

# COVID-19 Pandemic Simulation Studies on the Transmissibility

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## Abstract

COVID-19 was identified as the causative virus of pneumonia based on unknown etiology. COVID-19 has multiple characteristics distinct from other infectious diseases, including high infectivity during incubation, time delay between real dynamics and daily numbers of confirmed cases, and the intervention effects of quarantine and control measures. Public health concerns are being paid globally on how many people are infected and suspected reach to pandemics. Therefore, it is urgent to develop a mathematical model to estimate the transmissibility and dynamic of the transmission of the virus.

**Keywords:** COVID-19; Pandemic; Radiology; Machine learning; Mathematical model; Transmissibility

## Introduction

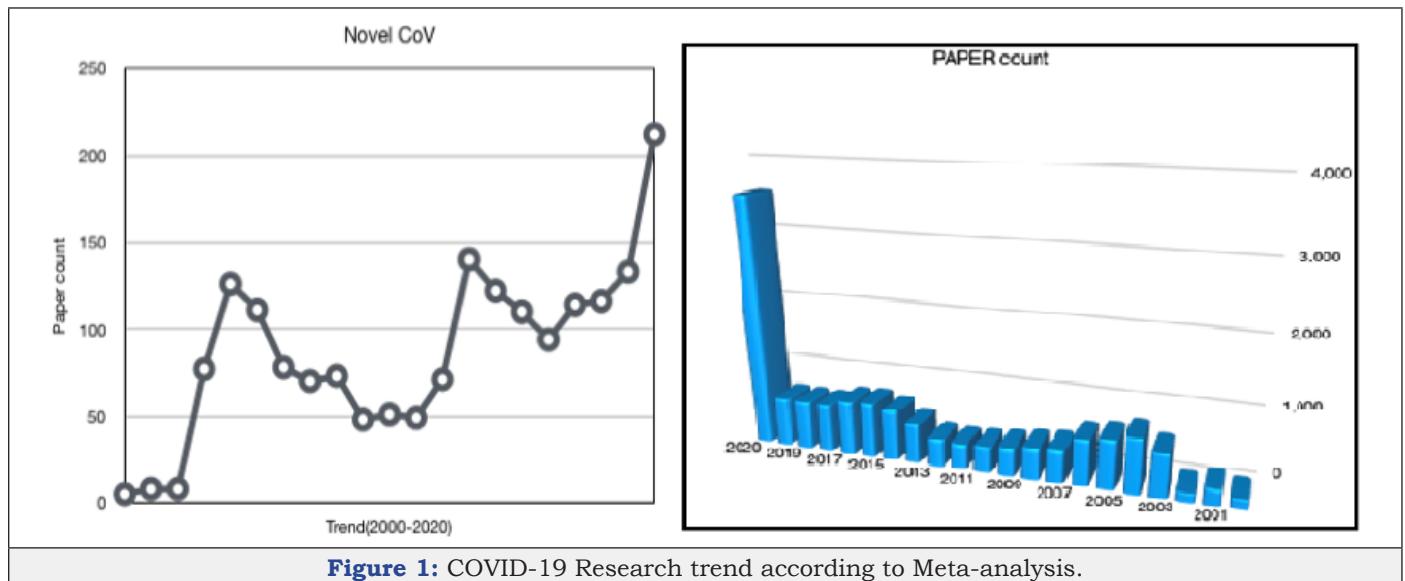
Emerging infectious diseases (EIDs) and their determinants have recently attracted substantial scientific and popular attention. Over 75% of EIDs consist of zoonotic, Coronaviruses are capable of interspecies transmission [1-4]. Some of them have caused worldwide panic as emerging human pathogens in recent years, e.g., severe acute respiratory syndrome coronavirus (SARS-CoV) [5-10] and Middle East respiratory syndrome coronavirus (MERS-CoV) [11-18]. Coronavirus are a group of enveloped positive-stranded RNA viruses responsible for a variety of diseases in birds and mammals and belongs to the Coronavirus genus of the family [19-21]. Corona-viridae; one of its variants, named SARS virus, can cause severe acute respiratory syndrome (SARS). The Coronaviruses genome, ranging from 26 to 32 kilo-bases in length, is probably the largest viral RNA known. Previously, there are six Coronavirus known to cause human diseases and can be divided into low pathogenic and highly pathogenic Coronavirus. The low pathogenic Coronavirus, including 229E, HKU1, OC43 and NL63, account for 10% to 30% of upper respiratory tract infections and typically cause mild respiratory diseases [20-22]. In contrast, the highly pathogenic Coronavirus, including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) Coronavirus, predominantly infect lower airways and cause fatal pneumonia [5,21]. These two highly pathogenic Coronavirus have posed a substantial threat to public health. World health organization (WHO) determined that the pathogen is novel coronavirus with many similarities to SARS virus. Subsequently, the full genomic sequence from Shanghai Public Health Clinical Center argued for a bat origin for the COVID-19 [23-33]. Despite several decades of research, specific vaccine or treatment for human Coronavirus is lack. In this review, we summarize the advance of the nature of the COVID-19 and its clinical characteristics and therapeutics, which may be critical for the response to the COVID-19 outbreak. In order to assess their threat to humans, we explored to infer the potential hosts of coronaviruses using a dual-model approach with discriminant model achieved high accuracies in leave-one-out cross-validation of training data consisting of standard representative coronaviruses [34-37]. Predictions on chosen additional coronaviruses precisely conformed to conclusions or speculations by other researchers. The novel coronavirus disease 19 (COVID-19) is rapidly spreading with a rising death toll and transmission rate reported in high income countries rather than in low income countries. The overburdened healthcare systems and poor disease surveillance systems in resource-limited settings may struggle to cope with this COVID-19 outbreak and this calls for a tailored strategic response for these settings. Here, we recommend blockchain

and artificial intelligence-coupled tracking systems for COVID-19 and other emerging infectious diseases. Prompt deployment and appropriate implementation of the proposed system have the potential to curb the transmissions of COVID-19 and the related mortalities, particularly in settings with poor access to laboratory infrastructure.

**Materials and Methods**

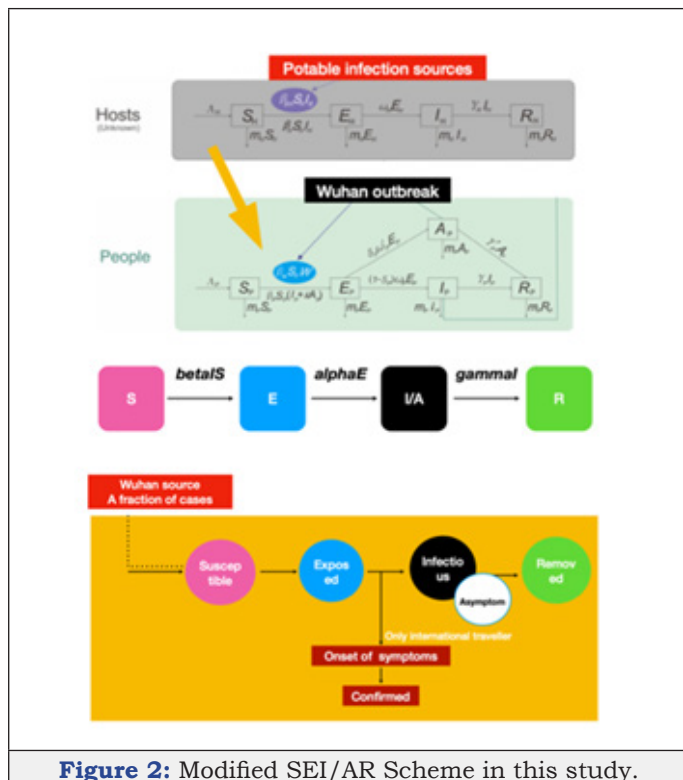
A literature search was performed using the PubMed database and the Cochrane library. Search terms included “novel coronavirus” and “2019-nCoV”. The MESH terms were: “novel” [All

Fields] AND (“coronavirus”[MeSH Terms] OR (“2019-nCoV”[All Fields]) OR (“COVID-19” [All Fields]. The defined search period from November 30 2019 to March 18 2020 was selected to compare studies regarding first outbreaks and findings. Given the nature of the review, no ethics approval was required. The search was performed by two investigators. A total of 4,587 studies were identified (PubMed: 4,585, Cochrane: 2) in accordance with the results shown in Figure 1. Two investigators then reviewed these articles, initially by title and abstract and then in detail, using a customized data abstraction form. Studies were excluded if they had an incorrect subject matter, were duplications or review.



**Figure 1:** COVID-19 Research trend according to Meta-analysis.

**Data source**



**Figure 2:** Modified SEI/AR Scheme in this study.

The reported cases of COVID-19, were collected for the modeling study from a published literature and Wikipedia coronavirus outbreak in South Korea. The epidemic curve from 20 January, 2020 to 18 April, 2020 was collected for our study, and the simulation time step was 1 day. We introduced the modified and simplified reservoir-people transmission network model from Chen (Figure 2) applying the assumption that COVID-19 might be imported to the South Korea in a short time. Therefore, we added the further assumptions as follows: During the outbreak period, the natural birth rate and death rate in the population was in a relative low level. Since there was no data on the proportion of asymptomatic infection of the virus, Since there was no evidence about the transmissibility of asymptomatic infection, we assumed that it could be died in the environment in a short time, but it could be stay for a longer time (14 days) in the unknown hosts.

**Results**

**Characteristics of the novel Coronavirus 2019**

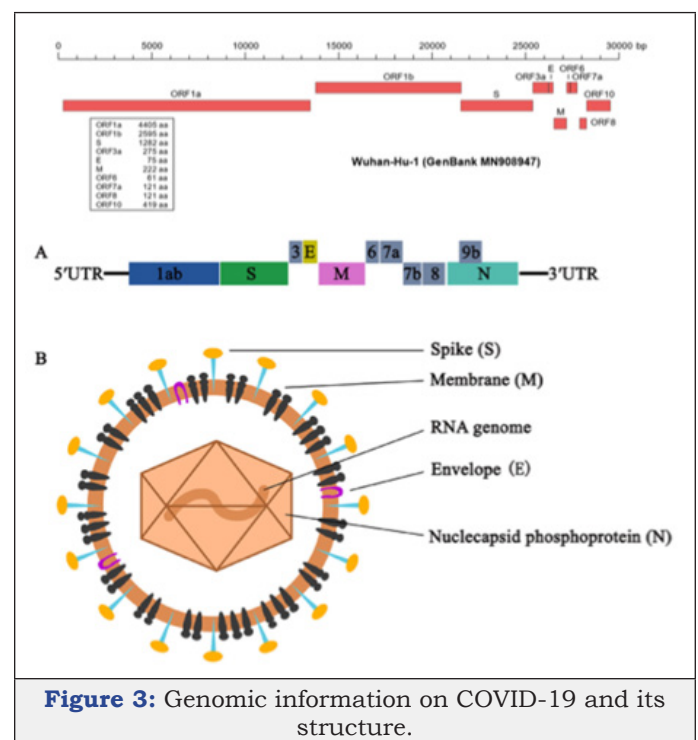
**Public health responses:** A few cases of unidentified pneumonia with a history of exposure were reported at Wuhan, Hubei Province of China in December 2019. As is known SARS-CoV-2, a novel coronavirus was identified to be accountable for this SARS outbreak. Human to human transmission was confirmed in this disease named COVID-19 by WHO spread rapidly around. This COVID-19 resulted in a much lower-case fatality rate

approximately 2.67% among the confirmed cases, compared with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [38-44]. According to the released official reports, the top four are fever, cough, short of breath, and chest tightness/pain. The major co-morbidities of the fatality cases include hypertension, diabetes, coronary heart disease, cerebral infarction, and chronic bronchitis. The source of the virus and the pathogenesis of this disease are still unconfirmed. No specific therapeutic drug has been found. The Chinese Government has initiated a level-1 public health response to prevent the spread of the disease. Meanwhile, it is also crucial to speed up the development of vaccines and drugs for treatment, which will enable us to defeat COVID-19 as soon as possible. World Health Organization (WHO) on March 11 declared COVID-19 a pandemic, pointing to the over 118,000 cases of the coronavirus illness in over 110 countries and territories around the world and the sustained risk of further global spread. A national state of emergency and quarantine have been declared in the USA and in the midst of the COVID-19 world pandemic [45-52], everything normal has been derailed. One obvious concern is the high risk of false positive results generated by unreliable, biased, or non-transparent algorithms. Another is "surveillance creep," when surveillance developed for a limited purpose, such as fighting a pandemic or filming traffic violations, becomes used in ever more pervasive and permanent ways. How can we design the health surveillance and AI tools [53-60] needed to control COVID-19 and future pandemics so they don't backfire or affect future wellbeing?

**The potential route of COVID-19 infection:** The bulk RNA-seq profiles [61-66] from two public databases including The Cancer Genome Atlas (TCGA) and Functional Annotation of The Mammalian Genome Cap Analysis of Gene Expression (FANTOM5 CAGE) dataset were collected (Figure 3). RNA-seq profiling data of 13 organ types with para-carcinoma normal tissues from TCGA and 14 organ types with normal tissues from FANTOM5 CAGE were analyzed in order to explore and validate the expression of ACE2 on the mucosa of oral cavity. Further, single-cell transcriptomes from an independent data generated in-house were used to identify and confirm the ACE2-expressing cell composition [67-70]. The results demonstrated that the ACE2 expressed on the mucosa of oral cavity. Interestingly, this receptor was highly enriched in epithelial cells of tongue. Preliminarily, those findings have explained the basic mechanism that the oral cavity is a potentially high risk for COVID-19 infectious susceptibility and provided a piece of evidence for the future prevention strategy in dental clinical practice as well as daily life.

**Genomic structure of COVID-19:** The genome of COVID-19 [71-81] is consist of 6 major functional open reading frames (ORFs), including ORF1a/b, S, E, M, N and several other accessory genes like ORF3b, ORF8 as shown in Figure 3. Replicase poly-proteins pp1a and pp1ab encoded by ORF1a/b would be proteolytic cleaved into 16 non-structural proteins (nsps) which are involved in the transcription and replication of the virus. In addition, the ORF3b encoded a completely novel short protein without exact function. The new ORF8 likely encodes a secreted protein formed by an alpha-helix, following with a beta-sheets containing six strands

without known functional domain or motif similarly. The S gene of COVID-19 was less than 75% sequence identity to those of two CoVs, bat SARS-like CoVs (SL-CoVZXC21 and ZC45) and human SARS-CoV. And likewise, the spike glycoprotein encoded by the S genes of COVID-19 was longer than that of SARS-CoV. The spike protein, composed of S1 and S2 domain, was crucial to determine host tropism and transmission capacity through mediating receptor binding and membrane fusion. Of which the S2 subunit of COVID-19 is highly conserved and has 99% identity with that of SARS-CoV. The receptor-binding domain, commonly located in the C-terminal domain of S1 to directly contact the human receptor. Although, S1 domain of 2019-nCoV is only approximately 70% identity with SARS-CoV, homology modeling revealed that 2019-nCoV has a similar receptor-binding domain structure to that of SARS-CoV. Since the genomic sequences of COVID-19 obtained from different patients were extremely similar to each other, exhibiting more than 99.9% sequence identity, we could reasonably believe that COVID-19 originated from one source rather than a mosaic and could be detected relatively rapidly. However, mutations need to be constantly monitored when the virus is transmitting to an increasing number of individuals.



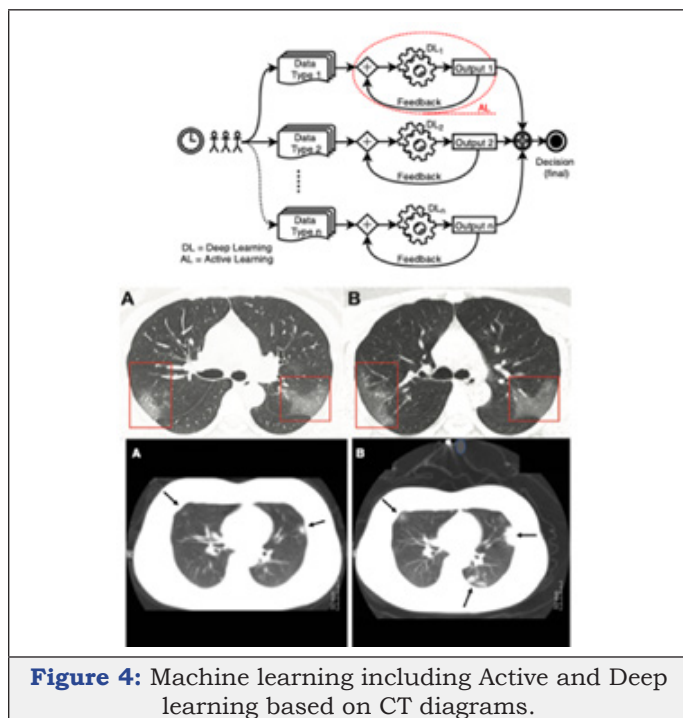
**Figure 3:** Genomic information on COVID-19 and its structure.

**Computational identification of small interfering RNA targets in covid-19; theoretical predictions of the potential siRNA targets in the virus genome:** There are still some challenges that needed to be overcome for the clinic applications of siRNA, progresses have been made to solve the fundamental problems, such as off-target effects and effective delivery. For example, the position-specific chemical modification of siRNAs could significantly reduce off targeting; safe and effective in vivo delivery systems have also been developed, such as nanoparticles, cationic lipids, antibodies, cholesterol, appetizes delivery strategies. Therefore, we hope that the above results (Table 1) would be useful in drug design and treatments against COVID-19.

**Table 1:** siRNA target sequence in plus strand of coronavirus (MN908947).

Target 5'-3'	Position	Region	Length	AR(RAR)	Number of Mutation Strain
AAUAGUUUAAAAUUACAGAAGA	6509-6531	Orf1ab	23	20(20)	1
UCCUUCUUUAGAAACUUAACA	7168-7188	Orf1ab	21	18(12.6)	0
UGGUUCACUACUUUCUGUUU	11,997-12,017	Orf1ab	21	15(10.5)	0
UUCACUACUUUCUGUUUUGCU	12,001-12,021	Orf1ab	21	15(10.5)	0
AUGUCAUCCCUACUUAACUCAAA	15,041-15,064	Orf1ab	24	18(18)	0
UUAAAAUAAUAGAAAAUGGA	22,391-22,411	S	21	18(12.6)	0
CUUGAAGCCCCUUUCUCAUCUUU	25,693-25,717	Orf3a	25	18(12.6)	0
CAACUAAAAUUAAACACAGA	27,128-27,148	M	21	19(19)	2
UUGAAUACACCAAAAGAUCACAUU	28,688-28,711	N	24	18(18)	0

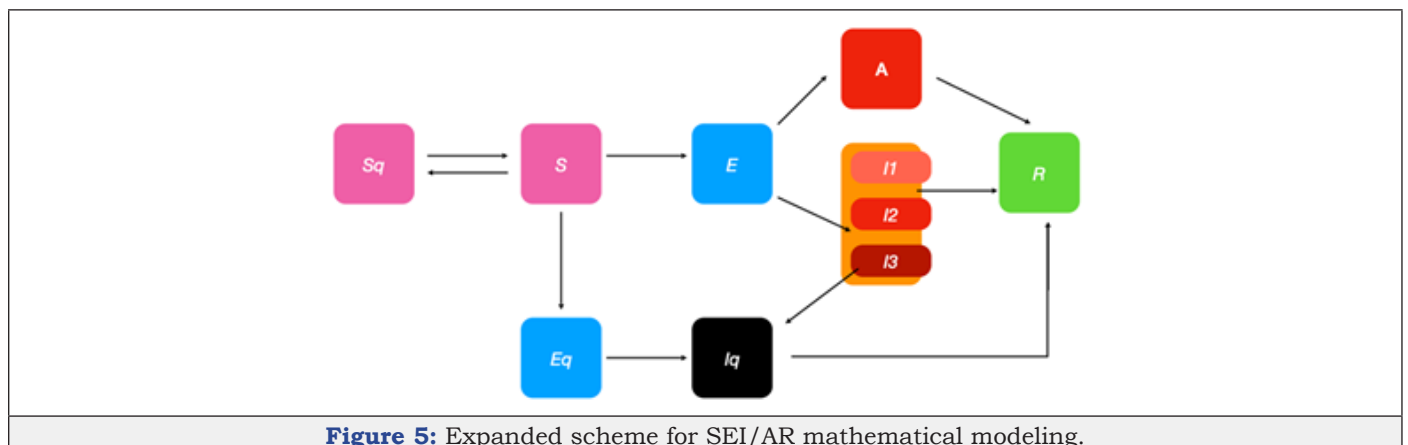
\*The bold and underlined characters indicate the SNP found in different strains.



**Figure 4:** Machine learning including Active and Deep learning based on CT diagrams.

**Machine learning as ai-driven tools:** The novel coronavirus (COVID-19) outbreak, which was identified in late 2019, requires special attention because of its future epidemics and possible global threats. Beside clinical procedures and treatments, since Artificial Intelligence (AI) promises a new paradigm for healthcare,

several different AI tools that are built upon Machine Learning (ML) algorithms are employed for analyzing data and decision-making processes. This means that AI-driven tools help identify COVID-19 outbreaks as well as forecast their nature of spread across the globe. However, unlike other healthcare issues, for COVID-19, to detect COVID-19, AI- driven tools are expected to have active learning-based cross-population train/test models that employs multi- tudinal and multi- modal data, which is the primary purpose of the paper. For time-series data, a schema of Active Learning (AL) model is provided. For better understanding, AL (in dotted red circle) is used with Deep Learning (DL) for all possible data types. In AL, expert’s feedback is used in parallel with the decisions from each data type. Since DL are data dependent, separate DLs are used for different data type. The final decision is made based on multi- tudinal and multimodal data (Figure 4). More often, AI-driven tools are limited to one data type. Decisions that are solely based on one data type (regardless of the data size) may be skewed away from the severity of coronavirus influence. In such a case, use of multi- tudinal and multimodal data can help support decision-making process with higher confidence. Since coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry, the most popularly used data for AI-driven tools mostly employ RNA sequences. Besides, Electronic Health Record (EHRs), Computerized Tomography (CT) scans, Chest X-rays (CRRs, Figures 5 & 6), and other data are considered and tested. Alibaba launched a new AI-based system to detect coronavirus infection via CT scans with an accuracy of up to 96%.



**Figure 5:** Expanded scheme for SEI/AR mathematical modeling.



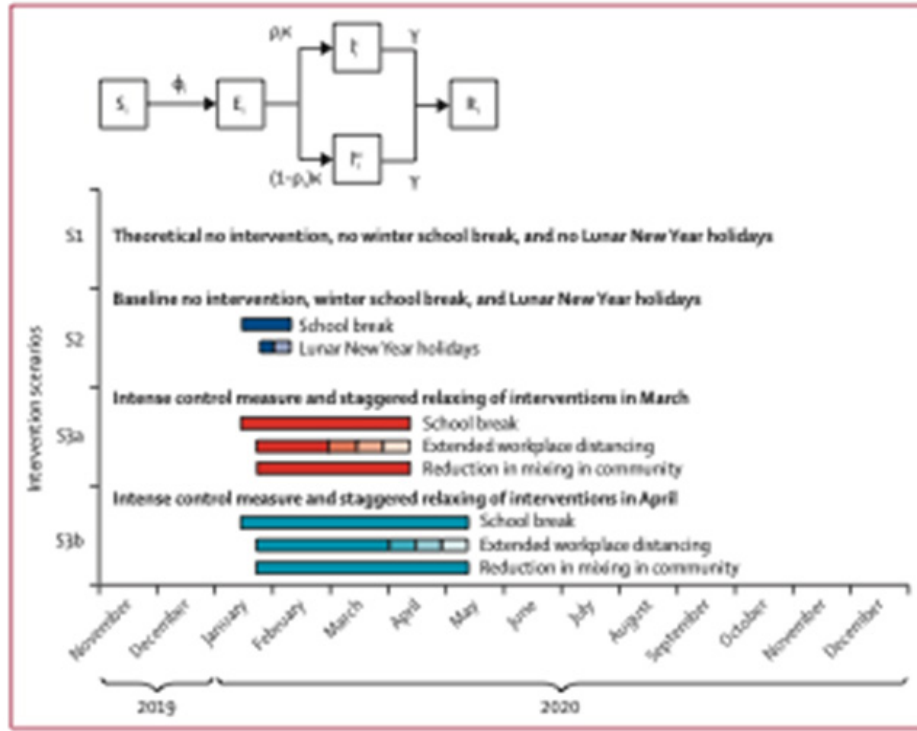


Figure 6: Physical distance invention simulation algorithms in infectious status.

**Validation of statistical models on predictions for viruses capable of interspecies transmission mathematical model of infection kinetics and its analysis for COVID-19 Epidemic transmission:** Based on the susceptible-exposed-infected/asymptomatic-removed (SEIAR) compartment model and the assumption that the infectious cases with symptoms occurred from free propagation without intervention, we estimate the basic reproduction number of COVID-19 according to the reported confirmed cases and suspected cases, as well as the theoretical estimated number of infected cases by other research teams, together with some epidemiological determinants learned from the severe acute respiratory syndrome (SARS). The modified SEIAR model is a classical epidemic model for the flows of people

between five states: susceptible (S), exposed (E), infected (I), Asymptomatic(A), and recovery (R). Each of those variables represents the number of people in those groups. The relationship among the four groups is elucidated in Figure 7, where  $\beta_1$  is the probability of S to E after I contacts S,  $\gamma_1$  is the probability of E to I, and  $\gamma_2$  is the probability of I to R. Since COVID-19 is also infectious in the incubation period, we introduced parameter  $\beta_2$  here to represent the probability of S to E after E contact S. We used the “susceptible-exposed-infected/asymptomatic-recovered” model to describe the prevalent characteristics of COVID-19. This is an ordinary differential equation model, described by the following equations:

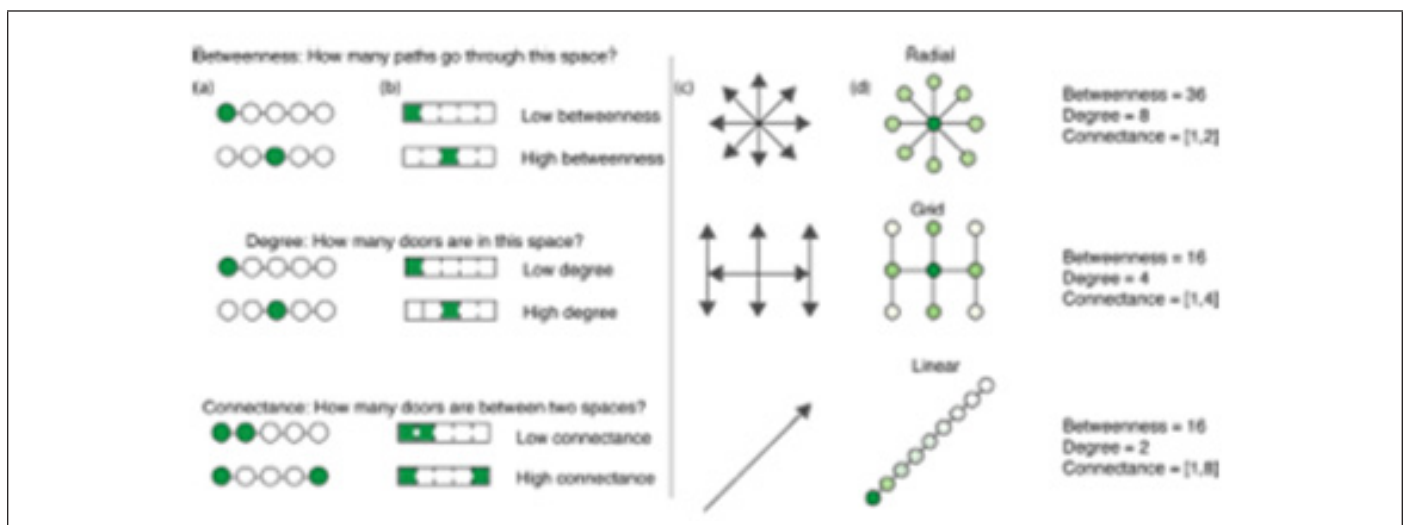


Figure 7: Environmental mitigation control in the transmission.

$$dS_{\omega} / d_{\omega} - \beta_1 \times I_{\omega} \times (S_{\omega} / N) - \beta_2 \times E_{\omega} \times (S_{\omega} / N)$$

$$dE_{\omega} / d_{\omega} - \beta_1 \times I_{\omega} \times (S_{\omega} / N) + \beta_2 \times E_{\omega} \times (S_{\omega} / N) - \gamma_1 \times E_{\omega}$$

$$dI_{\omega} / d_{\omega} - \gamma_1 \times E_{\omega} - \gamma_2 \times I_{\omega}$$

$$dR_{\omega} / d_{\omega} - \gamma_2 \times I_{\omega}$$

Among which, S(t), E(t), I(t), A(t), and R(t) represent the number of people in the group of the susceptible, the exposed, the infected and the recovered on the day t, respectively. N is the total number of possible contact people, which is assumed to be fixed and  $N=S+E+I/A+R$ .

$$\beta_1 - R_0 / T1$$

$$\beta_2 - R_0 / TE$$

$$\gamma_1 - 1 / TE$$

$$\gamma_2 - 1 / TI$$

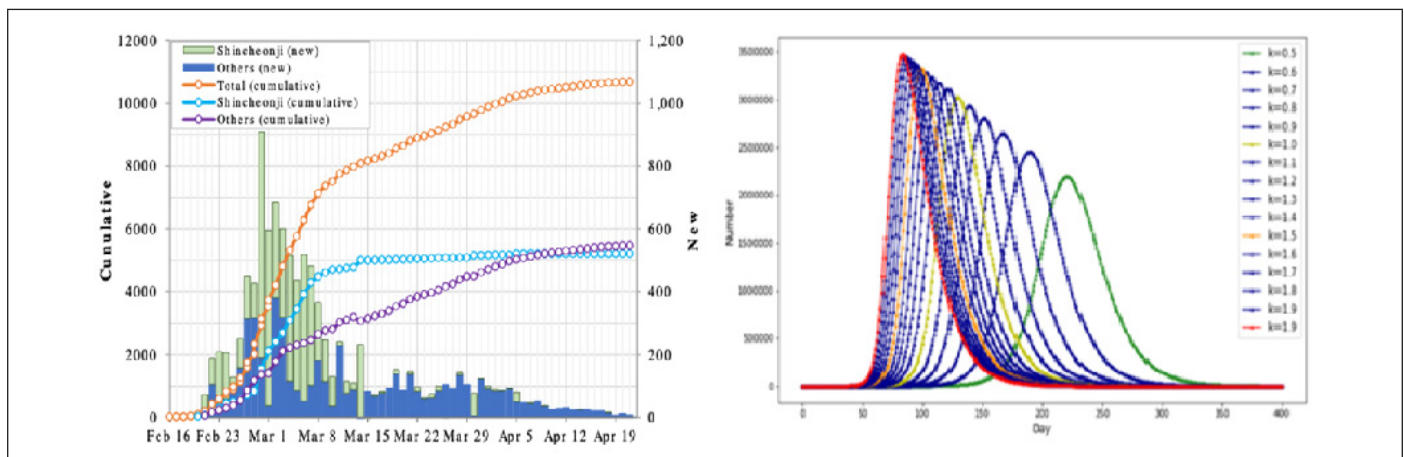
Parameters  $\beta_1$ ,  $\beta_2$ ,  $\gamma_1$  and  $\gamma_2$  were estimated according to the reference using the formula below: among which, R is the basic reproduction number, T1 is the time of infectious period, TE is the time of incubation period, and beta, beta, gamma, and gamma same meanings as in Figure 5.

**Conceptualization of COVID-19 deposition to reduce transmission:** Once an individual has been infected with COVID-19,

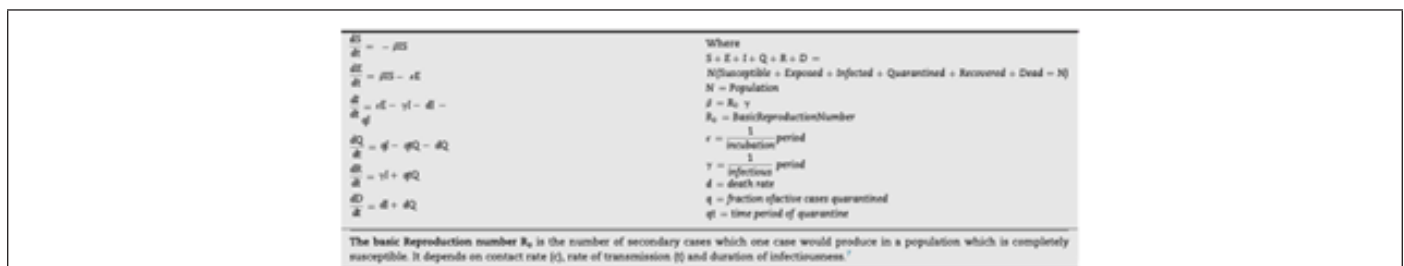
viral particles accumulate in the lungs and upper respiratory tract. Droplets and aerosolized viral particles are expelled from the body through daily activities, such as coughing, sneezing, and talking, and non-routine events such as vomiting, and can spread to nearby surroundings and individuals. Viral particles, excreted from the mouth and nose, are often found on the hands and can be spread to commonly touched items such as computers, glasses, faucets, and countertops. There are currently no confirmed cases of fomite-to-human transmission, but viral particles have been found on abiotic environmental surfaces.

**Details of the modeled physical distancing interventions:**

According to infection status, we divided the population into susceptible (S), exposed (E), infected (I), asymptomatic(A), and removed (R) individuals. An infected individual in an age group can be clinical (I) or subclinical (Ism), and prefers to the probability that an individual is symptomatic or clinical. The age-specific mixing patterns of individuals in age group i, C, alter their likelihood of being exposed to the virus given a certain number of infected individuals in the population. Younger individuals are more likely to be asymptomatic and less infectious, ie, subclinical. The transmission rate and  $\alpha$  is the proportion of transmission that resulted from a subclinical individual. SEIAR= susceptible-exposed-infected-asymptomatic-removed. In addition to it, other factors could be influenced on the transmutability should be taken into consideration. Therefore, the estimates of the unreported cases between initial date and final date 2020, the basic reproduction Figure 8. The estimates of the unreported cases during designated period 2020, the basic number (R), and fitting results of the number of COVID-19 cases time series, which illustrated in Figure 9.



**Figure 8:** I value the simulation curve of the infected population and 2020 CDC coronavirus cases in South Korea.



**Figure 9:** Differential equations utilized in the creation of mathematical models.

**Control of mitigation efforts in the environmental transmission:** The spread of COVID-19 is a rapidly developing situation, but there are steps that can be taken, inside and outside the host environment, to help prevent the spread of Coronavirus infection disease. Spatial connectivity, highlighting betweenness and connection of common room and door configurations as shown in Figure 7. Circles and lines follow the classic network representation. The rectangles follow the architectural translation of networks. Shaded areas correspond to a measure of betweenness (the number of shortest paths between all pairs of spaces that pass through a given space over the sum of all shortest paths between all pairs of spaces in the building), degree (the number of connections a space has to other spaces between any two spaces), and connection (the number of doors between any two spaces). The arrows represent possible directions of microbial spread as determined by the layout of the one. The circles represent the current knowledge of microbial spread based on microbial abundance through environmental factors as determined by layout. Darker colors represent higher microbial abundance, and lighter colors represent lower microbial abundance. The number of individuals who have contracted or have been exposed to S COVID-19 has been increasing dramatically. Over a decade of microbiology of the environmental research has been reviewed to provide the most up-to-date knowledge into the control and mediation of common pathogen exchange pathways and mechanisms in the parsimonious environment with as much specificity to COVID-19 as possible. We hope this information can help to inform the decisions and infection control mechanisms that are implemented by corporate entities, federal, state, county, and city governments, universities, school districts, places of worship, prisons, health care facilities, assisted living organizations, daycares, homeowners, and other building owners and occupants to reduce the potential for transmission through environmental transmission mediated pathways. This information is useful to corporate and public administrators and individuals responsible for building design and operation in their decision-making process about the degree and duration of social-distancing measures during viral epidemics and pandemics.

**Predictive mathematical models of the covid-19 pandemic:** Modeling studies have contributed vital insights into the COVID-19 pandemic, and will undoubtedly continue. Early models pointed to areas in which infection was likely widespread before large numbers of cases were detected; contributed to estimating the reproductive number, case fatality rate, and how long the virus had been circulating in a community; and helped to establish evidence that a significant amount of transmission occurs prior to symptom onset. As shown in Figure 8 mathematical models can be profoundly helpful tools to make public health decisions and ensure optimal use of re- sources to reduce the morbidity and mortality associated with the COVID-19 pandemic, but only if they are rigorously evaluated and valid and their projections are robust and reliable. Numerous mathematical models are being produced to forecast the future of coronavirus disease 2019 (COVID- 19) epidemics in the US and worldwide. These predictions have far-reaching consequences regarding how quickly and how strongly governments move to

curb an epidemic. However, the primary and most effective use of epidemiological models is to estimate the relative effect of various interventions in reducing disease burden rather than to produce precise quantitative predictions about extent or duration of disease burdens.

## Discussion

During the period of an epidemic when human-to-human transmission is established and reported case numbers are rising exponentially, nowcasting and forecasting are of crucial importance for public health planning and control domestically and internally. Our findings suggest that independent self-sustaining human-to-human spread is already present in multiple major cities, many of which are global transport hubs with huge numbers of both inbound and outbound passengers, which caused pandemic now.

$$\left. \begin{aligned} \frac{dS}{dt} &= -\alpha U(t)S(t) / N \\ \frac{dU}{dt} &= \alpha U(t)S(t) / N - \gamma_1 U(t) - (1 - \gamma_1)\delta U(t) \\ \frac{dQ}{dt} &= \gamma_1 U(t) - [\gamma_2 + (1 - \gamma_2\sigma)Q(t)] \\ \frac{dC}{dt} &= \gamma_2 + (1 - \gamma_2\sigma)Q(t) + (1 - \gamma_1)\delta U(t) \end{aligned} \right\} (1)$$

$$\left. \begin{aligned} \frac{dS}{dt} &= -\alpha U(t)S(t) / N \\ \frac{dU}{dt} &= \alpha U(t)S(t) / N - \gamma_1 U(t) \\ \frac{dQ}{dt} &= \gamma_1 U(t) - [\gamma_2 + (1 - \gamma_2\sigma)Q(t)] \\ \frac{dC}{dt} &= \gamma_2 + (1 - \gamma_2\sigma)Q(t) \end{aligned} \right\} (2)$$

## Conclusion

The implementation of more follow-up measures, including strict restrictions on people movement, accelerating the treatment of infected individuals, and clinical trials of new drugs would be required and the spread of COVID-19 pandemic will be effectively controlled, which the number of infected individuals will gradually decrease. It was expected that the epidemic would subside in early summer, and disappear gradually towards the late August. If the epidemic situation is not properly controlled, the peak of infected number can be further increased and the peak time will be a little postponed. Current best evidence indicates that the most effective strategy to control the outbreak is the use of social distancing to break the chain of transmission.

## Ethics

The study does not require ethical approval because the meta-analysis is based on published research and the original data are anonymous.

## Conflicts of Interest

The authors declare no conflict of interest.

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