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Estimation of the Basic Reproduction Rate (R_0) of the Novel Coronavirus (COVID-19)

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ABSTRACT

The notorious novel coronavirus has been causing various cases of pneumonia outbreak starting in Wuhan, Hubei province in China and spreading throughout the world. This paper presents a study of the information available on the outbreak, to provide a deeper understanding of the origin, transmission and danger of this newly discovered virus. The basic reproduction rate (R_0) is focused on to understand the transmission pattern of this virus. Results obtained from the studies conducted by various parties have been collected and compared. It is believed that this virus is highly related with the SARS-CoV and MERS-CoV that happened during 2003 and 2012, respectively, hence a lot of preliminary studies are based on these as there is lack of sufficient data specific to COVID-19. Studies reported R_0 within the range of 2-5, indicating that each infected patient will transmit the virus to 2-5 other individuals.

Key Words: Novel Coronavirus, COVID-19, Basic Reproduction Rate, Transmission patterns, Pandemic

INTRODUCTION

According to the Centre for Health Protection of the Hong Kong Special Administrative Region Government, a cluster of several unexplained cases of pneumonia was first introduced on 31st December 2019 by The Health Commission of Hubei province, China[1]. It was reported subsequently that among 41 patients, seven of them were in critical condition while one died[2]. Each patient was said to be geographically linked to this specific Huanan Seafood market that sold game animals such as cats, dogs, snakes and more, according to Juan, a reporter from China Daily[3]. The patients were tested positive for an unfamiliar novel coronavirus. Thereafter, several Chinese scientists isolated and sequenced the genome of the virus[4]. The virus was tentatively named by the World Health Organization (WHO) as the 2019 novel coronavirus (2019-nCoV), and later renamed Coronavirus Disease 2019 (COVID-19).On 11 March 2020, WHO officially declared COVID-19 a pandemic. This study aims to provide comprehensive information on the family of Coronaviruses, known findings of COVID-19 and studies conducted on estimating the basic reproduction rate (R_0) of the COVID-19.

Coronavirus (CoV)

CoVs come from the subfamily Coronavirinae in the family of Coronaviridae, under the order Nidovirales that consists of Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus[5]. A CoV uses single-stranded RNA that has a higher mutation rate compared to DNA viruses, as its genetic material, hence possessing a stronger adaptation ability for survival. As shown in Fig. 1 and briefly described in Table 1[7], the RNA is surrounded by protein spikes (*S*), protein-membrane (*M*), protein envelope (*E*) and nucleocapsid (*N*)[6], which forms a structure in the form of a crown, also known as corona in Latin. It has been noted that some CoVs do not need to have a full ensemble of structural proteins to make virions, hence certain proteins may be dispensable or compensated by the function of non-structural proteins.

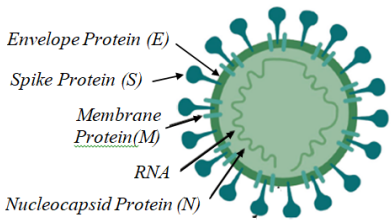

Figure 1: Main structure of coronavirus.

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Table 1: Functions of structural proteins

Structural Protein	Function of Protein
Nucleocapsid Protein(N)	Bound to *RNA* genome to make up nucleocapsid
Spike Protein (S)	Critical for binding of host cell receptors to facilitate entry of host cell
Envelope Protein (E)	Interacts with *M* to form the viral envelope
Membrane Protein (M)	i) Central organiser of CoV assembly ii) Determines the shape of the viral envelope

Transmission of Coronavirus

CoVs mainly infect the respiratory, gastrointestinal, hepatic and central nervous system of livestock, avian, bats, mice and other wild animals[8,9]. However, due to their high recombination and mutation rates, which enables them to bypass species barriers and easily adapt to new hosts, CoVs can also transmitted from animals to humans (zoonotic), which is known as spillover[9]. Before 2019, only six CoVs (HCoV-229E, HCoV-OC43, HCoV-NL63, HKU1, SARS-CoV and MERS-CoV) were known to be able to affect humans and cause respiratory disease[7]. Although most human CoV infections are mild, the epidemics of two Betacoronaviruses, i.e. the Severe Acute Respiratory Syndrome coronavirus(SARS-CoV)[10,11] and the Middle East Respiratory Syndrome coronavirus (MERS-CoV)[12], infected 8,096(SARS-CoV) and 2,519 (MERS-CoV)people respectively, with 10% mortality rate for SARS-CoV and 37% for MERS-CoV[13,14].

Treatment of Coronavirus

Currently, there is no known specific antiviral medication for CoVs. Cinatl et al.[15] tried treating SARS-CoVusing recombined interferons (IFN) with ribavirin but the results were insignificant. It was then later discovered that 6-mercaptopurine (6MP) and 6-thioguanine (6TG) were able to inhibit the papain-like protease (PL^{pro}) of SARS-CoV, which is responsible for viral maturation and interferon stimulation of the host. Immunosuppressive drug mycophenolic acid was also found to be able to inhibit MERS-CoV PL^{pro}, but none of them have been clinically proven[16]. Graham et al.[17] (2013) conducted a study on strategies for controlling CoVs using developed vaccines such as enacted virus vaccines, live-attenuated virus vaccines, viral vector vaccines, subunit vaccines and DNA vaccines. However, these vaccines did not provide promising results as they were only tested on animals. As there is a lack of effective medications, the best way to handleCoVinfections is through intensive medical care, early diagnosis and quarantine, to prevent spreading of the virus.

Coronavirus Disease 2019 (COVID-19)

Based on a study conducted by Huang et al.[18] on 41 patients infected by COVID-19 who were admitted into a designated hospital in Wuhan, patients with symptoms commonly experienced fever (98%), cough (76%) and myalgia (44%) during onset period. Some patients also suffered from sputum production (28%), headache (8%), hemoptysis (5%) and diarrhoea (3%). 22 patients later suffered from dyspnea (difficult breathing) and 26 patients had decreased level of lymphocytes. They also discovered pneumonia with abnormal findings in the chest CT of all 41 patients, including acute respiratory distress syndrome (29%), RNA anaemia (15%), acute cardiac injury (12%) and secondary infection (10%).

Diagnosis

Corman et al.[19] developed two 1-step quantitative real-time reverse-transcription Polymerase Chain Reaction (PCR) assays that target ORF1b and N genome of COVID-19. The primer and probe sets were designed to react with COVID-19 and closely related viruses (e.g. SARS CoV). These PCR-assays were then tested on COVID-19 patients. Positive results were obtained, with the N gene assay found to be 10 times more sensitive in detecting positive clinical specimens.

Risk Parameters

Basic Reproduction Rate (R_0)

R_0 refers to the average number of people who are infected (secondary cases) by a single person (primary case). WHO initially estimated COVID-19 to have an $R_0$of 1.4-2.5 on 23 January 2020. However, after analyzing the epidemic curve of COVID-19 cases times series in China from 10-24 January 2020, Zhao et al. reported a mean $R_0$of 2.24-3.58, which is similar to the$R_0$of SARS: 2-5[20] and MERS-CoV: 2.7-3.9[21]. Several preliminary studies also suggestedR_0 of 2.0-3.3[22], 2.6 with uncertainty range 1.5-3.5[23], 2.92 with 95% confidence interval of (2.28, 3.67)[24], 2.2 with 90% confidence interval of (1.4, 3.8)[25]. A more recent study conducted by Cao et al.[26] indicated a higher $R_0$of 4.08. Based on these research findings, every case of COVID-19 will cause 3-4 new cases.

Case Fatality Rate (CFR)

WHO had initially estimated a fatality rate of 2% during a press conference held on 29 January 2020[27], but Chan et al.[28] later reported a fatality rate of 2.9% based on a study conducted on the 41 patients. However, these estimations may be inaccurate since the epidemic was still on-going at the time of the research. According to a report released by WHO on 4 April 2020[30], there were 1, 051, 635 confirmed cases and 56, 985 deaths reported, resulting in a CFR of 5.41%. Compared to the CFR released by WHO for SARS-CoV and MERS-CoV, COVID-19 is less deadly, as shown in Table 2[30]. However, this does not indicate that COVID-19 is less serious, as the number of confirmed and death cases of COVID-19 is the highest among the three.

Table 2: Comparison of confirmed cases, death cases and CFR of well known CoV epidemics.

CoV	Confirmed Cases	Death Cases	CFR
COVID-19	1051635	56985	5.41% (4/4/2020)
SARS-CoV	8098	774	9.6%
MERS-CoV	2494	858	34.4%

Asymptomatic Transmission

Asymptomatic transmission is the transmission of the virus during the incubation period (time from exposure to an infection and the appearance of the first symptom). During a press conference on 26 January 2020, China's National Health Commission (NHC) reported an initial estimate of the incubation period of 10-14 days. WHO (2020)[29] released a report the next day, estimating the incubation period of 2 to 10 days. The United States' Centers for Disease Control and Prevention (CDC) also estimated an incubation period of 2-14 days. After conducting a study on the first 425 confirmed cases in Wuhan, Li et al.[31] found that COVID-19 could be transmitted between humans even before the first symptom occurs.

Table 3: Comparison of incubation period

Virus	Incubation Period
COVID-19	2-14 days (avg. 5.2 days)
SARS-CoV	2-7 days (up to 10 days)
MERS-CoV	2-14 days (avg. 5 days)

They further reported that the average incubation period was 5.2 days, varying greatly among people, hence suggesting an observation period of 14 days. As shown in Table 3[32,33], the incubation period of the CoVs are generally similar.

Analytical Studies on R_0 of COVID-19

Zhao et al.[34] obtained COVID-19 cases time series data in mainland China released by Wuhan Municipal Health Commission, China and National Health Commission of China from 10-24 January 2020. Cases of infection outside Wuhan due to travel was not included in the analysis. Since the official diagnostic protocol was not released by WHO until 17 January 2020, cases before 16 January 2020 were excluded. To compensate for this problem, a time-varying reporting rate method that follows a linear increasing trend was used[35]. Since 17 January, reporting rate, $\gamma(t)$, is assumed to be increasing and achieved a maximum value on 21 January. The fold change given below was calculated:

$$\gamma(t) = \frac{\gamma(10\,January)}{\gamma(24\,January)} - 1 \qquad (1)$$

Six cases of 0 (no changes), 0.5, 1, 2, 4 and 8-fold changes were computed. An exponential growth epidemic curve, which was adapted by Silva et al.[36] and Zhao et al.[37], was modelled. The data was fitted and the parameter estimated using nonlinear least square (NLS) framework. Due to the unclear COVID-19 transmission chain, the mean of serial interval (SI), k for SARS and MERS was used to estimate moment generation of probability function of SI, denoted as M(.). The R_0 is then computed using the formula:

$$R_0 = \frac{1}{M(-\gamma)} \qquad (2)$$

From 0-fold to 8-folds estimation, R_0 ranged from 2.24 (95% CI: 1.96-2.55) to 5.71 (95% CI: 4.24-7.54). However, the accuracy of R_0 depends on the accuracy of SI of COVID-19, which is still vague at the time of research, hence SI of MERS and SARS are used.

Reported COVID-19 cases were first collected from the WHO, the Chinese National Health Commission, and Wuhan Municipal Health Commission by Majumder and Mandl[22], and a reverse-L shaped curve describing reported cases over time was plotted. Incidence Decay and Exponential Adjustment (IDEA) model, initially proposed by Fishman et al.[38], was then used to anticipate the R_0 of COVID-19 by referring to the cumulative epidemic curve. The IDEA model is defined as (3), where t is the number of SI, I is incidence at serial t and d is the discount factor due to the decrease in affected cases and any public interventions in controlling the virus spreading over time:

$$I = \left[\frac{R_0}{(1+d)^t}\right]^t \qquad (3)$$

With the SI for SARS-CoV and MERS-CoV used to parameterize the model, an estimated R_0 of 2.0-3.1 was obtained using reported cases from 8 December 2019 to 26 January 2020, assuming d to be 0. To ensure the stability of the estimation, truncated input data (8-18 December and 19-26 January) were used and the estimated R_0 ranges were similar.

Cao et al.[25] modelled R, the expected number of secondary cases as $R = R_0 x$, where $x \in (0,1)$ is the proportion of the population susceptible. R was first calculated as $R = K^2(L\,x\,D) + K(L+D) + 1$, where L was the average latent period, D the average latent infectious period, and K the logarithmic growth rate of the case counts. By denoting t as number of days since outbreak (31 December 2019) and $\gamma(t)$ as the number of cases, K is estimated at 6 different time points. However, reported case during 5-20 January 2020 were excluded because of the change on probable cases reporting requirement that led to a significant increase in the number of cases. An estimated R of 4.08 was obtained, which indicates R_0 to be higher than 4.08. To test for sensitivity, different L and D values were generated using the Gaussian distribution and applied into the model, and a mean of 4.08 was still

obtained for R, with standard deviation of 0.36 and 95% CI (3.37, 4.77).

To estimate future outbreak cases, Susceptible Exposed– Infectious – Recovered – Death – Cumulative (SEIRDC), initially proposed by Chowell et al.[39], was used. The SEIRDC can estimate the early reported cases accurately but a better result is obtained by setting the start time earlier than reported. This suggests that human-to-human transmission might have happened earlier than reported. This model predicted CFR of 6.50%. Riou and Althaus[25] conducted stochastic simulations on the first few reported cases of COVID-19 with one index case. Negative-binomial offspring distribution of mean R_0 (initially parameterised from range 0.8-5.0) and dispersion k (estimated range 0.01-10), the measure of super spreading cases (lower k indicates a high probability of super spreading) were used to generate secondary cases. D, the generation time (GT) interval was parameterized to follow gamma 2 distribution, with mean range 7-14 days. Different ranges of parameters were combined and stochastic simulations run on each combination. The proportion of simulations that reached total infected cases within the range 1000-9700 by 18 January 2020, as estimated by Imai et al.[23], was calculated, and R_0 of 2.2 was obtained.

Imai et al.[23] simulated a set of epidemic projections using a mathematical model of COVID-19 transmission and identified projections that resulted in a similar number of outbreak cases as estimated. These estimations were made based on assumptions that the number of new cases caused by each infected individual is highly variable, following negative binomial offspring distribution with parameter k=0.16, adapted from SARS. The second assumption was that the mean GT was also the same as SARS, which was 8.4 days. It is estimated that R_0 ranges from 2.1 to 3.5, and the number of infected cases by 18 January 2020 ranges from 1000 to 9700, with mean of 4000cases.

GT is defined as the time interval between symptom onset of an index case and its secondary case. Due to the lack of information about GT, Liu et al.[24] used the GT for SARS, i.e. 8.4 days with a standard deviation of 3.8 days[40]. The R_0 is expected to be exponentially increasing during the start of an epidemic outbreak[41], hence Poisson regression was used to model the exponential growth rate. Maximum likelihood function was used to calculate R, as given by:

$$LL(R) = \sum_{t=1}^{T} \log\left(\frac{e^{-\mu_t}\mu_t^{N_t}}{N_t!}\right) \quad (4)$$

where, $\mu_t = R\sum_{i=1}^{t} N_{t-1}\omega_i$, N_t is the number of cases with symptoms onset on day t, and ω is the GT distribution. On 23 January 2020, R was 2.90 (95% CI:2.32-3.63) for exponential growth, and 2.92 (95% CI: 2.28-3.67) for maximum likelihood.

Zhou et al.[42] characterized the early spread pattern of COVID-19 by using the susceptible-exposed-infected-removed (SEIR) model. Each individual is classified into susceptible (S), exposed (E, infected individual during the incubation period), infected (I, confirmed cases) and removed (R, recovered patients). At each time step, there is a probability β for a susceptible individual to be exposed after being in contact with an infected individual. An exposed individual will become infected with probability γ_1, and an infected individual will recover at probability γ_2. R_0 is then approximated as $R_0 = 1 + \lambda T_g + \rho(1-\rho)(\lambda T_g)^2$, where $\lambda = \frac{\ln Y(t)}{t}$ ($Y(t)$ is the number of confirmed cases by time t), GT $T_g = \frac{1}{\gamma_1} + \frac{1}{\gamma_2}$ and $\rho = \frac{1}{\gamma_1 T_g}$. Due to the lack of information about GT, Zhou et al. took ρ as 0.65, which is a value that lies in the GT range for SARS (0.5-0.8)[43]. By taking account of extreme cases, the R_0lies in the range 2.3 – 5.2. However, Zhou et al. believed that the actual R_0 should be within the range 2.8-3.9.

CONCLUSION

Results from the studies conducted to estimate the $R_0$are compared in Table 4. As all the estimated R_0lie in the range 2-6, it is expected that every individual with COVID-19 will generate 2 to 6 secondary cases. Studies conducted in the year 2020 by Zhao et al., Majumder and Mandl, Imai, Liu et al. and Zhou et al. rely on parameters obtained from studies conducted on SARS-CoV and MERS-CoV due to their shared family. However, Wu et al.[44] noticed differences in the amino acid sequences of COVID-19 and SARS-CoV. They further explained that the COVID-19 has the closest genome structure to the bat SARS-like CoVs instead of SARS-CoV that evolved, and is more related to MERS-CoV, hence it is not confirmed that SARS-CoV and MERS-CoV can best describe COVID-19. Furthermore, due to the lack of available data at the time of the study, the accuracy and precision of the estimations remain unknown. There are also high chances that many COVID-19 cases are not being reported due to the lack of awareness during the early stage of the outbreak, hence the data may not be fully reliable.

Table 4: Comparison of Estimated R_o

Publications (2020)	Estimated R_o
Zhao et al.	2.24–5.71
Majumder & Mandl	2.0–3.1
Cao et al.	3.37–4.77
Riou and Althaus	2.2
Imai et al.	2.1–3.5
Liu et al.	Exponential Growth: 2.90 Max. Likelihood: 2.92
Zhou et al.	2.8–3.9

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Conflict of Interest

The authors involved in the current study does not declare any competing conflict of interest.

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