weeks, and entertainment titans like Disney expect a substantial blow to revenues.
4. Sporting events and other services.
5. Agriculture industry and other such industries that are less reliant on high social interaction are comparatively less vulnerable but still may face challenges as demand wavers.

Concluding remarks

This overview provides the basic, biomedical, and translational research communities some key insights on COVID-19. We believe that the focus of future studies still lies in the progress of effective drugs in general and development of SARS-CoV-2 vaccines in particular. While uncertainty lingers, credible, coordinated, and coherent policy responses would deliver the best chance at limiting the fallout from this human tragedy. Time alone can tell how the virus is going to affect our lives, but future outbreaks of pathogens of zoonotic origin and viruses are likely to continue. As such, besides curbing this

epidemic, efforts should be implemented to devise inclusive measures to avert future outbreaks of zoonotic origin. Though the virus has reshaped the geopolitical globalization, multilateralism and integration of countries are indispensable. Without a doubt, we must move toward policy making and greater coordination to combat the current health crisis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

Danish Rafiq and Asiya Batool collected the data and wrote the manuscript, M. A. Bazaz analyzed the data and helped in critical analysis and proof reading of the manuscript.

ETHICAL APPROVAL

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