ISSN xxxx-xxxx

Volume 3, Issue C-19 June 2020

MES BULLETIN OF APPLIED SCIENCES

SPECIAL ISSUE

NAAC Accredited with 'A' Grade

EXECUTIVE EDITORS

Prof. ACHALA L. NARGUND & Prof. N. M. BUJURKE

Post Graduate Department of Mathematics and
Research Centre in Applied Mathematics
M E S College of Arts, Commerce and Science
15th cross, Malleswaram, Bengaluru - 560003.

MES BULLETIN OF APPLIED SCIENCES

ISSN xxxx-xxxx

Volume 3, Issue C-19 June 2020

MES BULLETIN OF APPLIED SCIENCES

(Working Papers)

EXECUTIVE EDITORS

PROF. ACHALA L. NARGUND & PROF. N. M. BUJURKE

Post Graduate Department of Mathematics and
Research Centre in Applied Mathematics
M E S College of Arts, Commerce and Science
15th cross, Malleswaram, Bengaluru - 560003.

TABLE OF CONTENTS

The Mathematical Theory of Epidemics: A Great Contribution to Society

L.N. Achala
P. G. Department of Mathematics, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: anargund1960@gmail.com

Absract: *In this paper we have given small introduction about COVID-19 and discuss different mathematical models available to study an epidemic disease. We have also reviewed some of the papers dealing with mathematical modelling of the spread of the coronavirus disease. We have discussed in detail SI, SIS, SIR, SISR model equations and method of solution. We have also written brief introduction about corona virus disease spread and few important terminologies involved.*

Keywords: *Mathematical model, SIR model, SIRS model, SEIR model ,SEIHRD model, Pandemic, Epidemic. Outbreak, COVID-19, Corona virus. Quarantiine, Head Immunity*

1 Introduction

An epidemic disease is the one which affects many people at the same time and spreads from person to person in a locality where the disease is not permanently prevalent. According to the World Health Organization (WHO) epidemic is the one occurring at the level of a region or community. *Epidemic* is commonly used as a noun.

A pandemic disease is an epidemic that has spread over a large area, that is, throughout an entire country, continent, or the whole world. *Pandemic* is also used as a noun, meaning "a pandemic disease". The WHO more specifically defines a pandemic as a worldwide spread of a new disease.

WHO officially declared the COVID-19 outbreak a *pandemic* due to the global spread and severity of the disease on 11th March 2020. Thus COVID-19 is both an *epidemic* and *pandemic*, but is also an outbreak. It is so called because of its sudden occurrence or eruption. The other two important terms are quarantine and isolation. People are put in *quarantine* when they are not currently sick, but have been or may have been exposed to a communicable disease. This can help stop the spread of the disease. *Isolation* happens when a person is infected with a communicable disease, and is separated from people who are healthy. This also helps stop the spread of the disease.

In December 2019, a series of viral pneumonia cases emerged in Wuhan, Hubei, China. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named 2019 novel coronavirus (2019-nCoV). Thus far, more than 800 confirmed cases, including in health-care workers, have been identified in Wuhan, and several exported cases have been confirmed in other provinces in China, and in Thailand, Japan, South Korea, and the USA. All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. Data was shared to WHO. By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection. Most of the infected patients

were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). All 41 patients had been exposed to Huanan seafood market. Common symptoms at onset of illness were fever, cough and myalgia or fatigue ; less common symptoms were sputum production, headache, haemoptysis and diarrhoea. All 41 patients had pneumonia with abnormal findings on chest CT. Complications included acute respiratory distress syndrome, RNAaemia, acute cardiac injury and secondary infection. 13 patients were admitted to an ICU and six died.

Since the cause was unknown at the onset of these emerging infections, the diagnosis of pneumonia of unknown cause in Wuhan was based on clinical characteristics, chest imaging, and the ruling out of common bacterial and viral pathogens that cause pneumonia. Suspected patients were isolated using airborne precautions in the designated hospital, Jin Yin-tan Hospital (Wuhan, China), and fit-tested N95 masks and airborne precautions for aerosol-generating procedures were taken. This study was approved by the National Health Commission of China and Ethics Commission of Jin Yin-tan Hospital (KY-2020-01.01). Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Local centres for disease control and prevention collected respiratory, blood, and faeces specimens, then shipped them to designated authoritative laboratories to detect the pathogen (NHC Key Laboratory of Systems Biology of Pathogens and Christophe Merieux Laboratory, Beijing, China). A novel coronavirus, which was named 2019-nCoV, was isolated then from lower respiratory tract specimen and a diagnostic test for this virus was developed soon after that. Of 59 suspected cases, 41 patients were confirmed to be infected with 2019-nCoV.

A coronavirus is a kind of common virus that causes an infection in your nose, sinuses, or upper throat. Most coronaviruses aren't dangerous. In early 2020, after a December 2019 outbreak in China, the World Health Organization identified SARS-CoV-2 as a new type of coronavirus. The outbreak quickly spread around the world.

COVID-19

COVID-19 is a disease caused by SARS-CoV-2 that can trigger a respiratory tract infection. It spreads the sam5me way other corona viruses do, mainly through person-to-person contact. Infections range from mild to deadly. SARS-CoV-2 is one of seven types of corona virus, including the ones that cause severe diseases like Middle East respiratory syndrome (MERS) and sudden acute respiratory syndrome (SARS). The other corona viruses cause most of the colds that affect us during the year but aren't a serious threat for healthy people.

This COVID-19 disease journey starts from corona positive and has 3 stages, first stage is Corona positive, that is corona virus is in the body, second stage is infected, he is now communicable, third is deceased, that is all symptoms are serious, i. e COVID-19. Anyone can get COVID-19, and most infections are usually mild, especially in children and young adults. The risk of getting infected is very low if you aren't in an area where COVID-19 is spreading, haven't travelled from an area where it's spreading and haven't been in contact with someone who has it.

Mathematical Modelling

A mathematical model is a description of a system using mathematical concepts and language. The process of developing a mathematical model is termed mathematical modelling. Mathematical models are used in the natural sciences such as physics, biology, earth science, chemistry, engineering disciplines such as computer science, electrical engineering, and also in the social sciences such as economics, psychology, sociology, political science, etc. A model may help to explain a system and to study the effects of different components, and to make predictions about behaviour.

Differential equations have a remarkable ability to predict the world around us

The ordinary differential equations as used in mathematical modeling, to analyze and understand a variety of real-world problems.Mathematical models are not perfect predictors of what will happen in the real world.They can offer important insights and information about the nature and scope of a problem, and can inform solutions.

Using mathematics to model the spread of diseases is an incredibly important part of preparing for potential new outbreaks. As well as providing information to health workers about the levels of vaccination needed to protect a population. It also helps govern first response actions when new diseases potentially emerge on a large scale. For example, Bird flu, SARS and Ebola have all merited much study over the past few years.

Swine Flu, H1N1 influenza

In 1918, the Spanish flu pandemic, caused by a strain of the H1N1 influenza virus, killed an estimated 50 million deaths worldwide. To commemorate the 100^{th} anniversary of the outbreak – one of the deadliest natural events in human history – the BBC commissioned a documentary and citizen science experiment to simulate the outbreak of a flu pandemic in 2018. 5% of the entire global population at the time. Just ten years ago the H1N1 flu virus, popularly known as swine flu, re-emerged to cause a pandemic, infecting up to 200 million people and causing global concern.

Ebola

The Ebola virus is one of the deadliest human viruses. Infection begins with flu-like symptoms, progressing to vomiting, diarrhoea, a rash and in many cases bleeding internally and from the ears, eyes, nose or mouth. On average, half of those infected with the Ebola virus die from their symptoms. The biggest known outbreak of Ebola virus disease occurred in West Africa in 2014, eventually infecting over 28,000 people. The outbreak inspired a global forecasting challenge, in which several teams submitted forecasts of the outbreak to the US National Institutes of Health, using synthetic data sets under several different scenarios.

2 Mathematical Modelling of Epidemics

Epidemix : It is online disease modelling

The incorporation of mathematical and computational methods into the study of disease processes is now routine. Mathematical models are not just a research tool. They are already used in public health, where they provide answers to vital questions: “How big will the outbreak be?”, “How will it develop over time?” and, perhaps most importantly, “How can we

control it?" However, to many, mathematical models are a black box. This can lead to negative perceptions of models as unrealistic, unhelpful, or confusing, which means they are sometimes disregarded over other, more traditional methods.

There are different models from simple to complex and are all governed by ordinary differential equations. Many parameters are involved in formulating the equations. A very important parameter which helps us to effectively calculate immunity is epidemiological parameter R.

The Epidemiological Parameter or Reproduction number R_0

It is an important parameter which tells us whether a population is at risk from a given disease. The so called *basic reproduction number* (denoted by R_0) is a measure of how transferable is a disease. It is the average number of people that a single infectious person will infect over the course of their infection. This quantity determines whether the infection will spread exponentially, die out, or remain constant:

- If $R_0 > 1$, then each person on average infects more than one other person so the disease will spread
- If $R_0 < 1$, then each person infects fewer than one person on average so the disease will die out
- If $R_0 >= 1$, then each person will infect exactly one other person,
- If an infectious individual contacts β other people per unit time, if all of those people are assumed to contract the disease,
- If the disease has a mean infectious period of $\frac{1}{\gamma}$, then the basic reproduction number is just $R_0 = \frac{\beta}{\gamma}$.
- Some diseases have multiple possible latency periods, in which case the reproduction number for the disease overall is the sum of the reproduction number for each transition time into the disease.
- For example, Blower et al. [1] model two forms of tuberculosis infection: in the fast case, the symptoms show up immediately after exposure; in the slow case, the symptoms develop years after the initial exposure (endogenous reactivation).
- The overall reproduction number is the sum of the two forms of contraction: ${R_0}^{\text{FAST}} + {R_0}^{\text{SLOW}}$.

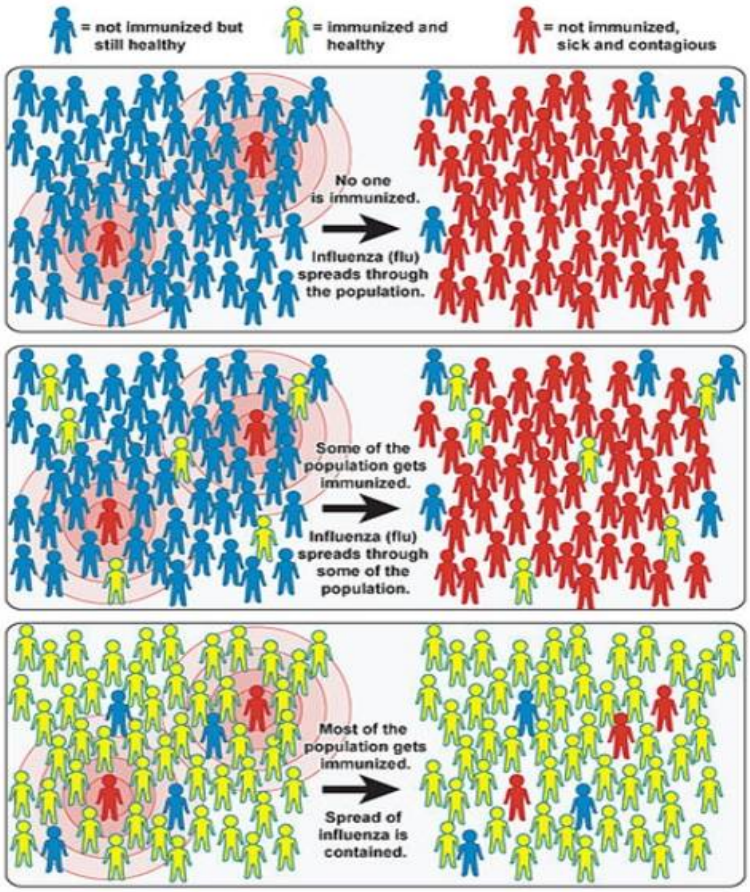
The value of R_0 for some well known diseases	
Disease	**R_0**
AIDS	2 to 5
Small pox	3 to 5
Measles	16 to 18
Malaria	> 100

Mathematics of mass vaccination

- ► If the proportion of the population that is immune exceeds the herd immunity level for the disease, then the disease can no longer persist in the population.
- ► Thus, if this level can be exceeded by vaccination, the disease can be eliminated.
- ► An example of this being successfully achieved worldwide is the global smallpox eradication, with the last wild case in 1977.
- ► The WHO is carrying out a similar vaccination campaign to eradicate polio.

Herd Immunity

Herd Immunity is the one when most of a population is immune to an infectious disease. Measles, mumps, polio, and chickenpox are examples of infectious diseases that were once very common but are now rare in the U.S. because vaccines helped to establish herd immunity. We sometimes see outbreaks of vaccine-preventable diseases in communities with lower vaccine coverage because they don't have herd protection.



- This graphic above shows how herd immunity works.
- In the first scenario no members of the population are immunized, and that leads to nearly all the population becoming ill –
- Though in the third scenario, enough members of the population are immunized to act as buffers against the spread of the infection to non-immunized people.

Other viruses (like the flu) mutate over time, so antibodies from a previous infection provide protection for only a short period of time. For the flu, this is less than a year. If SARS-CoV-2, the virus that causes COVID-19, is like other corona viruses that currently infect humans, we can expect that people who get infected will be immune for months to years, but probably not their entire lives. In the worst case (for example, if we do not perform physical distancing or enact other measures to slow the spread of SARS-CoV-2), the virus can infect this many people in a matter of a few months. This would overwhelm our hospitals and lead to high death rates. In the best case, we maintain current levels of infection — or even reduce these levels — until a vaccine becomes available. This will take concerted effort on the part of the entire population, with some level of continued physical distancing for an extended period, likely a year or longer, before a highly effective vaccine can be developed, tested, and mass produced. The most likely case is somewhere in the middle, where infection rates rise and fall over time;

we may relax social distancing measures when numbers of infections fall, and then may need to re-implement these measures as numbers increase again. Prolonged effort will be required to prevent major outbreaks until a vaccine is developed. Even then, SARS-CoV-2 could still infect children before they can be vaccinated or adults after their immunity wanes. But it is unlikely in the long term to have the explosive spread that we are seeing right now because much of the population will be immune in the future.

The United Kingdom and the Netherlands were the first countries to take herd immunity approach in dealing with COVID-19. However, the World Health Organisation (WHO) has warned that "herd immunity" strategy is experimental at best and dangerous at worst. National health organisations like National Institute of Epidemiology, Indian Council of Medical Research (ICMR) and Public Health Foundation of India (PHFI) have also highlighted that this process could harm a large number of individuals. The UK has now given up on its herd immunity building approach.

When enough of the population is resistant to a germ, its spread stops naturally because not enough people are able to transmit it.

According to Dr. Ambarish Dutta [2], herd immunity can be achieved in two ways. The first way is through mass vaccinations, which for COVID-19, is still under development. The second way is through the infection which means that a person gets infected and after a while, they develop antibodies to fight the infection and thus become immune to it. Since currently, the vaccine for COVID-19 is absent; countries around the globe like, the United Kingdom, the Netherlands, Sweden and Holland are experimenting with the second method.Dr. Dutta pointed out that the effectiveness of herd immunity approach for a country will depend on the structure of the population of that country. He said, In India, the dominating population is of youth. Young people are generally healthier with a stronger immune system than the elderlies. They can fight with the infection and build immunity against it in a much faster way. This is true with any kinds of viral infection.

Elaborating on the phenomenon, Dr. Rakesh Sahay [3], Endocrinologist and Diabetologist, and Professor at Osmania Medical College in Hyderabad, said that there are a large number of people who are asymptomatic – who show no symptoms at all or have just mild symptoms like mild fever, mild cough will recover from the virus without getting hospitalized and it will contribute to increasing the herd immunity. Bhadada [4], Murthy [5], Sahay [6, 7], Karla [8, 9], Unnikrishnan [10] have worked on infectious diseases.

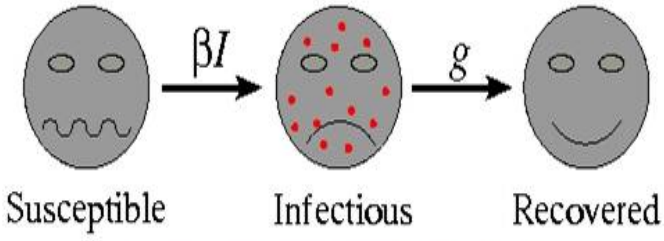
Mathematically, herd immunity is calculated as follows

Let S, is not immune population and q, is immune population. If we consider SI model where everyone is either immune or susceptible. Then $S = 1 - q$ or $q = 1 - \frac{1}{R_0}$.

Remember that this is the threshold level. If the proportion of immune individuals *exceeds* this level due to a mass vaccination programme, the disease will die out. This is also denoted as q_c.

Different Mathematical Models of Epidemic

The Basic Model is SIR Model, Modelling of Infectious Diseases flow is given below



Movement rates between classes of the SIR model

Simple SIR model (One more model is SIRS)

$$\frac{dS}{dt} = -\beta IS$$
$$\frac{dI}{dt} = \beta IS - \nu I$$
$$\frac{dR}{dt} = -\nu I$$

The constants β and ν are chosen depending on the type of disease being modelled. β represents the contact rate – which is how likely someone will get the disease when in contact with someone who is ill. ν is the recovery rate which is how quickly people recover and become immune.

Example: Modelling measles

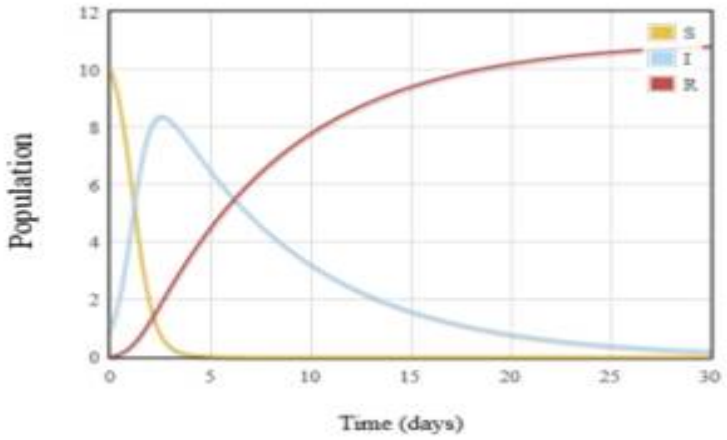
Lets say we have a total population of 11 people – 10 who are susceptible, 1 who is infected and 0 who are immune.

Consider measles, which has an average infection duration as about a week,
Thus $D = 7$, by using equation $D = \frac{1}{\nu}$ we get $\frac{1}{7}$. By table 1 we can choose $R_0 = 15$ and as $R_0 = \frac{\beta}{\nu}$, we get $\beta = 2.14$

Therefore our 3 equations for rates of change become:

$$\frac{dS}{dt} = -2.14IS,$$
$$\frac{dI}{dt} = 2.14IS - 0.14I,$$
$$\frac{dR}{dt} = 0.14I$$

Unfortunately these equations are very difficult to solve – but luckily we can use a computer program to plot what happens. We need to assign starting values for $S, I$and R – the numbers of people susceptible, infectious, recovered (immune) from measles.



This shows that the infection spreads incredibly rapidly – by day 2, 8 people are infected. By day 10 most people are immune but the illness is still in the population, and by day 30 the entire population is immune and the infection has died out.

Complex SIR model with vital parameters

The complex SIR model includes death, birth and infection period parameters and mathematical equations are as follows

$$\frac{dS}{dt} = B - \beta IS - dS,$$
$$\frac{dI}{dt} = \beta IS - dS - gI,$$
$$\frac{dR}{dt} = gI - dR,$$
$$R_0 = \frac{\beta}{g}$$

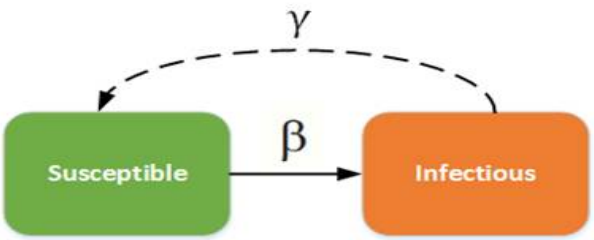
where B is birth rate, d is death rate, $\frac{1}{g}$ is infection period and β is contact rate.

The SI and SIS model

In SI model people never leave infectious state and have lifelong infections. One of the examples is Herpes, which is a viral disease with lifelong infectiousness. The equations are

$$\frac{dS}{dt} = -\frac{\beta IS}{N},$$
$$\frac{dI}{dt} = \beta I\left(1 - \frac{1}{N}\right)$$

where $N = S + I$, and the diagram shows how individuals move through each compartment



The SIRD model

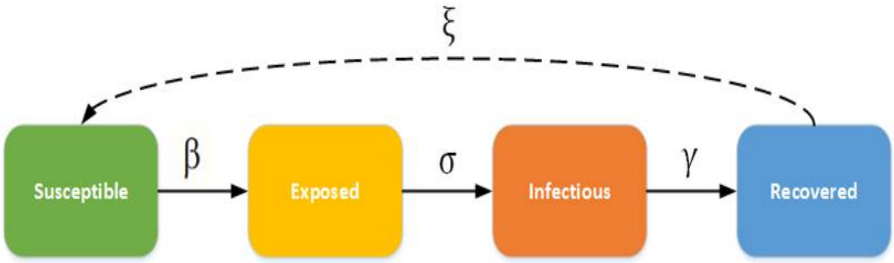
This is susceptible, infected, recovered and deceased model, where recovered means individuals survived from disease and now immune. This model uses the following system of equations:

$$\begin{aligned}\frac{dS}{dt} &= -\frac{\beta IS}{N},\\ \frac{dI}{dt} &= \frac{\beta IS}{N} - \gamma I - \mu I,\\ \frac{dR}{dt} &= \gamma I,\\ \frac{dD}{dt} &= \mu I\end{aligned}$$

where β, μ, γ are rate of infection, recovery and mortality respectively.

The SEIR and SEIRS model

The pictorial representation of these above models are as follow



The governing equations of these models with and without vital dynamics are as follows

$$\begin{aligned}\frac{dS}{dt} &= -\frac{\beta IS}{N},\\ \frac{dE}{dt} &= \frac{\beta IS}{N} - \sigma E,\\ \frac{dI}{dt} &= \sigma E - \gamma I,\\ \frac{dR}{dt} &= \gamma I\end{aligned}$$

where $N = S + E + I + R$ is the total population.

The following graphs drawn by using EMOD software show the inset chart and charts for all channels in a SEIR outbreaks, one with an incubation period of 8 days and one with an incubation period of 2 days. Notice how the outbreak depletes the susceptible population more quickly when the incubation period is shorter but that the cumulative infections remains the same.

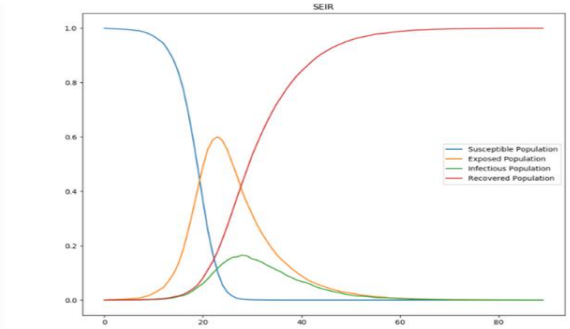


Figure 1: SEIR epidemic course for 8-day incubation period

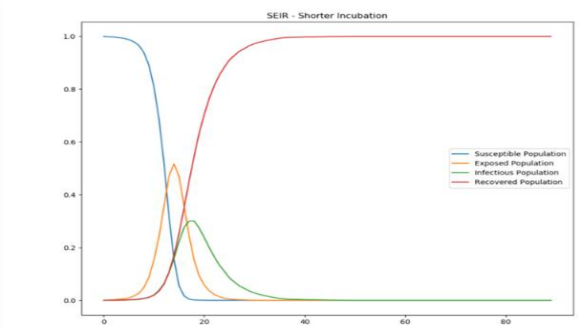


Figure 3: SEIR epidemic course for 2-day incubation period

SEIR with vital dynamics

The vital parameters like death and birth play important role in epidemics because new births provide more susceptible individuals. In such a realistic population disease dynamics reaches steady state where and represent the birth and death rates respectively. The ordinary differential equations representing this situation are

$$\begin{aligned}
\frac{dS}{dt} &= \mu I - \nu S - \frac{\beta IS}{N}, \\
\frac{dE}{dt} &= \frac{\beta IS}{N} - \sigma E - \nu E, \\
\frac{dI}{dt} &= \sigma E - \gamma I - \nu I, \\
\frac{dR}{dt} &= \gamma I - \nu R
\end{aligned}$$

where $N = S + E + I + R$ is the total population.

The SEIRS model

The SEIR model assumes people carry lifelong immunity to a disease upon recovery, but for many diseases the immunity after infection wanes over time. In this case, the SEIRS model is used to allow recovered individuals to return to a susceptible state.

$$\begin{aligned}
\frac{dS}{dt} &= \xi R - \frac{\beta IS}{N}, \\
\frac{dE}{dt} &= \frac{\beta IS}{N} - \sigma E, \\
\frac{dI}{dt} &= \sigma E - \gamma I, \\
\frac{dR}{dt} &= \gamma I - \xi R
\end{aligned}$$

where $N = S + E + I + R$ is the total population.

The SEIRS with vital dynamics

This equations for this model are

$$\frac{dS}{dt} = \mu N - \xi R \nu S - \frac{\beta IS}{N},$$

$$\frac{dE}{dt} = \frac{\beta IS}{N} - \sigma E - \nu E,$$
$$\frac{dI}{dt} = \sigma E - \gamma I - \nu I,$$
$$\frac{dR}{dt} = \gamma I - \xi R - \nu R$$

where $N = S + E + I + R$ is the total population.

The Epidemiological MODeling software (EMOD)

- EMOD helps to determine the combination of health policies and intervention strategies that can lead to disease eradication.
- EMOD calculates how diseases may spread in particular areas and is used to analyze the effects of current and future health policies and intervention strategies.
- EMOD supports infectious disease campaign planning, data gathering, new product development, and policy decisions.
- EMOD helps determine the combination of health policies and intervention strategies that can lead to disease eradication.
- EMOD calculates how diseases may spread in particular areas and is used to analyze the effects of current and future health policies and intervention strategies.
- It supports infectious disease campaign planning, data gathering, new product development, and policy decisions.

The major challenges faced by mathematicians trying to model a pandemic

The mathematical modelling of pandemic is a herculean task the deeper we understand the data the better we can build accurate models. Sometimes very little data is sufficient to build models, but in such cases, the predictions may have a wider range of windows within which we may fail to predict true case.

Rao et al. [11], have extensively studied mathematical modelling of epidemics. S. Rao and Krantz [3] have been trying to mathematically ascertain the number of unreported cases of Covid-19 in many countries, including China, Italy, Spain and the US, where the infection wreaked havoc. They visualised the disparities between reported cases and what they projected using what is called a Meyer wavelet. The higher the wave, the higher the under-reporting; lowering the wave means improved reporting. Accordingly, they projected that the number of cases reported in China was anywhere between 1 in 149 and 1 in 1,104, whereas that in Spain was 1 in 53. In South Korea and Italy 1 in 4 cases come to the fore while in Germany and in the US they detected 1 out of 3 and 2 out of 3 cases, respectively.

Rao and Krantz et al. [11] projected India may also be detecting 1 out of 4. Rao had earlier developed mathematical models to understand the spread of HIV, avian flu and swine flu in India. He also express that though there are many groups trying to mathematically model the pandemic. But the projections may not agree with one another because either two models might have expressed it differently with different variables or applied a different set of parameters, or it could be both.

The true magnitude of epidemic will not be clear till we conduct testing for the whole population. Arni [12] have studied several countries' data because the wave in each country could be different and the speed of the spread could be different based on the composition of the population and behaviors. The wavelets we have drawn for each country demonstrated these differences.

3 Results and Discussions

The steps taken by the Central and State Governments and Indian Council of Medical Research (ICMR) were in the right direction. People have to cooperate with the guidelines, and they are doing it to a large extend. If the spread among 60+ is somehow controlled — especially those who have prior medical conditions like hypertension, cardiovascular, lung diseases and diabetes — a large number of ICU admissions can be avoided. This will also reduce a large number of deaths. The youth may not see that many hospitalizations but they could be carriers to their elders in their homes if proper precautions are ignored.

The testing strategy by ICMR is in the correct direction because unnecessarily increasing the number tested randomly will have no gains if ICMR has pieces of evidence that they are predominantly negative people. Statistically, it is good to show that the positivity rate is low by testing many, but that could lead to a waste of resources. However, the advantage of large scale random testing is that it could catch people who are asymptomatic. But in any large country like India, it is not easy to conduct random testing in such a short time.

We have to search some positive results in each modelling they are Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus which is not deadly.Most people who fall sick with COVID-19 will experience mild to moderate symptoms and recover without special treatment.

The virus that causes COVID-19 is mainly transmitted through droplets generated when an infected person coughs, sneezes, or exhales. These droplets are too heavy to hang in the air, and quickly fall on floors or surfaces. We can be infected by breathing in the virus if we are within close proximity of someone who has COVID-19, or by touching a contaminated surface and then our eyes, nose or mouth.

4 Conclusions

India is in the early stage of the COVID-19 epidemic, with a lower growth rate than other countries studied. Our mathematical model shows that, unchecked, the epidemic is likely to cross 3 million cases by 25 May 2020 and overwhelm the available healthcare resources.

References

[1] R.K. Sahay and V.S. Nagesh, *Hypothyroidism in pregnancy*, Indian J. Endocr. Metab. 16(3) (2012) 364.

[2] A. Datta, *Effect of caste on health, independent of economic disparity: Evidence from school children of two rural districts of India*, Sociology of health & illness, Published online 2015 Nov 11. doi: 10.1136/bmjopen-2015-008608,PMCID: PMC4679837

[3] R.K. Sahay and V.S. Nagesh, *Hypothyroidism in pregnancy*, Indian J. Endocr. Metab. 16(3) (2012) 364-370.

[4] S.K. Bhadada, R.K. Sahay, V.P. Jyotsna and J.K. Agrawal, *Diabetic Neuropathy: Current Concepts*, J. Indian Acad. Clin. Med. 2(4) (2001) 305-18.

[5] G.L. Murthy, R.K. Sahay, V.R. Srinivasan, A.C. Upadhaya and V. Shantaram, *Clinical profile of falciparum malaria in a tertiary care hospital*, J. Indian Med. Assoc. 98(4) (2000) 160-2, 169.

[6] M. Sahay and R. Sahay, *Rickets–vitamin D deficiency and dependency*, Indian J. Endocr. Metab. 16(2) (2012) 164.

[7] M. Sahay and R. Sahay, *Hyponatremia: A practical approach*, Indian J. Endocr. Metab. 18(6) (2014) 760.

[8] S. Kalra, G.R. Sridhar, Y.P.S. Balhara, R.K. Sahay, G. Bantwal and M.P. Baruah, *National recommendations: Psychosocial management of diabetes in India*, Indian J. Endocr. Metab. 17(3) (2013) 376.

[9] S. Kalra, M. Vithalani, G. Gulati, C.M. Kulkarni, Y. Kadam and J. Pallivathukkal, *Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT)*, J. Assoc. Physicians India 61(7) (2013) 448-53.

[10] A.G. Unnikrishnan, S. Kalra, R.K. Sahay, G. Bantwal, M. John and N. Tewari, *Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India*, Indian J. Endocr. Metab. 17(4)(2013) 647.

[11] S.G. Krantz and A.S.R.A. Rao, *Level of underreporting including underdiagnosis before the first peak of COVID-19 in various countries: Preliminary retrospective results based on wavelets and deterministic modeling*, Infect. Cont. Hosp. Ep. 41(7) (2020).

[12] A.S. Rao and Krantz, *Model-based retrospective estimates for COVID-19 or coronavirus in India: continued efforts required to contain the virus spread*, Curr. Sci. 118(7) (2020).

[13] S. Samal, P. Panigrahi and A. Dutta, *Social epidemiology of excess weight and central adiposity in older Indians: analysis of Study on global AGEing and adult health (SAGE)*, Europe PMC 5(11) (2015).

Virus Family

L.N. Achala
P. G. Department of Mathematics, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: anargund1960@gmail.com

The following are the other viruses the world has seen so far

- 1886 – 1898: Demonstration of "filterable agent" infectivity, for Tobacco mosaic virus and Foot and mouth disease virus
- 1901: The first human virus described was the agent which causes yellow fever
- 1902 – 1906: Rinderpest, Vaccinia, Rabies and Cassava mosaic all shown to be filterable viruses
- 1908 – 1911: Avian leukosis and poliomyelitis and chicken sarcomas shown to be caused by viruses
- 1915 – 1917: Bacterial viruses discovered
- 1918-1922: The Spanish Flu kills more than 50 million people
- 1934 – 1936: Bacteriophage consists of equal amounts of protein and DNA – the first proof that viruses are nucleoprotein
- 1935-1937: TMV crystallised, shown to be a nucleoprotein too
- 1936: "Pock assays" on chorioallantoic membranes of eggs for influenza and other viruses
- 1939: "One step growth curve" experiment for phages shows they multiply inside cells
- 1949: The most important development for the study of animal viruses was the growing of poliovirus in cell culture
- 1952: Hershey-Chase experiment shows DNA is the genetic material of phages
- 1952 – 1954: mammalian cell monolayer cultures demonstrate "one virus, one plaque" principle for animal viruses. Measles and adenoviruses discovered using cell culture.
- 1950 – 1963: development of killed (by 1954) and live (1963) polio virus vaccines, credited to Jonas Salk and Albert Sabin respectively
- 1955 – 1958: proof that viral RNA from TMV was the infectious component of the virus and that chemically-induced mutations in it affected the viral phenotype
- 1958: proof that the ssRNA genome of poliovirus was infectious
- 1953 – 1964: discovery of reoviruses, and proof that their genomes not only consisted of dsRNA, but were also segmented
- 1962: proof that ssRNA from TMV and coliphage f2 could be translated into viral proteins in a cell-free bacterial extract

- ✠ 1965 – 1967: in vitro synthesis of both ssRNA (Qbeta) and ssDNA (PhiX174) bacteriophage genomes
- ✠ 1967 – 1971: discovery and characterisation of infectious naked RNA viroids – shown to be circular ssRNA by 1976
- ✠ 1970: proof that RNA tumour virus particles (=retroviruses) contained RNA-dependent DNA polymerase activity that converted viral ssRNA into dsDNA
- ✠ 1972 – 1976: complete sequencing of the genome of ssRNA MS2 coliphage: "... "the first living organism for which the entire primary chemical structure has been elucidated"
- ✠ 1977: complete sequencing of the genome of PhiX174 coliphage: the first complete genome sequenced for any DNA-containing organism
- ✠ 1977: proof of RNA splicing in adenovirus transcripts: later found to common in eukaryotes but not prokaryotes
- ✠ 1978: complete genome sequence of SV40 polyomavirus: first proof of RNA splicing for an entire genome and of extensive overlapping ORFs
- ✠ Sequencing of the first viroid genome – the first RNA ever sequenced using cDNA generated by retroviral reverse transcriptase and first complete structure for any pathogen
- ✠ 1979 – 1980: complete genome sequences of hepatitis B and cauliflower mosaic viruses, both shown to be pararetroviruses in 1983
- ✠ 1981: cDNA cloning and complete genome sequencing of poliovirus type 1, and proof that transfected cloned DNA transcribed RNA that was infectious in monkey cells
- ✠ 1982: complete genome sequencing of Tobacco mosaic virus
- ✠ 1986 – 1989: complete structural determination of TMV virions, including of the encapsidated RNA
- ✠ 2000: HIV/Aids
- ✠ 2003: SARS ,Nipah
- ✠ 2009: H1N1
- ✠ 2014: Ebola :The biggest known outbreak of Ebola virus disease occurred in West Africa in 2014, eventually infecting over 28,000 people.
- ✠ 2016: Zika
- ✠ 2019: Corona

An Epidemiological Study of COVID-19

P.K. Choudhary[1] and S.D. Thangam[2]
[1,2]Department of Zoology, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: [1]1975.pankaj@gmail.com and [2]devithangam9@gmail.com

Absract: *The world had come to standstill in March-April 2020 due to rapid spread of COVID-19. The disease has been identified to be caused by a virus of zoonotic origin. No one had any prior knowledge about this virus, so the entire medical fraternity was occupied in containing the disease and minimizing possible deaths. Over the last four months, there had been some headways into the pathogenesis of the coronavirus. Subsequently, efforts are now being made to gain more information on this disease. This article focuses on the interpretation of initial epidemiological data available so far. As the data indicates, we need to maximize our efforts on disease-control measures by wearing face masks and maintaining social distance. We also need to integrate our efforts being made worldwide on finding out a possible cure and vaccine. Additionally, robust data is required to gain more insight into the epidemiological effects of COVID-19.*

Keywords: *Zoonotic, COVID-19, Coronavirus, Epidemiology, Survey.*

1 Introduction

COVID-19 is the return of a very old and familiar enemy of human race - an infectious disease. History tells us that nothing has killed more human beings than microorganisms (viruses, bacteria, parasites). No natural disaster like volcanoes, floods, earthquakes, drought, etc., has ever caused so many casualties as infectious diseases [1]. COVID-19 has rapidly spread from its origin in Wuhan city of Hubei province of China to the rest of the world. To this date, more than 20 million people have been infected throughout the world, and the number is still increasing.

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses that have diameter ranging between 60 nanometers to 140 nanometers, with spike-like projections on its surface giving it a crown-like appearance under electron microscope, hence the name coronavirus [2]. They belong to two subfamilies - Coronavirinae and Torovirinae - in the family of Coronaviridae [3]. These viruses were first discovered in the 1960s, and can be further classified into four main genera:

1. Alphacoronavirus
2. Betacoronavirus
3. Gammacoronavirus
4. Deltacoronavirus

This classification is based on their phylogenetic relationship and genomic structures. Among those four genera, alphacoronaviruses and betacoronaviruses primarily cause respiratory and intestinal infections in mammals, whereas gammacoronaviruses and deltacoronaviruses mainly infect birds. Currently, there are seven strains of coronaviruses that are known to infect humans, viz., SARS-CoV-2, HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV and MERS-CoV [4]. Domestic or wild animals could have important roles as zoonotic reservoirs

that enable virus transmission to humans. On the basis of current sequence databases, the origins of SARS-CoV, SARS-CoV-2, MERS CoV, HCoV-NL63 and HCoV-229E are thought to be bats; whereas HCoV-OC43 and HCoV-HKU1 probably originated from rodents [5]. Although most coronavirus infections cause only mild respiratory symptoms, infection with SARS-CoV, SARS-CoV-2 and MERS-CoV can be lethal.

2 Origin and Spread of COVID-19

SARS-CoV first appeared in southern China and quickly spread around the world between 2002-03. This virus was identified as the causative agent of the global pandemic SARS which led to substantial morbidity and mortality. A decade later, an outbreak of MERS-CoV emerged in 2012. Most people with MERS had no previous contact with bats, leading to the identification of camels as an intermediate host. Patients with SARS or MERS present with a variety of clinical features ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory distress syndrome (ARDS) with extra-pulmonary complications. SARS-CoV-2 belongs to the genus of Betacoronavirus, and on the basis of evolutionary analysis, is most similar to the SARS-like coronavirus from the Chinese horseshoe bat, with a nucleic acid homology of 84 per cent. It has also 78 per cent similarity with SARS-CoV and 50 per cent with MERS-CoV at the nucleic acid level. Several reports later suggested that snakes, mink and pangolins could be intermediate hosts, based on codon preference and viral infection patterns [2].

At the onset of the COVID-19 pandemic, the main symptoms were fever (98 per cent), cough (76 per cent) and myalgia or fatigue (44 per cent). About half of the patients developed breathing difficulties in one week, and the severely ill patients soon developed ARDS, acute cardiac injury, secondary infections or a combination thereof. The diagnosis of the disease mainly depends on SARS-CoV-2 RNA detection in the nasopharyngeal swab by real-time polymerase chain reaction (RT-PCR), epidemiological history, clinical manifestations and lung imaging.

There have been two events in the past two decades wherein crossover of animal betacoronaviruses to humans has resulted in severe disease. The first such instance was in 2002-03, when a new coronavirus of the genus betacoronavirus, with origin in bats, crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus was designated as severe acute respiratory syndrome coronavirus (SARS-CoV). It affected 8422 people, mostly in China and Hong Kong, and caused 916 deaths (mortality rate 11%) before being contained [6]. Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with one-humped dromedary camels as the intermediate host. It affected 2494 people and caused 858 deaths (mortality rate 34%). Approximately seven years later, in December 2019, adults in Wuhan, the capital city of Hubei province and a major transportation hub in China, started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31, 2019, China notified the outbreak to the World Health Organization (WHO), and on January 1, 2020, the Huanan seafood market was closed. On January 7, 2020, the virus was identified as a coronavirus that

had greater than 95% homology with the bat coronavirus and greater than 70% similarity with the SARS-CoV. Environmental samples from the Huanan seafood market also tested positive, signifying that the virus originated from there [7]. The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring [8]. The first fatal case as well as seven cases outside mainland China was reported on January 11, 2020 and within months was spread to different continents except Antarctica [9]. Massive migration of Chinese people during Chinese new year celebrations would have aggravated the epidemic. Cases in other provinces of China and countries like Thailand, Japan and South Korea in quick succession were reported in people who were returning from Wuhan. Transmission to healthcare workers was reported on January 20, 2020. By January 23, 2020, the 11 million population of Wuhan was placed under lockdown with restrictions of entry and exit from the region. Soon, this lockdown was extended to other cities of Hubei province. Cases were also reported in countries with no recent history of travel to China suggesting that local human-to-human transmission was occurring in these countries [10]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon, it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India, who evacuated their citizens from Wuhan through special flights or had travelers returning from China, placed all people, symptomatic or otherwise, in isolation for 14 days and tested them for the virus.

Cases continued to increase exponentially, and modeling studies reported an epidemic doubling time of 1.8 days [11]. In fact, on February 12, 2020, China changed its definition of confirmed cases to include patients with negative/pending molecular tests but with clinical, radiologic and epidemiologic features of COVID-19, leading to an increase in cases by 15,000 in a single day [12]. It is important to note that while the number of new cases has reduced in China lately, they have increased exponentially in other countries. India, which had reported only 3 cases till March 2, 2020, has also seen a sudden spurt in cases. By March 5th, 29 cases had been reported; mostly in Delhi, Jaipur and Agra, Andhra Pradesh and Tamil Nadu [13] in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined. These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to human is uncertain. Pangolins and snakes are the current suspects [2].

3 Epidemiology and Pathogenesis

Epidemiology is the study and analysis of the distribution, patterns and determinants of health and disease conditions in defined populations. It is a cornerstone of public health, and shapes policy decisions and evidence-based practice by identifying risk factors for disease and targets for preventive healthcare [14]. All age groups are susceptible to COVID-19 infection. It is transmitted through large droplets generated during coughing and sneezing by symptomatic patients. It can also occur from asymptomatic people and before onset of symptoms [10]. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people [15]. People can be

infectious for as long as the symptoms last, and even on clinical recovery. The infected droplets can spread up to 1-2 meters and deposit on surfaces. The virus can remain viable on surfaces for many days in favourable atmospheric conditions, but is destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide, etc. [16]. The favourable atmospheric condition for this virus is 22-25 degree Celsius and relative humidity of 40-50 per cent, that is, typical air-conditioned environments. But its viability is rapidly lost at higher temperatures (above 38 degree Celsius) and higher relative humidity (above 95 per cent). The better stability of SARS corona virus at low temperature and low humidity environment may facilitate its transmission in community in subtropical areas (such as Hong Kong) during the spring season and in air-conditioned environments. It may also explain why some Asian countries in tropical areas (such as Malaysia, Indonesia or Thailand) with high temperature and high relative humidity environment did not have major community outbreaks of SARS [17].

Infection is acquired either by inhalation of the droplets or touching contaminated surfaces and then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/feco-oral route is also hypothesized [12]. As per current information, transplacental transmission from pregnant women to their fetuses has not been noticed; however, neonatal disease due to postnatal transmission has been described [18]. The incubation period varies from 2-14 days (median 5 days). Studies have identified angiotensin converting enzyme receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa. The basic case reproduction rate (BCR) is estimated to range from 2.0 to 6.47 in various modeling studies [19]. In comparison, the BCR of SARS and pandemic flu H1N1 2009 was 2 and 1.3 respectively.

The WHO has identified and suggested areas for research in COVID-19 epidemiology. India, a south-east Asian country, recorded its first COVID-19 case on January 30, 2020 from Thirssur, Kerala a student returning from Wuhan, China [20] By the second week of April it had spread to all the parts of India except Sikkim [9] and on 23rd April India reported about a total of 23,040 cases of which 20,590 cases (89. 4%) was reported from 10 states viz., Maharashtra, Gujarat, Delhi, Rajasthan, Madhya Pradesh, Tamil Nadu, Uttar Pradesh, Telangana, Andhra Pradesh and West Bengal [21]. As on May 4, 2020, a total of 42,533 cases and 1373 deaths have been reported in the country. In the first case study of Maharashtra, of the 168,374 tests performed till May 3, 2020, from 41 sentinel sites, 12,296 (7.3 per cent) patients were found positive for COVID-19. A total of 134 (1.2 per cent) patients were critically ill and 521 (4.7 per cent) patients were deceased [22] and by mid-May total counts raised to 82087 positive cases and 2648 deaths [23]. Though a higher case fatality rate (CFR) has been reported in males (4.8 per cent) compared to females (4.0 per cent), no significant association was found between gender and mortality. The age-specific mortality rate was also high among patients aged 61-70 years (19.2 per cent), 71-80 years (15.8 per cent) and 80 years and older (13.9 per cent). In the second case study of New Delhi, of the 21 cases, 9 (42.9 per cent) were asymptomatic and 6 (28.6 per cent) had comorbidities, most commonly hypertension (23.8 per cent) and diabetes mellitus (14.2 per cent). Of the symptomatic patients, fever and cough (42.9 per cent), sore throat (23.8 per cent), headache (13.6 per cent) and breathlessness (4.8 per cent) were the common clinical presentations. No death was reported in this study [22].

Data from the WHO website on COVID-19 situation reports were extracted from January 21, 2020, up until March 14, 2020. The total number of COVID-19 cases was 1,56,622 spread across 154 countries worldwide. China, Italy and Iran were the countries with the highest num-

ber of cases with a total of 80,849, 21,157 and 12,792 cases respectively. A total of 5,845 deaths from 47 different countries have been registered from COVID-19. The most affected country was China with 3,199 deaths followed by Italy with 1,411 deaths and Iran with 611 deaths. A total of 75,943 patients had recovered worldwide as on March 14, 2020. The country with the most resolved cases was China with 66,916 followed by Iran with 4,339 cases and Italy with 1,966 cases. The analysis shows a significant increase in the number of new COVID-19 cases worldwide from 0.074 cases per million persons at day 1 (January 22, 2020) to 1.81 cases per million persons at day 22 (February 13, 2020). A significant decrease then occurred between day 22 and day 33 (February 24, 2020) from 1.81 cases per million persons to 0.071 cases per million persons. This was followed by a significant increase up until day 53 (March 14, 2020) to 1.429 cases per million persons. The cured percentage in China continuously increased from 56.82 per cent on February 2, 2020, to 95.44 per cent on March 14, 2020. The death percentage among the resolved cases has continuously decreased from 43.18 per cent to 4.56 per cent. In Italy, the percentage of deaths among resolved cases continuously increased to 84.62 per cent on February 25, 2020. It then decreased temporarily to 38.59 per cent on March 10, 2020, and again reached a value of 44.3 per cent on March 14, 2020. In Iran, the percentage of deaths among resolved cases was 100 per cent between February 19, 2020, and February 22, 2020. It dropped continuously to a minimum of 12.34 per cent on March 14, 2020, coupled with a rise in the percentage of cured cases that reached 87.66 per cent. The total 5,845 deaths as of March 14, 2020, equate to around 3.5 per cent of all infected cases. This is relatively better than the rates of previous SARS-CoV and MERS-CoV, which reached 10 per cent and 35 per cent respectively [14].

3.1 Severity of the pandemic

According to Mazumder et. al. 2020 after SARS-CoV-2 set foot in India, the Indian Government took a number of steps to limit the spread of disease in the country. This study involved assessing how the disease affected the population in the initial days of the epidemic. Data was collected from government-controlled and crowd-sourced websites and then put through analysis and calculations. With a study on age and sex parameters of 413 patients, the median age of the affected individuals was found out to be 36 years, with 20-39 years males being the most affected group. The number of affected males (66.34 per cent) was more than that of the females (33.66 per cent). The role of public health interventions was assessed which proved that the interventions were effective for a little while, but the effect reduced due to violations. In study cohorts of Wuhan, the median age of affected patients ranged from 49-56 years. Thus, there are more people affected at a lower age in India when compared to China. This observation can be explained by the population distribution of India. According to the population demographics in India for 2020, there are more people in the younger age group and very few people in the above 80 years age group. Interestingly, according to this analysis, males in the 20-39 years age group are more affected than even in the 60-79 years age group or above 80 years age group males. This is something that had not been reported earlier, and it has to be seen whether this changes as the number of cases in India grows. Also, the mortality rate due to the disease was found to be lower as compared to other countries. The mean age of the deceased males and females implies male patients of younger age have higher risk of death than females of similar age. The explanation for a lower mortality rate could also be the universal immunization policy against tuberculosis (BCG vaccine). The government interventions in China of quarantine regulations, social distancing and isolation of infections have encourag-

ing results for other countries. Therefore, India should try to replicate this before community transmission starts by strict enforcement of lockdown measures, even at the cost of economic impact of COVID-19. It is encouraging to say that Indian government's timely decision to put a countrywide lockdown into place when the number of cases was documented to be only 415, and effective contact tracing definitely helped to prevent Italy/USA-like situation. However, in the context of violations of the lockdown, more data is awaited [24].

The results of two recent seroprevalence surveys in Delhi and Mumbai provide intriguing insights into COVID-19 in India. Both surveys measured how many people had developed immunoglobulin G (IgG) antibodies to the novel coronavirus. In Delhi, 22,823 random blood samples were tested from people of different age groups and demographics [25]. By early July, 23 per cent of those surveyed had developed IgG antibodies. In Mumbai, 6,936 people from three wards were tested. By around the same time, 57 per cent of those surveyed in slums and 16 per cent in non-slum areas had developed these antibodies. Assuming that about 40 per cent of Mumbai's population resides in slums, this would imply a city-wide seroprevalence of roughly 33 per cent by the time of the survey. From an international perspective, London and New York city reported estimated seroprevalences of 17.5 per cent and 23 per cent respectively in late April, when the epidemics in these two cities were winding down. These numbers will have grown subsequently, but not dramatically.

But when it comes to COVID-19 deaths, it appears that Delhi and Mumbai have not been hit so hard. Both Delhi and New York recorded about 23 per cent seroprevalence, amounting to about 1.9 million infections in New York and about 4.4 million in Delhi. The notable difference is that New York had 15,000 fatalities while Delhi had only about 3,200 fatalities, shortly after their surveys. At face value, COVID-19 appears to have been 10 times deadlier in New York than in Delhi. On the other side, both London and Mumbai recorded about 5,500 COVID-19 deaths shortly after their seroprevalence surveys. The difference this time is that London's deaths occurred among an estimated 1.6 million infected people while Mumbai's deaths were among an estimated 4.5 million infected people. At face value, COVID-19 appears to have been 3 times deadlier in London than in Mumbai. The seroprevalence data from Delhi and Mumbai provides valuable pieces of information but needs to be interpreted with care. It indicates rapid spread of COVID-19 in cities, particularly in areas with poor housing, and casts doubts on feel-good stories about the successful control of the disease in urban slums [26].

4 Conclusion

COVID-19 has put forth a serious challenge for public health infrastructure in all countries. It is noteworthy that the developed countries where there were better public health facilities, have recorded higher death rates. This directly implies that we need to review our existing public health infrastructure in those countries. More robust data will tell what will be the impact of COVID-19 on our lives. Additionally, future outbreaks of viruses and pathogens of zoonotic origin are likely to continue. We seriously need to rethink on our strategies to tackle such pandemics. Apart from curbing such outbreaks, efforts should be made to find out comprehensive integrated measures to prevent future outbreaks of zoonotic origin.

References

[1] B. Walsh, *COVID-19: The history of pandemics*, (2020) https://www.bbc.com/future/article/20200325-covid-19-the-history-of-pandemics.

[2] T. Singhal, *A review of Coronavirus disease-2019 (COVID-19)*, The Indian Journal of Pediatrics (2020) 87(4) 281-286.

[3] J. Zhong, J. Tang, C. Ye and L. Dong, *The immunology of COVID-19: Is immune modulation an option for treatment?*, Lancet Rheumatology 2(7) (2020) E428-E436.

[4] F. Li, *Structure, function, and evolution of Coronavirus spike proteins*, Annual Review of Virology 3 (2016) 327-361.

[5] M. Corman, M. Doreen, N. Daniela and D. Christian, *Hosts and sources of endemic human Coronaviruses*, Advances in Virus Research 100 (2018) 163-188.

[6] Namita, S. Chitra and K. Vivek ,*Covid 19 pandemic: Impact on masses and prevention knowhow*, Int. J. Medical and Health Research 6(9) (2020) 09-12.

[7] Xinhua, *China's CDC detects a large number of new coronaviruses in the South China seafood market in Wuhan*, https//:www.xinhuanet.com/2020-01/27/c_1125504355.html.

[8] C. Huang, Y. Wang, X. Li et. al. *Clinical features of patients infected with 2019 with novel coronavirus in Wuhan, China*, Lancet 395 (2020) 395-406.

[9] Choudhary, D. Sudipta and Oommen, Anu Mary, *Epidemiology of COVID-19* J. Digestive Endoscopy 11(1) (2020) 3–7.

[10] C. Rothe, M. Schunk, P. Sothmann, G. Bretzel, et. al. *Transmission of 2019n-CoV infection from an asymptomatic contact in Germany*, The New England Journal of Medicine (2020) https://doi.org/10.1056/NEJMc2001468.

[11] Q. Li, X. Guan, P. Wu, X. Wang, et al. *Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia*, The New England Journal of Medicine (2020) https://doi.org/10.1056/NEJMoa2001316.

[12] World Health Organization. Situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/ situation-reports

[13] R. Laxminarayan, B. Wahl, S.R. Dudala, K. Gopal, C. Mohan, et. al. *Epidemiology and transmission dynamics of COVID 19 in two Indian states* (2020) medRxiv preprint doi: https://doi.org/10.1101/2020.07.14.20153643

[14] H.H. Khachfe, M. Chahrour, J. Sammouri, H. Salhab, B.E. Makki and M. Fares, *An Epidemiological Study on COVID-19: A Rapidly spreading disease*, Cureus 12(3) (2020) e7313.

[15] L. Zou, F. Ruan, M. Huang, L. Liang, et al. *SARS-CoV-2 viral load in upper respiratory specimens of infected patients*, The New England Journal of Medicine (2020) https://doi.org/10.1056/NEJMc2001737

[16] G. Kampf, D. Todt, S. Pfaender, E. Steinmann, *Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents*, J. Hospital Infection (2020) pii: S0195–6701(20)30046–3

[17] K.H. Chan, J.S. Malik Peiris, S.Y. Lam, L.L.M. Poon, K.Y. Yuen and W.H. Seto, *The Effects of Temperature and Relative Humidity on the Viability of the SARS Coronavirus*, Advanced Virology (2011) 1-7.

[18] H. Chen, J. Guo, C. Wang, F. Luo et al., *Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records*, Lancet 395 (10226) (2020) 809-815.

[19] Z.J. Chen and J. Shan, *Novel coronavirus: Where we are and what we know*, Infection

2020 1–9.

[20] S.S. Chakrabarti, U. Kaur, A. Banerjee, Ganguly, Upasana, et al. *COVID-19 in India: Are biological and environmental factors helping to stem the incidence and severity?* Aging and Disease 11(3) (2020) 480-488.

[21] A. Mitra, A.P. Pakhare, A. Roy and A. Joshi (2020) *Impact of COVID-19 epidemic curtailment strategies in selected Indian states: an analysis by reproduction number and doubling time with incidence modelling*, medRxiv preprint doi: https://doi.org/10.1101/2020.05.10.20094946

[22] Gandhi, P Aravind and Kathirvel, Soundappan.*Epidemiological studies on coronavirus disease 2019 pandemic in India: Too little and too late*. Med. J. Armed Forces India, 76(3), p 364-365.

[23] T. Sardar, S.S.K. Nadim, R. Sourav and J. Chattopadhyay, *Assessment of lockdown effect in some states and overall India: A predictive mathematical study on Covid-19 outbreak*, (2020) arXiv:2004.03487v2 [q-bio.PE]

[24] A. Mazumder, M. Arora, V. Bharadiya, P. Berry, M. Agarwal, M. Gupta, G.G. Parameswaran and P. Behera, *Study of epidemiological characteristics and in-silico analysis of the effect of interventions in the SARS-CoV-2 epidemic in India*, MedRxiv (2020) doi:https://doi.org/10.1101/2020.04.05.20053884.

[25] M.N. Babu, The Hindu (2020) https://www.thehindu.com/

[26] M. Banaji, Science: The wire (2020) https://science.thewire.in/health/

A Review on Action of Antiviral Drug Remdesivir against SARS-Cov-2 and other known coronaviruses

G. Pavithran[1], B.S. Pavan Kumar[2], V.H. Anusha[3] and B. Praveena[4]
[1,2,3]II B.Sc. CBZ, M.E.S. College of Arts, Commerce and Science
[4]Department of Chemistry, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: [1]gpavithrannair2000@gmail.com, [2]pavansiddharth001@gmail.com,
[3]stephsweety28@gmail.com and [4]tina.praveena@gmail.com

Absract: *The current pandemic of COVID-19 has highlighted the importance of developing treatment options to mitigate impact on Human life. Currently available information of the antiviral activity of remdesivir is based on in-vitro and in-vivo studies. As the pandemic progresses, studies like this will help us to understand more about the treatments available for COVID-19. The study regarding the antiviral activity of remdesivir against SARS-CoV-2 has been favorable to us. Although several clinical trials are now underway to test possible therapies for the current pandemic, COVID-19. Remdesivir was actually developed by Gilead Sciences which worked for the treatment of Ebola and it is now showing antiviral activity against SARS-CoV-2. Several studies are being conducted worldwide to prove that remdesivir is effective against SARS-CoV-2. Several studies were also published regarding the antiviral activity of remdesivir against RNA virus families like Filoviridae, Paramyxoviridae, Pneumoviridae, and Orthocoronavirinae, all the studies showed positive results. This article gives complete information regarding the antiviral activity of remdesivir against Human Coronaviruses such as MERS-CoV, SARS-CoV, SARS-CoV-2, OC43, 229E, and Porcine delta coronavirus. Information regarding the clinical trials of remdesivir against SARS-CoV-2 based on the available human data has also been highlighted in this article. The purpose of this review article is to provide the knowledge to date about remdesivir as a therapeutic option for COVID-19.*

Keywords: *Antiviral Activity, Covid 19, Remdesivir.*

1 Introduction

Remdesivir was originally created and developed by Gilead Sciences in 2009, as a part of company's research and development program for Hepatitis C. It did notwork against Hepatitis C as hoped, but was then repurposed and studied as a potential treatment for Ebola virus disease and Marburg virus infections [1]. Gilead Sciences subsequently discovered that remdesivir had antiviral activity *in vitro* against multiple filoviruses, pneumoviruses, paramyxoviruses and coronaviruses [2, 3, 4].

Remdesivir was rapidly pushed through clinical trials due to West African Ebola Virus epidemic of 2013 -2016, eventually being used in people with the disease. Preliminary results were promising, it was used in the emergency setting during the Kivu Ebola epidemic that started in 2018, along with further clinical trials, until August 2019, when Congolese health officials announced that it was significantly less effective than monoclonal antibody treatment such as mAb114 and REGN-EB3. The trials, however, established its safety profile [1]. Earlier studies found antiviral activity of Remdesivir against several RNA viruses including SARS-CoV and

MERS-CoV (Severe Acute Respiratory Syndrome Coronavirus and Middle East Respiratory Syndrome Coronavirus) [5, 6].

In January 2020, Gilead began laboratory testing of remdesivir against SARS-CoV-2, stating that remdesivir has been shown to be active against Severe Acute Respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in animals models [4, 7, 8]. In March 2020, a small trail of remdesivir in Rhesus Macaque Monkeys with COVID-19 infections found that it prevents disease progression [9, 10]. On 29 April 2020, based on result of the ACTT trail, the National Institute of Allergy and Infectious Disease (NIAID) announced that remdesivir was better than a placebo in reducing time of recovery for people hospitalized with advanced COVID-19 and lung involvement [11, 12].

2 Mechanism of action of remdesivir

Remdesivir is a Pro Tide (prodrug of nucleotide) that is able to diffuse into cells where it is converted to GS-441524 mono-phosphate via the actions of esterase and phosphoramidase, thus in turn in further phosphorylated to its active metabolite triphosphate by nucleotide-phosphate kinases [4]. The active metabolite of remdesivir interferes with the action of viral RNA-dependant RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production [5, 13]. For the RNA dependent RNA polymerase of MERS-CoV, SARS-CoV-1 and SARS-CoV-2 arrest of RNA synthesis occurs after incorporation of three additional nucleotides [6, 14, 15]. Hence remdesivir is classified as a delayed chain terminator [16].

Studies on remdesivir on and coronaviruses

The existing studies on the potential antiviral effects of remdesivir that are of highest relevance to the virus underlying the current pandemic COVID-19, caused by the virus SARS-CoV-2, are those that have been conducted on genetically similar coronaviruses, within the *coronaviridae* family of viruses, there is a substantial amount of genetic heterogeneity, even among humans strains [17]. This genetic diversity is posited to be attributable large viral genome and the molecular nuances of the viral RNA replication processes [18].

In-vitro studies

In studies of SARS-CoV and MERS-CoV in human respiratory epithelial cell cultures, remdesivir has demonstrated strongly antiviral activity ($EC_{50} \approx 0.07\mu M$ for either virus) with relative consistency, and has been shown to be capable of inhibiting MERS-CoV replication at levels below those that would result in unacceptable cytotoxicity [4, 19]. Interestingly, a study published in February 2020 by Wang and team, was first to our knowledge to examine the effect of remdesivir against SARS-CoV-2, the HCoV involved in current pandemic [20], this study investigated the impact of seven drugs on viral titers, cytotoxicity, and infection rates, using veroE6 cells (a cell line originated from African green monkey kidney epithelial cells). They found low potency of most of these drugs for inhibiting SARS-CoV-2. Among all the seven drugs, chloroquine and remdesivir, were the two drugs that required the lowest concentration for blocking viral infection.

A few in vitro studies have also investigated the utility of remdesivir against non-human CoVs. For example, a study by Murphy and team, reported anti CoV activity of remdesivir's parent nucleoside, GS-441524, against an alpha coronavirus that only infects wild and domestic cats, the feline infections peritonitis (FIP)virus $(EC50 \approx 0.78\mu M)$ [21]. In 2019, Brown and team observed some antiviral effects of remdesivir against SARS like bat CoVs (specially, Bat-CoV HKU3, Bat-CoV SH014 and Bat-CoV W1V1)and MERS like Bat CoVs (Specially Bat-CoV HKU5) [6]. Further this study detected a weaker antiviral effects against porcine delta coronavirus, particularly when tested in porcine cell lines. Among currently known CoVs, PDCoV has the least similar RdRb sequence compared to SARS-CoVand MERS-CoV (only 67%-69% similarity in amino acid sequence) [6]. In fact, the RdRb of PDCoV has a different amino acid at a specific site (phenylalanine to leucine at residue 483), a dissimilarity that has been previously associated with increased resistant to remdesivir in other CoVs [6, 19]. Therefore, it was important to attempt to disentangle whether the lower antiviral activity observed could be related to a viral characteristic of PDCoV or if it could be attributable to differences in the cell lines used.While diminished potency of remdesivir against PDCoV was noted in cultures of porcine kidney epithelial cells (LLC-PK1), in human liver cell line (Huh7), the EC_{50} was relatively low. Similarly, the EC_{50} was substantially higher for antiviral activity against an endemic HCoV (229E) in the porcine cell line, again indicating the likely lower potency of the drug in this context. Thus, the observed variations in remdesivir potency against the same viruses in the different cell lines may imply that there is some factors associated with the cell line, rather than the virus, that may be affecting the drug's antiviral activity. In fact, the author state that these findings may imply that LLC-PK1 cells lack a cellular process necessary for remdesivir antiviral activity, which could also support the hypothesis that remdesivir may have another mechanism of action that is not presently understood [22].

In-vivo studies

Animal studies on remdesivir efficacy against CoVs have utilized transgenic mice and rhesus macaques [4, 5, 7, 19]. For example, using a mouse model with a (es1c-knockout which better stimulates human metabolism of remdesivir compared to wild type mice) and a humanized MERS-CoV receptor, Sheahn and team found that both prophylactic and therapeutic remdesivir had protective effects against MERS-CoV replication and associated pathology, generally resulting in less lung damage and better pulmonary function compared to controls [5]. Interestingly, among mice that were infected with a higher virus quantity (i.e. more plague-forming units), those receiving prophylactic remdesivir one day before infection had significantly better 6 days survival than infected controlled mice that did not receive remdesivir. However, the mice were sacrificed before longer follow up data could be obtained. Similarly, in a Rhesus Macaque model of MERS-CoV pathogenesis, prophylactic and therapeutic administration of remdesivir demonstrated favorable results, reducing respiratory tract viral titers and pulmonary pathology. Prophylactic use was initiated 24 hours prior to viral challenges, whereas therapeutic use was initiated 12 hours after challenge. While respiratory rate was not substantially different between the prophylactic, therapeutic, and controlled groups, x-ray scores, representing the severity of pulmonary infiltrates, were significantly better in prophylactic and therapeutic groups, comparing each to controls [7]. Incidentally, remdesivir has also been associated with beneficial effects, including reduced severity of respiratory signs and improved survival, against challenge with Nipah virus, which is non-CoV virus in *Pramyxoviridae* family, in African green monkeys [18].

In a ceslc-knockout mouse model of SARS-CoV infection, prophylactic and therapeutic remdesivir treatment resulted in lower lung viral titers and if therapy was administered 1 day post - infection (which is before peak viral replication), it was associated with greater pulmonary functions, compared to controls [4]. However, there were no differences in pathology or survival if treatment was administered 2 days post-infection.

Some veterinary studies have also examined the effects of the parent nucleoside, GS-441524, in cats with FIP, a condition associated with very high mortality in cats [21, 23]. Gilead sciences (Foster city, California) had provided this drug to researchers at the University of California, Davis to evaluate its potential utility in veterinary indications [24]. Subsequently, GS-441524 became an intermediate in the production of the prodrug, remdesivir, which has superior ability to transport the active compound into cells [2, 7]. Because both drugs yield same active metabolite in host cells, some prior studies on the antiviral activity of remdesivir also investigate GS-441524 [7, 25], and discuss its relevance in the veterinary studies [2, 6].

In 2018, Murphy and team examined the efficacy of GS-441524 against FIP in 12 experimentally infected cats [21]. Controls were not included, as historical dates on untreated cats were available, demonstrating a mortality rate close to 100% [21, 26]. After experimental challenge with the FIP virus, 2 cats did not develop FIP related signs and remained untreated [21]. In the 10 infected cats, treatment was initiated upon onset of FIP associated clinical signs (approximately 10-18 days post infection), continued for 2 weeks of these cats, half $(n = 5)$ were treated with $2\,\mathrm{mg/kg}$ daily. If diseases recurred after initial treatment, cats were re-treated using the same regiment for another 2 weeks follow-up continued for 8 months. All treated cats demonstrated favorable responses to GS-441524 treatment within 24-48 hours, regardless of dose, and were still alive and clinically unremarkable 8 months post infection. Two cats (one from each dose group) experienced disease recurrence at 4 weeks and 6 weeks after initial treatment and werere-treated. Adverse events related to treatment, other than temporary discomfort at the injection site, were not observed. This study was based on a small number of animals, and it is unclear whether experimental infection is a relevant representation of naturally occurring FIPV infection in cats. Further studies with additional follow-up time would be hopeful for assessing whether unexpected long term sequelae are observed in the cats, since such information on surviving animals is sparse given in the high fatality rate [21, 22].

In a field trail of treatment with GS-441524 for naturally occurring FIP, Pedersen and team treated 31 cats with an initialdose of $2\,\mathrm{mg/kg}$ [23] within the first week of treatment, 4 cats (13%) with severe disease died or were euthanized, a fifth cat died after 26 days, and another was euthanized about 2 weeks post relapse due to the development of neurological signs and a lack of response to treatment. The remaining cats completed at least 12 weeks of treatment, but 8 experienced relapses requiring re-treatment with GS-441524. Dose escalation from $2\,\mathrm{mg/kg}$ to $4\,\mathrm{mg/kg}$ daily was required for 5 cats. A total of 25 treated cats (81%) survived FIP for at least 44 weeks of follow up, indicating that GS-441524 (and presumably, its prodrug remdesivir) is also a promising therapeutic candidate for treatment of alpha coronavirus related disease in cats, most cats in this study had "wet" or effulsive FIP, the hallmark of which is the accumulation of fluids in the abdominal or thoracic cavities. There were only 3 cats in the study with abdominal non-effusive ("dry") FIP, which is a more chronic condition, and another 4 cats initially had dry FIP that progressed into wet FIP. One cat in the dry FIP group and one in the dry-to-wet group did not survive. Because of the small number of cats with dry FIP, conclusions cannot be drawn about whether remdesivir has greater efficacy in the treatment of

some clinical manifestations of FIP than others. A strength of this study is that it was conducted among animals with naturally occurring CoV infection as a field trial better representing real world circumstances [23, 22].

Human data

The first patient to present with COVID -19 in the U.S was treated with intravenous remdesivir under the compassionate use clause after developing pneumonia in January 2020 [27]. He was treated with intravenous remdesivir on the seventh day and his condition was reportedly improving on the eighth day. No adverse events related to remdesivir use were noted. The case report was written prior to the patient's discharge [22].

Human data on redemsivir use for COVID-19 will likely continue to become available from compassionate use cases before the clinical trial is completed. In fact, there are many non-reliable reports already circulating about treatment of COVID-19 patients with remdesivir. According to a recent newspaper article, 17 passengers on the diamond princess cruise ship were treated with intravenous remdesivir for 10 days and were alive at the time of article release. One of the physicians involved in the their treatment, who is affiliated with the U.S. National Institutes of Health (NIH), felt that the patients were less dependent on ventilators after receiving the drug. Nevertheless, no conclusions can be drawn based on such reports [22].

A preprint of a case series on the first 12 COVID-19 patients in U.S (who had disease onset between January 14 and 29, 2020) recently become available, though it had not been peer-reviewed at the time of writing [28]. This report, authored by a team from the Centers for Disease Control (CDC), described the demographic and clinical characteristics of the patients, as well as information on course of disease and clinical management. Seven of the 12 patients (58%) were hospitalized, and three of these patients received remdesivir intravenously at the onset of worsening symptoms (two on the eleventh day of illness and one on the seventh day). Treatment with remdesivir was tolerated, though temporary gastrointestinal upset and elevated aminotransferase levels were obsessed in all these patients after administration. Treatment was discontinued after respiratory symptoms improved (total treatment duration of 4 days, 5days and 10 days). It should be noted that one of these three patients is the same patient described in the case report discussed above [27].

Some safety data were formally collected during a clinical trial conducted in the Democratic Republic of Congo that randomized 175 patients to be treated with remdesivir for Ebola [29]. Incidentally, randomization of remdesivir treatment was discontinued in this trial after an interim analysis showed superior survival for two other trial drugs, despite preclinical and compassionate use data having been favorable for remdesivir against the Ebola virus prior to the trial [2]. Interestingly, patients who received remdesivir had slower rates of viral clearance compared to patients who received single dose antivirals (specifically, Mab114 and REGNEB3), which the authors hypothesized may be related to the fact that the treatment plan for remdesivir involved multiple intravenous infusion. However, for now, information on the potential efficacy of remdesivir specifically against CoVs is largely limited to *in-vitro* and animal studies, through COVID-19 related knowledge is evolving quickly [22].

Overall, past studies on other CoVs may have limited generalizability to the virus underlying the current pandemic because of the high genetic diversity of the *coronaviridae* family,

although broad-spectrum drugs tend to be directed at well-conserved targets [4, 30]. In addition to this issue, there are a number of factors that can impact how predictive findings from *in-vitro/ in-vivo* models maybe of clinical efficacy against SARS-CoV-2. For example, drugs that may be effective *in-vitro* may not have clinical utility if the therapeutic dose induces severe adverse events in the patient. Alternatively, if the treatment dose does not attain an effective serum concentration in patients, or if EC_{50} is greater than the achievable maximum serum concentration (C_{max}), then the drug is less likely to have therapeutic utility. With regards to animal models, how closely the model represents disease pathogenesis and drug metabolism in humans can be challenging to gauge [22].

Clinical trails

Multiple clinical trials are under way on the use of remdesiver for treatment of COVID -19 [31, 32]. The NIH-sponsored clinical trials, ongoing in the US and the Republic of Korea, is double blinded, placebo-controlled trail in which patients are randomized to receive either placebo or an initial dose of 200 mg of intravenous remdesiver on the first day, followed by a maintained dose of $100\,\mathrm{mg}$ per day, through discharge up to a maximum of 10 total treatment days [33]. The primary outcome of the trail, as described in the U.S. National Library of Medicine clinical trials registry, will be expressed as the proportion of patients in each category of a seven-category clinical severity scale on the fifteenth day post treatment initiation [34, 35]. Additionally, Gilead Sciences is sponsoring a remdesiver study among patients with severe COVID-19 with a composite primary outcome measure of fever normalization and oxygen normalization [36, 37].

Two double-blinded placebo controlled trails are also recruiting in Hubei Province, China [38, 39]. One targets hospitalized patients with mild-to-moderate Covid-19 [38], while other's focused on severe cases [39]. The primary outcome measure for the study on mild or moderate cases is time to clinical recovery, as defined by normalization of body temperature, respiratory rate and oxygen saturation, and the resolution of cough for at least 72 hours [38]. In the study on severe cases, time to clinical improvement is the primary outcome and is defined using a six-category scale, ranging from discharge to death [39].

3 Antiviral effect of remdesivir against human coronaviruses

In vitro antiviral assays were developed for human coronavirus OC43 and 229E and the zoonotic porcinedelta coronavirus (PDCoV). The nucleoside analog RDV inhibited HCoV-OC43 and 229E as well as deltacoronavirus members PDCoV. RDV has broad- spectrum antiviral activity against CoV and should be evaluated for future emerging CoV [6].

The genetically diverse *Orthocoronavirinae* (CoV) family is divided into four genera (*alpha, beta, gamma* and *delta* coronavirus) thus for human CoV are limited to the *alpha* and *beta* genera. Human CoVs OC43, 229E, NL63 and HKU1 cause 10% of all upper and lower respiratory tract infections, which typically present with common-cold like symptoms but can cause more sever disease in young children as well as people with underlying respiratory conditions (i.e. asthma, OPD) and the elderly [40, 41]. In children's, severe respiratory track CoV infections require hospitalization in about 10% of cases and have been associated with fertile seizure in those less than 1 year old [42, 43]. CoV infection can also be severe in the elderly requiring hospitalization and can even cause acute respiratory distress syndrome (ARDS) [41, 44].

Zoonotic CoVs have a natural prediction for emergence into new host species giving rise to new diseases mostly recently exemplified in humans by Severe Acute Respiratory Syndrome Coronavirus (SASR-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [45]. Interestingly, all known human CoVs are thought to have emerged as zoonosis from wild or domestic animals [46, 47, 48, 49]. This emergence paradigm is not unique to human CoVs. Novel animal CoVs like porcine epidemic diarrhea virus (PEDV), porcine delta coronavirus (PDCoV) and swine acute diarrhea syndrome coronavirus (SADS-CoV) have recently emerged causing the deaths of millions of piglets and billions of dollars in agricultural losses [50, 51, 52]. While chloroquine, ribavirin, lopinavir and interferons have all been tested against multiple CoV *invitro*, currently there are no approved therapeutics for any human CoV [53, 54]. To address an unmet medical need for the treatment of current human CoV infections and to maximize pandemic preparedness, broad spectrum antiviral therapies are need that are effective against current and future emerging CoV given numerous examples of novel CoV emergence [6].

Remdesivir (RDV, GS-5734) is amonophosphoramidate prodrug of an adenosine analog with demonstrated antiviral activity against an array of RNA virus families including *Filosiridae, Paramyxoviridae, Pneumoviridae* and CoV [1, 2, 4]. The antiviral mechanism for RDV had been demonstrated to be through delayed chain termination of nascent viral RNA for Ebola virus, Nipha virus and respiratory syncytial virus [55, 56, 57, 2, 1]. The antiviral activity of RDV against a genetically diverse panel of humans endemic, emerging and zoonotic CoV including HCoV-NL63 (alpha lb), mouse hepatitisvirus (MHV, Beta 2a), SARS-CoV and related Bat CoVs W1V1 AND SHCO14 (beta 2b), as well as MERS-CoV and related Bat CoV HKU5 (beta 2c) was already reported in this article [19, 4] upon passage of MHV in the presence of RDV, resistance mutations arise in the RNA dependent RNA polymerase(RdRp) that confer resistance (i.e. up to a 5-fold shift in EC_{50}) demonstrating that the RdRp is a target of RDV antiviral activity [19]. The CoVRdRp is highly conserved with in genogroups (i.e. beta 2b) but amino acid identity between group varies from 70 to 90% [4].

Remdesivir (RDV) is a potent antiviral against human coronavirus OC43:

The EC_{50} values of RDV for MERS-CoV is $0.03\mu M$ in calu-3-cells; $0.074\mu M$ in primary human airway epithelial cells (HAE), for SARS-CoV it is $0.069\mu M$ in HAE and for MHV ($0.03\mu M$ in DBTcells) [19, 4]. Since HCoV-OC43 does not cause an overt cytopathic effect (CPE) in huh 7 cells, researchers established a focus forming reduction assay (FFRA) for HCoV-OC43 in 96-well plates based on nucleocapsid antigen staining and quantification via Elispot reader for increased throughput. Among the numerous viral genomic and sub genomic messenger RNAs and protein products generated during CoV replication, the nucleocapsid viral messenger RNA and protein are the most abundant. Researchers consistently observe on RDV dose-dependent reduction in HCoV-OC43 antigen foci. Similarly, the EC_{50} was highly consistent from experiment to experiment. Importantly, the C_{50} obtained in huh7 cells was $> 10\mu M$. Thus, for this assay system, the selective index ($SI = CC_{50}/EC_{50}$) was > 66. This assay is driven by the detecting nucleocapsid, the most abundant viral protein during CoV replication. Thus, dynamic range of detection is maximized due to the cutibody and viral, antigen pairing, which may have been notably lower when chosen to measure the expression of a viral protein with lower expression (e.g. non-structural protein 2) [58]. Conversely, due to the high abundance of nuleocapsid mRNA RDV may cause reductions in viral RNAs that are not detectable in this assay until a certain threshold is achieved that results in significant diminishment of nucleocapsid protein production [6].

Potent antiviral activity of RDV against human coronavirus 229E

Unlike HCoV-OC43, HCoV-229E infection of huh 7 cause CPE. Thus, CPE and cell titer-Glo-based antiviral assay for HCoV-229E was established. An RDV dose dependent reduction in HCoV-229E replication was observed without drug induced cytotoxicity. Over five independent experiments, an average EC_{50} of $0.024 \pm 0.018\mu M$ (mean $\pm$ standard deviation) was obtained. Importantly, since cytotoxicity ($CC_{50} > 10\mu M$), was not observed in Huh 7 cells across the dose range measured in the assay ($10\mu M - 0.0015\mu M$), the SI for this assay was > 400 [6].

Porcine delta coronavirus is susceptible to the antiviral activity of RDV

The genetically diverse CoV family infects a wide variety of avian and mammalian host of the four CoV genera, the *deltacoronavirus* have the most divergent RNA dependent RNA polymerase (RdRp) as compared to SARS-CoV and MERS-CoV (67-69% amino acid similarity to SARS-CoV or MERS-CoV). Interestingly, *deltacoronavirus* RdRp naturally harbor a leucine at residue 483 which is associated with partial resistance (i.e. up to a 5-fold shift in EC_{50}) to RDV in MHV (F476L) and SARS-CoV (F480L), at the homologous position. Researchers mapped the percent amino acid identity for the CoVs to determine if variation was localized to one specific region or function domain. While there is variation was localized to one specific region of functional domains. While there is variation across the entire protein, there are regions of concentrated heterogeneity in between motifs B (nucleotide binding) and C (SDD motif in the active site) and in the C-terminal region of the thumb domain. Importantly, most of the RdRp functions domains (A-G) as described by Xu and team in 2003 for SARS-CoV are highly conserved(i.e. 100% identity) [59, 6].

Given the divergence of the *deltacoronavirus* RdRp and the naturally occurring putative resistance mutation, researchers sort to determine the susceptibility of members of the *deltacoronavirus* genes to the antiviral effect of RDV. Using porcine deltacoronavirus (PDCoV) as a model, researchers first established an antiviral assay in the porcine in kidney epithelial cell line, LLC-PK1,with support robust PDCoV replication. EntericCoV (i.e. PDCoV, PEDV) require the addition of digestive enzymes (i.e. trypsin, pancreatin) to culture medium for efficient replication and CPE [60, 50]. In LLC-PK1 cells with serum free medium and pancreatic, RDV did not diminish PDCoV replication greater than 50% this the EC_{50} could not be determined. To ascertain whether PDCoV was naturally resistant to RDV or if the LLC-PK1 cell harbored an unknown defect in a cellular process required for antiviral activity (i.e. Nucleotideuptake, metabolism etc.), similar antiviral assays were performed with HCoV-229E in LLC-PK1cells, yet the antiviral activity of RDV against HCoV-229E in Huh 7 cells in PDCoV assay medium were similar. These data suggest LLC-PK1 cells are deficient in a cellular process required for the antiviral activity of RDV. Importantly in Huh 7 cells cultured in TPCK trypsin-containing and serum free media, PDCoV replication was dose dependently reduced with an EC_{50} value of $0.02\mu M$. Altogether with previous publications, these data demonstrate that a panel of CoV representing family-wide genetic diversity in the RdRp are susceptible to the inhibition by RDV [6].

4 Conclusion

While previous studies on remdesivir are promising, formal clinical evaluation is strongly warranted. In general, there are many reasons why favorable preclinical data can fail to translate

directly into human clinical trial results, such as inadvertent use of irrelevant models, inability to achieve effective serum drug concentration in patients, or the occurrence of unanticipated severe adverse events among patients. Therefore, postulating on expected results of the trials is extremely challenging [61]. Nonetheless, there are hundreds of clinical trials ongoing internationally on different drugs that utilize various mechanism of action [31, 32, 33, 62], including trials on other nucleosides inhibitors (e.g. ribavirin) protease inhibitors (e.g. lopinavir/ ritonavir) and interleukin-6-receptor inhibitors (e.g. sarilumab) [31, 32, 33, 63]. Another well-known candidate that is being evaluated in multiple trials against COVID-19 is chloroquine (or Hydroxychloroquine) which is already approved as antimalarial (and for extra intestinal amebiasis) [31, 32, 33]. Results of the clinical trials currently underway in U.S and China will provide crucial information about whether remdesivir represents a viable treatment option for COVID-19 [64]. If the trail findings are ultimately positive, it will be imperative to ensure that the drug is produced on a commercial scale capable of meeting the demand generated by both the current pandemic and future outbreaks. Such a change in production may also allow for the added benefit of the drug becoming more available for agricultural and veterinary use for relevant use for relevant indications [22].

Effective broad-spectrum therapies are need for emerging viral threats of today, like Ebola and MERS-CoV, as well as those that have yet to emerge. There are multiple examples of novel CoV emergence including all six human CoV, which are known to cause more sporadic outbreaks, the other four human CoV, which are thought to have emerged as zoonosis [46, 47, 48, 49]. Unlike SARS-CoV and MERS-CoV which are known to cause more sporadic outbreaks, the other four Human CoV are endemic causing annual widespread morbidity in infants and the elderly, potentially requiring hospitalization [41, 42, 65]. Although rare, endemic human CoV like HCoV-229E and HCoV-OC43 can also cause severe respiratory disease (pneumonia, ARDseta) in subsets of patients, with presentation similar to SARS-CoV and MERS-CoV [41, 66, 67]. RDV has potent antiviral activity against HCoV-OC43, HCoV-229E and PDCoV which are in subgenera beta 20, alpha 1b and delta 4, respectively the other outstanding subgenera yet to be evaluated is beta 2d, which is currently comprised of only bat CoV [68].

Fututre Propspective

Recent pandemic of coronavirus associated illness underscore the urgent medical and public health need for vaccine development and regulatory body approved therapies. In particular, the current coronavirus disease 2019 (COVID-19) pandemic has quickly intensified interest in developing treatment options to mitigate impact on human life. Discovery of a new antiviral drug for COVID-19 and marketing it will take more than a decade. So scientists are looking to repurpose the previously FDA approved drugs for COVID-19. One such drug which is showing positive result is remdesivir. Immense research is needed to prove that this can be used as an effective antiviral drug against SARS-CoV-2.

References

[1] T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva and N. Larson, *Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys*, Nat. 531(7594) (2016) 381-385.

[2] M.K. Lo, R. Jordan, A. Arvey, J. Sudhamsu, P. Shrivastava-Ranjan, A.L. Hotard and R.L. Mackman, *GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo- and*

Paramyxoviruses Sci. Rep. 7 (2017) 43395.

[3] T.P. Sheahan, A.C. Sims, S.R. Leist, A. Schafer, J. Won, A.J. Brown and J.E. Spahn, *Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV*, Nat. Commun. 11(1) (2020) 1-14.

[4] T.P. Sheahan, A.C. Sims, R.L. Graham, V.D. Menachery, L.E. Gralinski, J.B. Case and R. Bannister, *Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses*, Sci. Transl. Med. 9(396) (2017).

[5] C. Scavone, S. Brusco, M. Bertini, L. Sportiello, C. Rafaniello, A. Zoccoli and A. Capuano, *Current pharmacological treatments for COVID-19: What's next?*, Br. J. Pharmacol. (2020).

[6] W.C. Ko, J.M. Rolain, N.Y. Lee, P.L. Chen, C.T. Huang, P.I. Lee and P.R. Hsueh, *Remdesivir for SARS-CoV-2 pneumonia*, Int. J. Antimicrob. Agents (2020).

[7] E. de Wit, F. Feldmann, J. Cronin, R. Jordan, A. Okumura, T. Thomas and H. Feldmann, *Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection*, Proc. Natl. Acad. 117(12) (2020) 6771-6776.

[8] A.J. Pruijssers, A.S. George, A. Schafer, S.R. Leist, L.E. Gralinksi, K.H. Dinnon and X. Lu, *Remdesivir potently inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice*, bioRxiv (2020).

[9] V. Munster, F. Feldmann, B. Williamson, N. Van Doremalen, L. Perez-Perez, J. Schultz and V. Avanzato, *Respiratory disease and virus shedding in rhesus macaques inoculated with SARS-CoV-2*, bioRxiv (2020).

[10] B. Williamson, F. Feldmann, B. Schwarz, K. Meade-White, D. Porter, J. Schulz and A. Okumura, *Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2*, bioRxiv (2020).

[11] https://clinicaltrials.gov/ct2/show/NCT04280705

[12] https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

[13] R.E. Ferner and J.K. Aronson, *Remdesivir in covid-19*, Br. Med. J. (2020).

[14] C.J. Gordon, E.P. Tchesnokov, J.Y. Feng, D.P. Porter and M. Gotte, *The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus*, J. Biol. Chem. 295(15) (2020) 4773-4779.

[15] C.J. Gordon, E.P. Tchesnokov, E. Woolner, J.K. Perry, J.Y. Feng, D.P. Porter, and M. Gotte, *Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency*, J. Biol. Chem. 295(20) (2020) 6785-6797.

[16] R.T. Eastman, J.S. Roth, K.R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik and M.D. Hall, *Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19*, ACS Cent. Sci. (2020).

[17] A. Vabret, J. Dina, T. Mourez, S. Gouarin, J. Petitjean, S. van der Werf and F. Freymuth, *Inter-and intra-variant genetic heterogeneity of human coronavirus OC43 strains in France*, J. Gen. Virol. 87(11) (2006) 3349-3353.

[18] P.C. Woo, S.K. Lau, Y. Huang and K.Y. Yuen, *Coronavirus diversity, phylogeny and interspecies jumping*, Exp. Biol. Med. 234(10) (2009) 1117-1127.

[19] M.L. Agostini, E.L. Andres, A.C. Sims, R.L. Graham, T.P. Sheahan, X. Lu and A.S. Ray, *Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease*, MBio 9(2) (2018) e00221-18.

[20] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu and G. Xiao, *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro*,

Cell Res. 30(3) (2020) 269-271.

[21] B.G. Murphy, M. Perron, E. Murakami, K. Bauer, Y. Park, C. Eckstrand and N.C. Pedersen,*The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies*, Vet. Microbiol. 219 (2018) 226-233.

[22] E.S. Amirian and J.K. Levy, *Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses* Int. J. One Health (2020) 100128.

[23] N.C. Pedersen, M. Perron, M. Bannasch, E. Montgomery, E. Murakami, M. Liepnieks and H. Liu, *Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis*, J. Feline Med. Surg. 21(4) (2019) 271-281.

[24] J.W. Black, *Recovery and in vitro cultivation of a coronavirus from laboratory -Induced cases of feline infectious peritonitis (FIP)*, Vet. Med. Small Anim. Clin. 75(5) (2020) 811-814.

[25] A. Cho, O.L. Saunders, T. Butler, L. Zhang, J. Xu, J.E. Vela and C.U. Kim, *Synthesis and antiviral activity of a series of 1ı-substituted 4-aza-7, 9-dideazaadenosine C-nucleosides*, Bioorg. Med. Chem. Lett. 22(8) (2012) 2705-2707.

[26] N.C. Pedersen, C. Eckstrand, H. Liu, C. Leutenegger and B. Murphy,*Levels of feline infectious peritonitis virus in blood, effusions, and various tissues and the role of lymphopenia in disease outcome following experimental infection*, Vet. Microbiol. 175(2-4) (2015) 157-166.

[27] M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce and G. Diaz, *First case of 2019 novel coronavirus in the United States*, N. Engl. J. Med. (2020).

[28] S.A. Kujawski, K.K. Wong, J.P. Collins, L. Epstein, M.E. Killerby, C.M. Midgley and K.N. Anderson, *First 12 patients with coronavirus disease 2019 (COVID-19) in the United States*, MedRxiv (2020).

[29] S. Mulangu, L.E. Dodd, R.T. Davey Jr, O. TshianiMbaya, M. Proschan, D. Mukadi and R. Ali, *A randomized, controlled trial of Ebola virus disease therapeutics*, N. Engl. J. Med. 381(24) (2019) 2293-2303.

[30] H. Yang, W. Xie, X. Xue, K. Yang, J. Ma, W. Liang and R. Hilgenfeld, *Design of wide-spectrum inhibitors targeting coronavirus main proteases*, PLoS biology 3(10) (2005).

[31] E.T. Thurber, E.P. Bass and W.H. Beckenhauer, *Field trial evaluation of a reo-coronavirus calf diarrhea vaccine* Can. J. Comp. Med. 41(2) (1977) 131.

[32] E. Callaway, *Coronavirus vaccines: five key questions as trials begin*, Nat. 579(7800) (2020) 481.

[33] National Institutes of Health, *NIH clinical trial of remdesivir to treat COVID-19 begins*, (2020).

[34] A.C. Kalil, *Treating COVID-19—off-label drug use, compassionate use, and randomized clinical trials during pandemics*, J. Am. Med. Assoc. (2020).

[35] P. Ahmadpoor and L. Rostaing *Why the immune system fails to mount an adaptive immune response to a Covid-19 infection*, Transpl. Int. (2020).

[36] K.J. Clerkin, J.A. Fried, J. Raikhelkar, G. Sayer, J.M. Griffin, A. Masoumi and A. Schwartz,*Coronavirus disease 2019 (COVID-19) and cardiovascular disease*, Circ. 141(2) (2020).

[37] J.A. Al-Tawfiq, A.H. Al-Homoud and Z.A. Memish, *Remdesivir as a possible therapeutic option for the COVID-19*, Travel Med. Infect. Di. (2020).

[38] B. Cao, *Mild/moderate 2019-nCoV remdesivir RCT*, ClinicalTrials gov. (2020)

[39] B. Cao and Y. Wang, *Mild/Moderate 2019-nCoV Remdesivir RCT NIH US*, Natl. Libr. Med. Clin. (2020).

[40] R. Dijkman, M.F. Jebbink, E. Gaunt, J.W. Rossen, K.E. Templeton, T.W. Kuijpers and L. van der Hoek, *The dominance of human coronavirus OC43 and NL63 infections in infants*, J. Clin. Virol. 53(2) (2012) 135-139.

[41] A.R. Falsey, E.E. Walsh and F.G. Hayden, *Rhinovirus and coronavirus infection-associated hospitalizations among older adults*, Int. J. Infect. Dis. 185(9) (2002) 1338-1341.

[42] K.B. Carman, M. Calik, Y. Karal, S. Isikay, O. Kocak, A. Ozcelik and M. Dinleyici, *Viral etiological causes of febrile seizures for respiratory pathogens (EFES Study)*, Hum. Vacc. Immunother. 15(2) (2019) 496-502.

[43] I. Heimdal, N. Moe, S. Krokstad, A. Christensen and L. Hosoien, *Human Coronavirus in Hospitalized Children with Respiratory Tract Infections: A Nine-year-long, Population-based Study from Norway*, J. Infect. Dis. 219(8) (2019) 1198–1206.

[44] F. Vassilara, A. Spyridaki, G. Pothitos, A. Deliveliotou and A. Papadopoulos, *A rare case of human coronavirus 229E associated with acute respiratory distress syndrome in a healthy adult*, Case Rep. Infect. Dis. (2018).

[45] E. de Wit, N. van Doremalen, D. Falzarano and V.J. Munster, *SARS and MERS: recent insights into emerging coronaviruses*, Nat. Rev. Microbiol. 14(8) (2016) 523.

[46] B. Hu, X. Ge, L.F. Wang and Z. Shi, *Bat origin of human coronaviruses*, Virol. J. 12(1) (2015) 221.

[47] J. Huynh, S. Li, B. Yount, A. Smith, L. Sturges, J.C. Olsen and M.B. Frieman, *Evidence supporting a zoonotic origin of human coronavirus strain NL63*, J. Virol. 86(23) (2012) 12816-12825.

[48] V.D. Menachery, B.L. Yount, A.C. Sims, K. Debbink, S.S. Agnihothram, L.E. Gralinski and J. Swanstrom, *SARS-like WIV1-CoV poised for human emergence*, Proc. Natl. Acad. Sci. 113(11)(2016) 3048-3053.

[49] L. Vijgen, E. Keyaerts, E. Moes, I. Thoelen, E. Wollants, P. Lemey and M. Van Ranst, *Complete genomic sequence of human coronavirus OC43: molecular clock analysis suggests a relatively recent zoonotic coronavirus transmission event*, J. Virol. 79(3) (2005) 1595-1604.

[50] H. Hu, K. Jung, A.N. Vlasova, J. Chepngeno, Z. Lu, Q. Wang and L.J. Saif, *Isolation and characterization of porcine deltacoronavirus from pigs with diarrhea in the United States*, J. Clin Microbiol. 53(5) (2015) 1537-1548.

[51] Y.M. Huang, A.W. Dickerman, P. Pineyro, L. Li, L. Fang, R. Kiehne and X.J. Meng, *Origin, evolution, and genotyping of emergent porcine epidemic diarrhea virus strains in the United States*, MBio 4(5) (2013) e00737-13.

[52] P. Zhou, H. Fan, T. Lan, X.L. Yang, W.F. Shi, W. Zhang and X.S. Zheng, *Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin*, Nat. 556(7700) (2018) 255-258.

[53] J.F. Chan, K.H. Chan, R.Y. Kao, K.K. To, B.J. Zheng, C.P. Li and F.G. Hayden, *Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus*, J. Infect. 67(6) (2013) 606-616.

[54] A.H. de Wilde, D. Jochmans, C.C. Posthuma, J.C. Zevenhoven-Dobbe, S. van Nieuwkoop, T.M. Bestebroer and E.J. Snijder, *Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture*, Antimicrob. Agents Chemother. 58(8) (2014) 4875-4884.

[55] L. Shen, Y. Yang, F. Ye, G. Liu, M. Desforges, P.J. Talbot and W. Tan, *Safe and sensitive antiviral screening platform based on recombinant human coronavirus OC43 expressing the luciferase reporter gene*, Antimicrob. Agents Chemother. 60(9) (2016) 5492-5503.

[56] P.C. Jordan, C. Liu, P. Raynaud, M.K. Lo, C.F. Spiropoulou, J.A. Symons and J. Deval, *Initiation, extension, and termination of RNA synthesis by a paramyxovirus polymerase*, PLoS Pathog. 14(2) (2018) e1006889.

[57] E.P. Tchesnokov, P. Raeisimakiani, M. Ngure, D. Marchant and M. Gotte, *Recombinant RNA-dependent RNA polymerase complex of Ebola virus*, Sci.Rep. 8(1) (2018) 1-9.

[58] B.W. Neuman, J.S. Joseph, K.S. Saikatendu, P. Serrano, A. Chatterjee, M.A. Johnson and R.C. Stevens, *Proteomics analysis unravels the functional repertoire of coronavirus nonstructural protein 3*, J. Virol. 82(11) (2008) 5279-5294.

[59] X. Xu, Y. Liu, S. Weiss, E. Arnold, S.G. Sarafianos and J. Ding, *Molecular model of SARS coronavirus polymerase: Implications for biochemical functions and drug design*, Nucleic Acids Res. 31(24) (2003) 7117-7130.

[60] A. Beall, B. Yount, C.M. Lin, Y. Hou, Q. Wang, L. Saif and R. Baric, *Characterization of a pathogenic full-length cDNA clone and transmission model for porcine epidemic diarrhea virus strain PC22A*, MBio 7(1) (2016) e01451-15.

[61] J.A. Bolker, *Animal models in translational research: Rosetta stone or stumbling block?* Bioessays 39(12) (2017) 1700089.

[62] H. Devlin and I. Sample, *Hopes rise over experimental drug's effectiveness against coronavirus*, The Guardian (2020).

[63] Q. Zhang, Y. Wang, C. Qi, L. Shen and J. Li, *Clinical trial analysis of 2019-nCoV therapy registered in China*, J. Med. Virol. 92(6)(2020) 540-545.

[64] National Institutes of Health, *NIH clinical trial of remdesivir to treat COVID-19 begins* (2020).

[65] L. Varghese, P. Zachariah, C. Vargas, P. LaRussa, R.T. Demmer, Y.E. Furuya and L. Saiman, *Epidemiology and clinical features of human coronaviruses in the pediatric population*, J. Pediatric Infect. Dis. Soc. 7(2) (2018) 151-158.

[66] D.M. Patrick, M. Petric, D.M. Skowronski, R. Guasparini, T.F. Booth, M. Krajden and D. MacDonald, *An outbreak of human coronavirus OC43 infection and serological cross-reactivity with SARS coronavirus*, Can. J. Infect. Dis. Med. Microbiol. 17(6) (2006) 330-336.

[67] F. Vassilara, A. Spyridaki, G. Pothitos, A. Deliveliotou and A. Papadopoulos, *A rare case of human coronavirus 229E associated with acute respiratory distress syndrome in a healthy adult*, Case reports in infectious diseases (2018).

[68] S.K. Lau, R.W. Poon, B.H. Wong, M. Wang, Y. Huang, H. Xu and B.J. Zheng, *Coexistence of different genotypes in the same bat and serological characterization of Rousettus bat coronavirus HKU9 belonging to a novel Betacoronavirus subgroup*, J. Virol. 84(21) (2010) 11385-11394.

A Review on Necessity of Aarogya-Setu application in present situation

B. Praveena
Department of Chemistry, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: tina.praveena@gmail.com

Absract: ***AarogyaSetu*** *which is a trending app for the present situation of Covid19. This application is Indian COVID-19 tracking mobile application which is developed by the National Informatics Centre and that comes under the government Ministry of Electronics and Information Technology. This is a short review representing the details and necessity of the Arogya- Setu app.*

Keywords: *Arogya-Setu, Application, Technology.*

1 Introduction

AarogyaSetu which is a trending app for the present situation of Covid19. It is great initiative by the Indian government in this corona period. This application is Indian COVID-19 tracking mobile application which is developed by the National Informatics Centre and that comes under the government Ministry of Electronics and Information Technology. The main purpose of this app is to spread awareness of COVID-19 and to connect essential COVID-19 - related health services to the people of India. It is a tracking application which uses the smartphone's GPS and Bluetooth features to track the coronavirus infection surrounding the person. This app is available for Android and iOS mobile operating systems [1]. With Bluetooth, it tries to determine the risk of Covid19 if one has been come close within six feet of a COVID-19 - infected person, by scanning through a database of known cases across India. This app mainly uses the location information to give the person is in infected area by using the database available. This app tells how many Covid19 positive cases are likely in a radius of $500\,\mathrm{m}$, $1\,\mathrm{km}$, $2\,\mathrm{km}$, $5\,\mathrm{km}$ and $10\,\mathrm{km}$ from the user. The app is built on a platform that can provide an Application Programming Interface (API) so that other computer programs, mobile applications and web services can make use of the features and data available in Aarogya-Setu.

Aarogya-Setu app (image source -www.timesnownews.com [2])

2 Different Sections of AarogyaSetu

Aarogya-Setuhas four sections:
1. Your Status (tells the risk of getting COVID-19 for the user),
2. Self Assess (lets the user know the risk of being infected),
3. COVID-19 Update (gives updates on local and national COVID-19 cases) and
4. E-pass (yet to be operationalized).

Benefits of the app

- ⋆ This app works mainly using GPS and bluetooth of the smart phones and provides the information about the infected persons close to the user and infected locations.
- ⋆ It tells the risk factors of the particular areas about the different zones (red,orange and green).
- ⋆ It gives alert to the user of whether the user had crossed the infected person in his path nearby 6feet distance approx.
- ⋆ It gives necessary precautions to be taken by the user like social distancing, Do's and Don'ts by the user.
- ⋆ The app is also equipped with a chatbot that answers all the basic questions on coronavirus disease or COVID-19.
- ⋆ The users can also find the helpline numbers for each state in India.
- ⋆ In case, a user is at high risk, the app will advise him/her to go for a test at a nearby testing centre and call the toll-free number 1075 immediately.

Responses for the App

AarogyaSetu crossed five million downloads within three days of its launch, making it one of the most popular government apps in India. It became the world's fastest-growing mobile app beating Pokemon Go, with more than 50 million installs, 13 days after launching in India on April 2, 2020. In an order on 29 April 2020 the central government made it mandatory for all employees to download the app and use it - "Before starting for office, they must review their status on AarogyaSetu and commute only when the app shows safe or low risk". The Union Home ministry also said that the application is mandatory for all living in the COVID-19 contaminent zone. The government gave the announcement along with the nationwide lockdown extension by two weeks from the 4^{th} May with certain relaxations. Recent new says it is close to nine crore users who have downloaded the AarogyaSetu mobile application and it has been made mandatory that government and private sector employees use it to bolster efforts to fight the COVID-19 pandemic [3]. The AarogyaSetu app supports 11 languages (English, Hindi, Telugu, Kannada, Malayalam, Tamil, Punjabi, Bengali, Oriya, Gujarati, and Marathi). Once you have downloaded the app from Google Play Store, you need to register with your mobile number. Later, the app has an option to enter your health stats and other credentials. To enable tracking, you need to keep your location and Bluetooth services on. Once you are into the app, the app will scan your location and share your data with the government in case you've been tested positive for coronavirus or have been in close contact with a person who was tested positive. Besides this, the app also has a dedicated a chatbot that asks you a series of questions to determine if you have any symptoms of Covid-19 as well as inform you about the various facilities and updates from the health ministry along with a series of helpline numbers nationally and state-wise [4].

Controversy

Rahul Gandhi, opposition party leader, termed the AarogyaSetu application as a "sophisticated surveillance system" after the government announced that downloading the app is manda-

tory for both government and private employees [5]. Following this, others raised the same concerns about the AarogyaSetu. The Minister of Electronics and Information Technology responded to this announcement by asserting that Gandhi's claims are false, and that the app was being appreciated internationally. On Tuesday (5^{th} May, 2020), a French hacker and cyber security expert Elliot Alderson had claimed that "a security issue has been found" in the AarogyaSetu app and that "privacy of 90 million Indians is at stake". Dismissing the claims, the government said "no personal information of any user has been proven to be at risk by this ethical hacker". India's Covid-19 contact tracing app AarogyaSetu released a statement today responding to the claims of French hacker Robert Baptiste of a privacy issue in the app. While the hacker did not disclose the details of the app's vulnerability, the AarogyaSetu developers issued a statement saying that user data is safe and secure.

Necessity of the app in present situation

Arogya-Setu is a app which is already available in the android smart phones google play stores and app store in iphones. This app is designed mainly to bring the awareness in the people about Covid19 in present situation. This is mainly a tracking app which tracks and notify the infectious areas based on the location data available using the GPS of smart phones and Bluetooth in it. It mainly gives the information whether the user is close to the infected locations and also determine if you have been within six feet from the infected person.

The use of this app will be more at the present situation because of the relaxation of the lockdown in certain places with some restrictions. Those who are going out to their regular works can have this app in their phones so that they will have the awareness of the places and persons they are surrounding by. The Indian government plan of this app to the people is very appreciative and useful for the society in present situation of corona. As there is a relaxation in the lockdown it is very much useful after the lockdown only as so many are moving to their works. The users can easily handle the situations and maintain social distance if they are close to an infected person and also deviate the locations of infected areas if they are updating with the locations of infection.

This app can be continued and updated time to time until the vaccine comes to the markets for use. This app will be a part of other apps in the phone as a mandatory to all. Despite of all controversies this app may control the spread of the infection to some extent and brings awareness to the people more about this Covid19.

References

[1] https://www.mygov.in/aarogya-setu-app/, Retrieved 5 April 2020.

[2] https://www.timesnownews.com/technology-science/article/aarogya-setu-app-security-issues-explained-5-important-takeaways-for-aarogya-users/588106, Updated May 07, 2020.

[3] https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/9-cr-people-have-downloaded-aarogya-setu-app-govt/articleshow/75573552.cms

[4] https://www.livemint.com/technology/apps/govt-launches-aarogya-setu-a-coronavirus-tracker-app-all-you-need-to-know-11585821224138.html, Retrieved 5 April 2020.

[5] https://www.moneycontrol.com/news/technology/rahul-gandhi-raises-questions-on-aarogya-setu-app-says-it-is-a-sophisticated-surveillance-system-5215381.html, Retrieved 2 May 2020.

A Review on Structure and Genome of NOVEL CORONAVIRUS 2019 (2019-nCoV)

B. Praveena[1] and J. Bhavana[2]
[1]Department of Chemistry, M.E.S. College of Arts, Commerce and Science
[2]III B.Sc. CBZ, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: [1]tina.praveena@gmail.com, [2]bhavanaj596@gmail.com

Absract: *The 2019 novel coronavirus (2019-nCoV) outbreak has caused a large number of deaths with thousands of confirmed cases worldwide especially in East Asia. Coronaviruses are responsible for upper and lower respiratory tract infections in humans. It is estimated that 1to 10%of the population suffers annually from cold like symptoms related to infection This 2019 novel coronavirus (2019-nCoV) outbreak has caused a large with human coronavirus. This recent outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in December 2019 raised global health concerns. The viral 3-chymotrypsin like cysteine protease (3CLPro) enzyme control coronavirus.*

Keywords:*Coronavirus structure, Covid 19, Genome.*

1 Introduction

The virus is highly homologous to the coronavirus (CoV) that caused an outbreak of severe acute respiratory syndrome (SARS) in 2003; thus, it was named SARS-CoV-2 by the World Health Organization (WHO) on February 11, 2020, and the associated disease was named CoV Disease-19 (COVID-19) [1]. The epidemic started in Wuhan, China, and quickly spread throughout the entire country and to near 50 others all over the world. As of March 2, 2020, the virus has resulted in over 80,000 confirmed cases of COVID-19, with more than 40,000 patients discharged and over 3,000 patients who died. WHO warns that COVID-19 is "public enemy number 1" and potentially more powerful than terrorism [2].

2 Structure of Corona Virus

The coronavirus is a single-stranded RNA virus with envelope and it has a diameter around 0.1μm. The virus spreads via droplets from such as cough, direct contact with infected person or contact of hands with contaminated environmental surfaces. So far the 6 types of corona viruses are confirmed to infect humans

- Flu virus among humans: 4 types Human Coronavirus (HCoV): HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1
- SARS (Severe Acute Respiratory Syndrome) - CoV
- MERS (Middle East respiratory syndrome) - CoV

Coronavirus are large pleomorphic spherical particles with bulbous surface projections. The average diameter of the virus particles is around 120 nm (.12 μm). The diameter of the envelope is $\sim$ 80 nm (.08 μm) and the spikes are $\sim$ 20 nm (.02 μm) long. The envelope of the virus in electron micrographs appears as a distinct pair of electron dense shells.

The viral envelope consists of a lipid bilayer where the membrane (M), envelope (E) and spike (S) structural proteins are anchored. A subset of coronaviruses (specifically the members of betacoronavirus subgroup A) also have a shorter spike like surface protein called hemagglutinin esterase (HE)

Inside the envelope, there is the nucleocapsid, which is formed from multiple copies of the nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous beads-on-a-string type conformation. The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host cell.

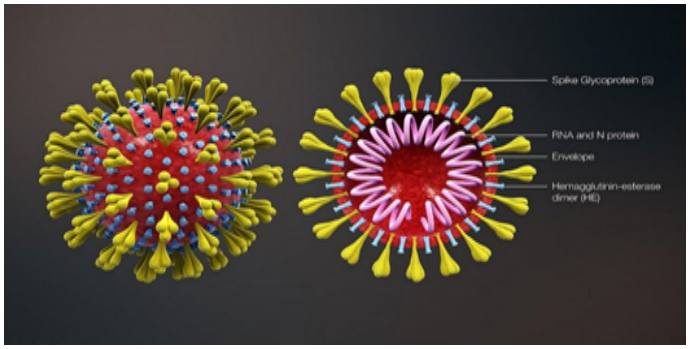


Figure 1: Structure of SARS-CoV-2. [3, 4]

The body of COVID-19 is basically a genome enveloped in glycoproteins, with a smear of fat and bearing the crown of spikes that inspired the name “coronavirus”. The genome is single strand of RNA that is termed “positive sense”. That means that the infected cell treats the viral genome as if were its own messenger RNA (mRNA), translating it into proteins. A “negative-sense” RNAvirus requires more manipulation; a host enzyme must make a positive-sense copy. A coronavirus genome typically is 26,000-32,000 bases long. That’s hefty for a virus, but tony compared to a human gene. Our BRCA1 gene, for example, is 125,951 bases long. Coronavirus RNAs are embellished with “caps” and “tails” like those of human mRNAs. Once ensconced in a human cell, a half dozen or more viral mRNAs are peeled off. The first, representing about two-thirds of the viral genome, encodes 16 proteins, and transcription factors to continually renew the RNA instructions.

The other third of the viral genome encodes four “structural” proteins that are the nuts and blots that build the virus:

- Spike, or S protein, is made early in infection. One part of it, S1, grabs a receptor molecule sticking out of a host cell and another part fuses to the cell membrane. Three copies of S protein from each spike.
- Membrane (M) glycoprotein lies beneath the spikes, where it shapes mature viral particles and binds the inner layers
- Lipid (fat) is borrowed from host cell membranes during past infections.
- Envelope (E) glycoproteins control the assembly, release, and infectivity of mature viruses.
- Nucleocapsid (N) proteins knit a characteristic shell of identical subunits, like the panes of a greenhouse, that binds and packages the RNA genome. It also serves as a cloaking device, hiding viruses from our immune systems interferons and RNA interference.

Genome of COVID-19

Comparison of the genome sequences of the COVID-19, SARS-CoV, and MERS-CoV showed that 2019-CoV has a better sequence identify with SARS-CoV than the MERS-CoV. The COVID-19 amino acid sequence varies from the other coronaviruses exclusively in the region of lab polyprotein and surface glycoprotein or S-protein. S-protein has two subunits with one subunit binding directly to the host receptor aiding the virus entry into the cells. The RNA binding domain of the S-protein in COVID-19 has a higher homology with SARS-CoV. Though some of the residues critical for binding the receptor are different, overall the non-identical residues did not alter the structural conformation. studies suggest that the human receptor for COVID-19 could be angiotensin-converting enzyme 2 (ACE2). Other coronaviruses including SARS-CoV gain entry in human cells through ACE2.

COVID-19's Spikes bind at ACE2 Receptors

Viruses have co-evolved with us, using proteins that jut from our cell surfaces. HIV and West Nile virus enter through CCR5 receptors, which dot white blood cells. Influenza viruses bind sialic acid residues. Coxsackievirus and adenovirus target part of an antibody. And herpes simplex uses 3 different doorways. To, us ACE2 is an enzymethat has an effect on blood pressure. To, COVID-19, ACE2 is a receptor, an entranceway, in the airways and alveoli(air sacs) as well as in blood vessel linings. ACE2 is also a receptor for SARS-CoV and NL63-CoV. The key to developing vaccines and treatments is the three dimensional shapes of the parts of the virus that contact our cells. SARS and NL63-CoV bind to a helical part of ACE2 that snakes up from cell membranes, forming distinctive tunnels and bridges that comprise a "hot spot" for viruses.

Researchers knew from SARS that the S1 parts of the viral spikes hug the ACE2 receptor at a region of five amino acids. Even though four of the amino acids differ in COVID-19, they are similar in size and change to their counterparts in SARS.

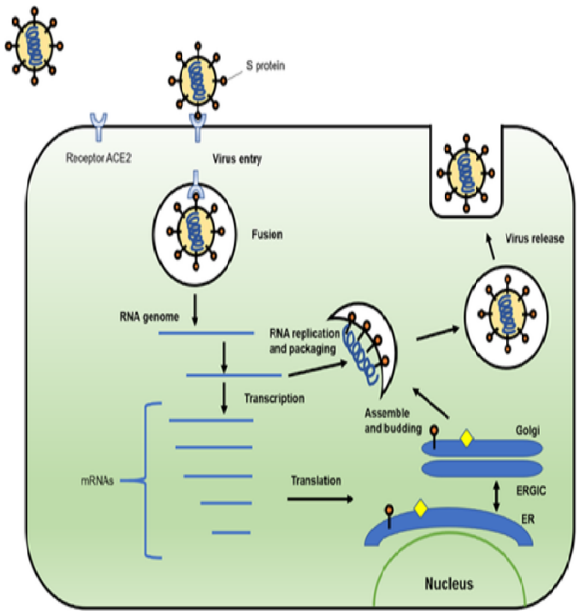


Figure 2: Schematic model of SARS-CoV-2 life cycle [5]

Epidomology

Briefly, cases tend to be in clusters which arrive in waves, and develop into larger outbreaks all over the world. The first documented outbreak occurred primarily in Wuhan [1]. According to the daily report of the World Health Organization, the epidemic of SARS-CoV-2 so far registered 78,630 cases and 2747 deaths in China, spread to 46 other countries that reported a total of 3664 cases by 27 February 2020.There are evidence suggest that transmission mode is human to human [6, 7]. The major route of transmission of COVID-19 is droplet and close contact [7]. Whether infection can occur through the oral or conjunctival routes is unknown, but SARS-CoV-2 has been detected in tears, which is resemble to SARS-CoV [8]. Reproductive number (R_0) was estimated by some studies. On the basis of clinical data of patients in COVID-19 early outbreak, the mean R_0 was ranging from 2.20 to 3.58, meaning that each patient has been spreading infection to two or three other people [6, 9]. It is still too early to develop an accurate R_0 estimate or to assess the dynamics of transmission. More research is needed in the future. The mean incubation period is about 5 days, ranging from 1 to 14 days and 95% of patients are likely to experience symptoms within 12.5 days of contact [6, 10]. These data suggest a 14-day medical observation period or quarantine for exposed and close contact persons. However, an asymptomatic carrier was reported and the incubation period was 19 days, suggesting the complicated challenge to contain the outbreak [11].

Immune responses to CoVs

The entire human population generally lacks immunity to SARS-CoV-2 and hence is susceptible to the novel virus. Currently, no detailed study has been reported regarding the immunological response to SARS-CoV-2. Thus, we can only refer to previous studies on other CoVs, especially SARS-CoV and MERS-CoV. In general, after a virus invades the host, it is first recognized by the host innate immune system through pattern recognition receptors (PRRs) including C-type lectin-like receptors, Toll-like receptor (TLR), NOD-like receptor (NLR), and RIG-I-like receptor (RLR) [12]. Through different pathways, the virus induces the expression of inflammatory factors, maturation of dendritic cells, and synthesis of type I interferons (IFNs) which limit the spreading of the virus and accelerate macrophage phagocytosis of viral antigens [12]. However, the N protein of SARS-CoV can help the virus escape from the immune responses [13].

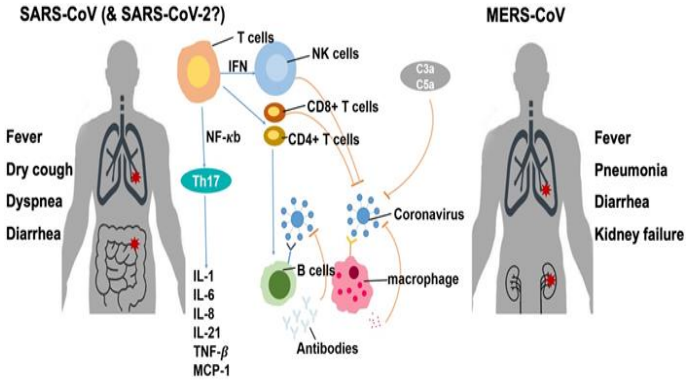


Figure 3: Immune response of the host to coronavirus infection [14]

Soon, the adaptive immune response joins the fight against the virus. T lymphocytes including $CD4^+$ and $CD8^+$ T cells play an important role in the defense. $CD4^+$ T cells stimulate B cells to produce virus-specific antibodies, and $CD8^+$ T cells directly kill virus-infected cells. T

helper cells produce proinflammatory cytokines to help the defending cells. However, CoV can inhibit T cell functions by inducing apoptosis of T cells. The humoral immunity including complements such as C3a and C5a and antibodies is also essential in combating the viral infection [15, 16]. For example, antibodies isolated from a recovered patient neutralized MERS-CoV [17]. On the other hand, an overreaction of the immune system generates a large number of free radicals locally that can cause severe damages to the lungs and other organs, and, in the worst scenario, multi-organ failure and even death [18].

Symptoms

The 2019-nCoV is a newly identified coronavirus. The common symptom is fever and respiratory symptoms including cough and breathing difficulties. The viral infection also causes pneumonia, severe acute respiratory syndrome and kidney failure for severe cases. The estimated incubation period is ranged from 2 to 11 days but it could be up to 14 days according to the previous other coronavirus experiences. Detailed information is not yet confirmed including the animal source of infection. Thus, it is recommended to stay focus on the reliable latest information such as WHO. Fever is often the major and initial symptom of COVID-19, which can be accompanied by no symptom or other symptoms such as dry cough, shortness of breath, muscle ache, dizziness, headache, sore throat, rhinorrhea, chest pain, diarrhea, nausea, and vomiting. Some patients experienced dyspnea and/or hypoxemia one week after the onset of the disease. In severe cases, patients quickly progressed to develop acute respiratory syndrome, septic shock, metabolic acidosis and coagulopathy. Patients with fever and/or respiratory symptoms and acute fever, even without pulmonary imaging abnormalities, should be screened for the virus for early diagnosis [19, 20, 21, 22].

Treatment

Due to the lack of experience with the novel CoV, physicians can mainly provide supportive care to COVID-19 patients, while attempting a variety of therapies that have been used or proposed before for the treatment of other CoVs such as SARS-CoV and MERS-CoV and other viral diseases. These therapies include current and potential treatments with antiviral drugs, immunosuppressants, steroids, plasma from recovered patients, Chinese medicine, and psychological support. Even plasma from recovered patients was proposed to be used for treatment [23]. Pharmaceutical companies are racing to develop antibodies and vaccines against the virus [24].

References

[1] T.P. Velavan, C.G. Meyer, *The COVID-19 epidemic*, Trop. Med. Int. Health (2020), https://onlinelibrary.wiley.com/doi/full/10.1111/tmi.13383.

[2] https://www.abc.net.au/news/2020-02-12/coronavirus-public-enemy-number-one-vaccine/11956446

[3] G. Pavithran, V.H. Anusha and B. Praveena, *COVID-19 (CORONA VIRUS DISEASE-2019)*, World J. Pharm. Med. Res. 6(6) (2020) 285-294.

[4] A.S. Fauci, H.C. Lane and R.R. Redfield, *Covid-19 - Navigating the Uncharted*, N. Engl. J. Med. 328 (2020) 1268-1269.

[5] F. He, Y. Deng and W. Li, *Coronavirus disease 2019: What we know?*, J. Med. Virol. (2020) 1-7.

[6] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang and Y. Zhao, *Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China*, J. Am. Med. Assoc. 323(11) (2020) 1061-1069.

[7] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren et al., *Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia*, N. Engl. J. Med. 382 (2020) 1199-1207.

[8] J.F.W. Chan, S. Yuan, K.H. Kok, K.K.W. To, H. Chu, J. Yang, F. Xing, J. Liu, C.C.Y. Yip, R.W.S. Poon and H.W. Tsoi, *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster*, The Lancet 395(10223) (2020) 514-523.

[9] J. Xia, J. Tong, M. Liu, Y. Shen and D. Guo, *Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection*, J. Med. Virol. 92(6) (2020) 589-594.

[10] S.C. Loon, S.C.B. Teoh, L.L.E. Oon, S.Y. Se-Thoe, A.E. Ling, Y.S. Leo and H.N. Leong, *The severe acute respiratory syndrome coronavirus in tears*, Brit. J. Ophthalmol. 88(7) (2004) 861-863.

[11] S. Zhao, Q. Lin, J. Ran, S.S. Musa, G. Yang, W. Wang and M.H. Wang, *Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak*, Int. J. Infect. Dis. 92 (2020) 214-217.

[12] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang and Y. Zhao, *Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China*, J. Am. Med. Assoc. 323(11) (2020) 1061-1069.

[13] Y. Bai, L. Yao, T. Wei, F. Tian, D.Y. Jin, L. Chen and M. Wang, *Presumed asymptomatic carrier transmission of COVID-19*, J. Am. Med. Assoc. 323(14) (2020) 1406-1407.

[14] A.B. Addi, A. Lefort, X. Hua, F. Libert, D. Communi, C. Ledentand B. Robaye, *Modulation of murine dendritic cell function by adenine nucleotides and adenosine: Involvement of the A2B receptor*, Eur. J. Immunol. 38(6) (2008) 1610-1620.

[15] Y. Yi, P.N. Lagniton, S. Ye, E. Li and R.H. Xu, *COVID-19: What has been learned and to be learned about the novel coronavirus disease*, Int. J. Biol. Sci. 16(10) (2020) 1753-1766.

[16] X. Lu, J.A. Pan, J., Tao and D. Guo, *SARS-CoV nucleocapsid protein antagonizes IFN-β response by targeting initial step of IFN-β induction pathway, and its C-terminal region is critical for the antagonism*, Virus Genes 42(1) (2011) 37-45.

[17] R.M. Douglas and H.S. Peter, *Molecules great and small: the complement system*, Clin. J. Am. Soc. Nephro. 10(9) (2015) 1636-1650.

[18] E. Traggiai, S. Becker, K. Subbarao, L. Kolesnikova, Y. Uematsu, M.R. Gismondo and A. Lanzavecchia, *An efficient method to make human monoclonal antibodies from memory B cells: Potent neutralization of SARS coronavirus*, Nat. Med. 10(8) (2004) 871-875.

[19] P. Niu, S. Zhang, P. Zhou, B. Huang, Y. Deng, K. Qin and L. Zhang, *Ultrapotent human neutralizing antibody repertoires against Middle East respiratory syndrome coronavirus from a recovered patient*, J. Infect. Dis. 218(8) (2018) 1249-1260.

[20] R. Channappanavar and S. Perlman *Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology*, Semin. Immunopathol. 39(5) (2017).

[21] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, *Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study*, The Lancet 395(10223) (2020).

[22] A.E. Gorbalenya, S.C. Baker, R.S. Baric, et al. *Severe acute respiratory syndrome - related coronavirus: The species and its viruses - a statement of the Coronavirus Study Group*, Nat. Microbiol. 5(4) (2020) 536-544.

[23] L.L. Ren, Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, *Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study*, Chin. Med. J. (Engl) 133(9) (2020) 1015-1024.

[24] https://www.wired.com/story/darpa-cranks-up-antibody-research-to-stall-coronavirus/

A Brief Analysis and Comparative Study on Video Conferencing Application Softwares

C.S. Sudha
Department of Computer Science, M.E.S. College of Arts, Commerce and Science
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: saisudha211@gmail.com

Absract: *The usage of video conferencing tools has increased due to Covid-19. Video conferencing can facilitate online meetings, particularly when many platforms offer extensive features for free or very little cost. While selecting a video conferencing tool, instructor should take into considerations their end motive of using the tool and based on it select either a paid or free web conferencing tool. The major difference between the two- a paid and free version is that in the paid version, it comes loaded with advanced features. However, users can make use of the free tools and when they find they require more advanced features, they can switch to the paid version tools any time. This paper analyzes various popular video conferencing applications and helps the instructor in choosing the right app for conducting online class.These apps let users share their screen, record meetings, collaborate in real time and many other facilities like chat via text, exchange files, communicate via digital whiteboards, and even broadcast conferences to large groups of passive viewers. Some are part of business-geared* ***Voice-over-IP*** *(VoIP) packages, which allows for dynamically changing voice calls to video calls and shared meetings at the touch of a button without establishing new connections.A comparative study on some of these apps has been done.*

Keywords: *Video Conferencing, VOIP, Screen Sharing, Apps, Online Classes, Encryption, Hosting.*

1 Introduction

Video conferencing has become increasingly popular in business and education over the past few years. This rapid growing technology not only allows people to connect in real time through audio and video but also makes sharing of documents and files live over the internet easier. Many educators are utilizing this technology for teaching and to share live experiences with students through direct video streaming. Many MOOCs use e-learning and screen sharing software's to deliver their courses. e-learning training is beneficial because it is instantly accessible and offers flexible scheduling. But it is also beneficial because it is useful during times of crisis such as work absences or pandemics. Teachers can use virtual classrooms to teach from home with all necessary tools at their disposal. This renders their online sessions to be just as effective as traditional ones and even more advantageous since they can offer a great deal of content, interaction, reinforcement, and real-time feedback during virtual sessions.

The spread of COVID-19 has led to the closure of educational institutions all over the world. Such closure accelerated the development of the online learning environments within those institutions so that learning would not be disrupted. The corona virus pandemic has tested the readiness of centers to deal with a crisis that requires online and remote measures. Many were not prepared, but it is important to review the reasons for offering students online classes, which go beyond periods of confinement.

Important factors to offer Online Classes

1. Offer highly effective learning environments
2. Offer complementary interactive reinforcements that allow students to study 24/7 and work at their own pace
3. Offer flexible scheduling
4. Available in any location, with an internet connection; students can attend using their devices (e.g., computers, tablets, etc.)
5. Use of instructor time (e.g., no time-consuming trips to companies)
6. Direct teacher feedback
7. Real-time student monitoring and corresponding reports
8. Allow franchises to share schedules and classes online (to increase class attendance)
9. Improve the image of institution by offering technological solutions that solve real problems

1.1 Advantages of Video Conferencing in Education

★ **Allows Different Colleges to Connect and Collaborate Easily:** Collaboration between or among colleges allows for a healthy interaction that can boost overall performance. Colleges can organize teacher training, academic conferences and online education webinars and deliver them via live audio and video streaming.The video conferencing system allows participants to enjoy a high-definition live streaming, saves time and conserves money resources.

★ **Facilitates Virtual Field Trips:** The event where a College has minimal budget or its travel plans seem impractical, video conferencing can be the best alternative to go for. Only a few representatives can be sent on the field to bring live coverage. That way, students can be able to look at exhibits in real-time from museums or learn about company operations live from the comfort of their classrooms. That minimizes on time and money resources that would have otherwise been incurred in the actual trip while still providing practical solutions to learning.

★ **Makes Out-Of-Class Learning More Convenient and Easier:** With video conferencing, students can enjoy out-of-class learning from the comfort of their homes. Teachers can organize and schedule for classes and invite students to attend at any time and from wherever they may be. Students will only need to have HD cameras and stable internet connection to start learning from out of class. Teachers and students can even create study groups to enjoy unlimited interaction and learning from home.

★ **Enables Students to Record Lessons for Later Review:** One of the greatest advantages of video conferencing in education is that it allows participants to record and save lessons and meetings. This can be a relief to students who miss class due to absenteeism or those who would simply want to review the lessons later.

★ **Makes Scheduling of Parents/Teacher Meetings Convenient:** Video conferencing eliminates time and district barriers, making it possible for people to hold meetings at anytime and from anywhere. When a school or college adopts video conferencing in holding parent/teacher conferences, it minimizes scheduling conflicts on both parties.

1.2 Disadvantages of Video Conferencing in Education

Video conferencing software comes with a share of its own challenges or disadvantages. The benefits of video conferencing technology may be great but its setbacks may just be enough

to disappoint users who depend on it on a daily basis.

- **Eliminates the Aspect of Personal Interaction:** One of the main disadvantages of video conferencing in education is that it lacks the aspect of personal interaction. As much as live streaming of lessons or meetings might be effective, participants might miss out on important facial expressions and body language. That may happen when one experiences a stuttering video or a pixilated image from the live presentation due to bad equipment or internet connection. Such things can limit learning and lead to wastage of resources like time and internet data subscription.
- **Costs more to acquire and Set up a Video Conferencing System:** A College may think it's saving on travel or operational expenses by purchasing a video conferencing system but the cost of acquiring related equipment and software might turn out to be enormous. The need for extra training to use video conference system's special program can lead even more costs. Paying for data connection and carrying out regular maintenance may also mean added operational costs.
- **Bound to Experience Technical Problems:** The smooth transmission of a live lesson or meeting may sometimes be affected by technical difficulties of the video conference system. That may be caused by hardware, software or network failure. Such circumstances require the help of technical support team to intervene and in their absence, it might be difficult to continue enjoying a live presentation.
- **Limits the Number of Users Engaging At the Same Time:** Different video conferencing systems are designed with a certain limit of the number of participants they can accommodate in one sitting. While some allow for 25 to 50 participants to engage in video conferencing at the same time, others can accommodate up to 500 participants and more. Even so, we may need to get high quality speakers and microphones to be able to attend to a large group of class members. We also need to invest in quality video as it uses more bandwidth than audio.

Desirable features of video conferencing software platforms include

- Affordable,
- Able to be used on all kinds of devices: smart phones, tablets, laptops, desktop computers,
- Can accommodate any number of people we need to include on a given call ,
- Duration of Calls can be long enough to meet our needs (some free programs have time limits),
- Dependable – low rate of dropped audio and video,
- Low latency ,
- Easy to install,easy to create account for use,
- Easy to teach others how to use,
- Security features, Privacy controls ,
- Desktop sharing, file sharing,
- Recordable sessions: this is a very valuable feature for families, practitioners, and for coaches and supervisors.

2 A Study on Various Video Conferencing Software

2.1 Cisco WebEx Meeting

Cisco WebEx Meeting builds on years of innovation by one of the most recognizable software companies. Integrated video devices, new desktop application, mobile experience, all of

these deliver more powerful and intuitive software.

Key features of Cisco WebEx Meeting are as follows:
◇ One Meeting - converged video and web conferencing delivering a first class experience all from the WebEx Cloud.
◇ Superior Scale - up to 200 video endpoints & 500 video enabled WebEx users in a single meeting, which can include joining from WebEx Teams/Jabber, and limited based on the participant cap forour specific account/subscription.
◇ Scheduled and always-on personal Cisco WebEx Meetings video conferencing options.
◇ Two-way video sharing with up to 720p screen resolution between the WebEx application and Telepresence devices.
◇ Integrated audio and presentation sharing - including application and desktop content sharing capability for all users in a meeting.
◇ Integrated roster for WebEx participants, including Telepresence device display names.
◇ Network-based recording (NBR) of meetings including content share, chat and polling
◇ Integrated meeting scheduling with the Cisco WebEx and TelePresence Integration to Outlook or the WebEx web site.
◇ Secure call control and connectivity enabled by media encryption provided by Cisco Expressway-E or Cisco Unified Expressway.
◇ Interoperability with third-party Telepresence devices.

WebEx gives us a simple and modern video meeting with the easiest schedule and join experience. Some unique features like background noise detection and video call back make sure we get a seamless video conference. At the same time, the software delivers essential tools like application sharing, screen sharing, and whiteboard to help people collaborate together. The software delivers reliability, quality, and high security.

While there are various plans available for WebEx Meetings, for most circumstances the free version is enough. This enables us to hold HD video meetings with up to 100 participants, and to take advantage of options such as screen sharing and private chat rooms.When we sign up for an account, we will be assigned a personal URL that can be used to manage all of our meetings, schedule video conferences, and access the recording we have made.

The free package includes 1GB of cloud storage, unlimited meetings of unlimited length and the ability to make MP4 recordings of them. Security is catered for by TLS 1.2 and AES 256-bit encryption, and backed by Cisco's networking know-how means performance is impressive.

It also offers optional end-to-end encryption for up to 100 users. Users with a free account can call WebEx customer support and request end-to-end encryption be enabled. It can also be self-hosted.

2.2 Zoom Meeting

Zoom started as a company for calls, and it is now one of the best in terms of video conferencing software. It provides an enterprise-level video communication solution. We can also get a cloud platform for video and audio collaboration, chat, and webinar.It works on mobile devices, desktops, and room systems that aims to be very quick and easy to set up, and offer a wide range of scalable features.

Key features of Zoom Meeting are as follows:

- Easy adoption with WebRTC technology
- Join from anywhere on any device
- Access robust security solutions throughout
- Built-in tools for screen sharing
- HD video and audio calls
- Support for up to 1,000 video participants and 49 videos
- Meet securely with role-based user permissions
- Streamlined calendaring services with Outlook and Google
- Built-in recording and transcripts
- Team chat both for groups and one-on-one messaging
- Access to extra features like webinars, chat, and phone

The best features of Zoom are HD audio and video, as well as built-in collaboration tools. We can get recordings and transcripts of the conference. The free option gives us a 40-minute group meeting maximum.

We can use Zoom to save every interaction, video, or audio conference. That makes it extremely helpful in sharing. It will take a while for non-techie people to understand how to setup Zoom and use it. Zoom our way to more productive remote meetings with this affordable, easy-to-use video conferencing software. It can support up to 1,000 participants at the same time, and up to 49 videos on a single screen, though such large gatherings are probably best suited to big-screen monitors.

Meetings can be saved locally or to the cloud, along with transcripts that have searchable text to work with. Additionally, collaboration is built in with the ability for participants to share their screens and work together to provide their own notes as required.

On top of this a team chat feature allows for file sharing, a searchable history, and a ten year archive. Meetings can also be escalated into one-on-one calls. Security is built-in, using 256-bit TLS encryption for both meetings and shared files, and automated scheduling can be done from Gmail, Outlook, and iCal.

Even better is that a feature-rich free tier is available, and able to accommodate up to 100 people for up to 40 minutes, but to include additional tools for team administration and management pricing starts at $14.99 a month, rising to $19.99 a month per host for more dedicated business and enterprise packages.

2.3 GoTo Meeting

GoTo Meeting is one of the most popular platforms for webinars and video conference software. The pricing is suitable for mid-level companies that want features found in premium packages. The web conferencing tool from Citrix is a hosted solution that can run through desktop and laptop conveniently. The multi-feature video conferencing software is simple to use, and it can be easily integrated with our Microsoft Outlook account and IBM's Lotus Notes.

Key features of GoTo Meeting are as follows:

- Supports Windows, Mac, OS, iOS and Android
- Screen sharing abilities
- HD faces
- Dial-in support

∗ File sharing
∗ Online Meeting recording
∗ Easy to invite participants

Some of the other useful features include generate reports for source tracking and attendees, integrations with multiple CRMs, and customer engagement with polls and a dashboard. Most people can begin working without much training or experience. Participants can virtually raise their hand to interact with the presenter. Or they can use the chat. The downside of GoToMeeting is the constant update. The company updates the product often, which can become frustrating and annoying. And the recording quality could be better. There are also settings to maximize call and image quality, as well as one-tap invites to join meetings as well as chats. In terms of pricing, almost all standard features are available with the most basic payment tier, which costs $14 per month, or $12 per month with an annual payment. Even the limit of 150 participants is generous, and for most businesses this is all that will be required.

A Business plan tier is available for $19 per month (or $16 when paid annually) which increases the number of participants to 250 and includes a few admin features plus drawing tools and mouse sharing. An Enterprise plan is available to accommodate up to 3,000 participants. Like any other cloud meeting app, GoToMeeting can perform any kind of online meeting irrespective of where we are located. The platform offers customization, so that our team is able to join from the company page itself. It also allows hosting of webinars for a flat charge with 1000 people at one time. It has various email templates that are automatically generated and can be used for sending invitations to employees for meetings.

We can also get post-meeting report, as we are able to record virtual meeting sessions. No other software needs to be installed for using this online meeting software. It comes at reasonable price and starts at $100 per month for 100 participants and $500 monthly in case of 1000 people.

2.4 Skype for Business

Skype is Microsoft's consumer video chat application, offering reliable video conferencing for up to 50 people. Using Meet Now, Skype allows hosts to invite anyone to join a meeting without registering an account. It's not-end-to-end encrypted, and cannot be self-hosted. With paid version it allows Skype user to call someone even if he or she is not a Skype user. A Skype company account can be created for screen sharing and collaboration.

Key features of Skype are as follows:
◦ It allows us to see when members are in a meeting, offline or available
◦ Screen sharing
◦ Ability to create a closed group
◦ File sharing
◦ Record meetings
◦ Redirect messages to user emails if they are offline
◦ Instant messaging

Skype for business is an inexpensive solution that still delivers great features. We get a good quality in terms of audio and video, and reliable service. While it is not a free video conferencing software, Skype for business is quite cheap.

Despite the low cost, we still get the most important collaborative tools. Skype benefits from the integration with Microsoft office applications, including meeting notes. The downside is we cannot get Skype for Business as a standalone app. We have to get the whole Office 365 package.

While Microsoft's video chat tool is often thought of as being little more than a way of keeping in touch with friends and family, the cross-platform app also supports group video calling for up to 50 people. Skype can also be used in a browser, which is great for chatting with people without the app installed – we can simply invite them to join in using their email address.

As we would hope, there is a screen sharing option, and to make it easier to focus on who we are speaking to, there is the ability to automatically blur backgrounds. Other handy features include live subtitling of conversations, and the ability to record chats.

If we need to have video meetings that involve more people, Skype for Business is a paid-for upgrade. For a low monthly per-user fee, we gain support for chats with up to 250 participants, Office integration, and stronger security options.

2.5 Google Meet

Google Meet is a solid and free video conference call application built into Gmail and Google Calendar. It is one of the simplest ways to make a video call with colleagues and friends. We can still use Hangouts video calls. But if we have a scheduled a meeting with a team, Meet works much better.

Google Hangouts Meet is part of the GSuite office productivity platform which is developed specifically for business needs, it can cater for a large number of users at once, and also uses smart participation and a fast interface to reduce the need to wait Therefore, we can use Meet directly from a Calendar event or Email event. Hardware by Polycom and Cisco seamlessly work with a Meet application.We can use Google meet by entering the website in our browser, and then click on Start a new meeting. Click Start meeting and then copy and share the info with the people we want to invite.

As an improved version of the standard Google Hangouts, it aims to make it easier to work with external clients. It does this first by providing a web app experience, which means there is no software to download. Secondly, it also provides a dedicated dial-in number, which not only means that employees on the go can join in, but this also ensure that line quality is maintained and that there are no drop-outs.

Another key advantage is that by being within the G Suite platform it's easy to use data from other applications, not least Google Calendar, to not just plan meetings but also set up event information as required when users do sign in.

The other big plus is that Hangouts itself doesn't come with the big monthly costs that other providers might charge.Ultimately, Meet is a serious business-grade conferencing platform that doesn't require big up-front costs for hardware, making it especially accessible for businesses of any size.It's not end-to-end encrypted, meaning the company holds the encryption keys needed to read our data. We cannot host calls on our own server. It enables as many as 250 users to

participate in calls. We don't need to log into a Google account to join a meeting.

Key features of Google Meet are as follows:
– HD Voice and Video calling
– Auto screen focusing, Instant messaging tools
– Google application integrations, Intelligent muting
– File and screen sharing
– Custom admin control options
– Private or group messaging
– Access to various integrations, Searchable history

2.6 Lifesize

This award-winning video conference and meeting room software has become the go-to cloud based communication solution. The software is quite easy to set up and small business enterprises can conduct their meetings using this software. With the perfect blend of plug-and-play HD camera systems, we can enjoy the great video conferencing experience. Used by thousands of organizations in more than 100 countries, Lifesize is the first 4K video conferencing solution. Some of the benefits of Lifesize are also its downsides. For example, the software comes with its own hardware. While that might be great, it also increases the price of the product by a mile. Mostly big organizations and enterprises use Lifesize. Smaller and medium companies can hardly afford the software.

Some of the features of the software include monitor meeting rooms, set up a centralized directory of users, configure the home screen, and more. Lifesize was founded in 2003. Lifesize provides high definition video conferencing endpoints, touch screen conference room phones and a cloud-based video collaboration platform.

Lifesize has three pricing tiers. There was no free tier, however that has changed with Lifesize Go, a completely free browser-based version of Lifesize's service that allows users to host an unlimited number of video calls (plus screen sharing on desktop) with up to 8 participants, no caps on meeting length and no app downloads.

Lifesize Standard is designed for small teams and costs $16.95 per host per month, and offers unlimited meetings for up to 100 participants, along with Single Sign on (SSO) support, personal meeting support, as well as lone chat and support.

Lifesize Plus is aimed at small and midsize companies, offering more features but a minimum of 15 hosts and costs $14.95 per host per month. This allows for up to 300 participants, includes Microsoft integrations, and offers real-time meeting insights, phone and email support, as well as 1 hour cloud recording per host. Lifesize Enterprise costs $12.95 per month with a minimum of 50 hosts. This plan allows for live streaming of up to 1,000 viewer events, unlimited US audio calling, branding and customization, premium support, as well as unlimited video recording.

Outside of the free version, Lifesize's prices may seem a bit steep compared to other video conferencing solutions. This is more than made up for with the inclusion of its own hardware into the mix. Users receive numerous devices in each plan, freeing them from not having to

rely on their own integrated camera systems. Lifesize also supports 4k video conferencing.

Key features of Lifesize are as follows:
- The video calls can be made easily and people can join the meeting rooms in a simplified manner.
- The software also works from a mobile device and the participant can join the conference room.
- The software supports 40+ participants in video meetings.

2.7 Microsoft Teams

Microsoft announced Teams in 2017, and since, the software has spread around countries and companies. Same as Skype for Business, Microsoft Teams is part of the Office 365 package. We cannot get it as a standalone product.

Some people view it as an upgraded version of the Skype for Business. Teams allow communities, groups, and teams to join through a specific URL or invitation sent by the host. Admins can set up specific teams for classes, professional learning communities, or staff members. Within the team, members can set up channels, which are topics of conversation. Users can reply with text, images, GIFs, and even memes. Meetings can be scheduled or created ad-hoc. Users visiting the channel can see that a meeting is in progress. With a plugin for Microsoft Outlook, Teams allows us to invite others into the meeting.

It includes Microsoft's business and enterprise video conferencing software, supporting up to 250 participants. Because it is integrated into Microsoft's broader online Office 365 offerings, it's not possible to keep it truly self-hosted, nor is it end-to-end encrypted. However, participants to join meetings without registering an account.

Now, to support the growing demand for video conferencing and remote working, the Microsoft brand is offering a free six month trial for the premium tier of Teams too.

Key features of Microsoft Team are as follows:
- □ Fully integrated with Office 365.
- □ Conversation channels.
- □ Reduced email.
- □ Direct access to email, Skype, OneDrive, and SharePoint.
- □ Collaborate live in real time.
- □ Access Teams across all of your devices.
- □ Collaborate internally and externally securely.

2.8 Say Namaste

Made by Mumbai-based company Inscripts, Say Namaste launched in India a few days ago and has already crossed half a million users (five lakhs). Say Namaste is basically an online tool and not an app that is available on Google Play store and Apple App store. But Say Namaste has confirmed to launch an official application on iOS. Key features of Say Namaste App are as follows:
- ✓ Video Calling
- ✓ Live Chat

✓ Inviting Other Users
✓ Accepting Meeting & Conference Links
Just like other popular video-conferencing platforms, Say Namaste offers users with live calling and chat options. It allows us to invite other users to a conference call using a meeting link and a code.To begin a new call, Say Namaste will request for user camera and microphone access on the device, however, we can choose to turn off the camera and mute the audio once we're on a call.

2.9 FreeConferenceCall

FreeConference keeps things beautifully simple for users by not requiring any software to be installed. There are mobile apps available, but it is possible to take part in a video conferencing session from just about any device with a web browser installed. We can participant in text or video chats, and use features such as screen and file sharing – but FreeConference is not without its limitations.

The maximum number of conference participants is five, which rules this out as a tool for many small businesses who may regularly want to host meetings for more people.

A number of international dial-in numbers are available for conference calls, and we have the option of recording calls if we like. Configuring, managing and scheduling meetings are very simple with FreeConference – including from Outlook – and there are some nice touches such as being able to set up recurring meetings. It's a shame that features such as advanced security, video recording and transcriptions are only part of premium packages, but the free version is still pretty powerful.

Key features of FreeConferenceCall App are as follows:
⁕ Calendar management and Calendar sync with Google
⁕ Call recording, Chat / messaging
⁕ Data encryption
⁕ Instant messaging, Live / video conferencing
⁕ Multi-presenter
⁕ Screen sharing
⁕ Video call recording,Video support

2.10 FaceTime

FaceTime is a video chat application developed by Apple. Apple developed it on an open standard, which means that technically it could be used across a range of platforms, and other manufacturers can leverage FaceTime's protocol. However, in reality, FaceTime remains available only to users of Apple products. Specifically, we can use FaceTime from our iPhone 4, iPad 2, iPod Touch, or Mac computer, and we'll need to be contacting someone on one of these devices as well. However, Apple has priced the FaceTime app so low, to encourage all Apple users to adopt this software for their video chat, even if they can only talk to other Mac devices/users with it.

FaceTime is simple and reliable, supporting end-to-end encrypted video calls for as many as 32 users. This is great for small and medium-sized meetings. If all participants have an Apple device. FaceTime is entirely proprietary, and can't be self-hosted. Some of the other features

in FaceTime are the picture in picture view. With this feature, we can see exactly what our conversation partner is seeing of us. We can also use either the front or rear view camera on our device, as well as easily transition between landscape and portrait view.

2.11 WhatsApp

With over two billion users, WhatsApp has announced several new features recently including the new Together at Home sticker pack that has started rolling out to all users globally which aims to help people stay connected throughout the COVID-19 pandemic and beyond. It leverages the same encryption behind Signal, so it is also end-to-end encrypted. WhatsApp is owned by Facebook, and while it cannot share the content of our conversations, it still shares a fair bit of information with the company. For example, users' contact lists . If we're comfortable with Facebook, WhatsApp is a reliable way to video chat with a group as large as four people. It cannot be self-hosted.

2.12 Wire

Wire uses an independent implementation of the Signal protocol called Proteus, with similar encryption properties to Signal, but Wire is a different beast. For example, it allows users to self-host, register without a phone number, and enables four video chat participants instead of two. Unlike Signal, it also allows guests to join calls. The price of this flexibility: Wire stores our contact list on their servers. If we're not concerned about Wire having access to this data, it's a reasonable solution for smaller video calls. At Freedom of the Press we sometimes use Wire, but the video call quality can sometimes be spotty.

2.13 Google Hangouts

With Google Hangouts, we get multiple communication options like video conferencing, phone calls, texting, and instant messaging. For video conferencing, it allows as many as 10 participants at a time. One participant initiates the meeting, then sends links to the rest who join the meeting through those links.

Key features of Google Hangouts are as follows:
⋆ We get numerous add-ons
⋆ We can use it on many platforms, on mobile devices and computers
⋆ Ease of using other Google products
⋆ Allows video conferencing anywhere
Google has had a free version of Hangouts available for a while now, but it hasn't offered many of the enterprise-level tools that modern businesses demand. Fortunately, the company announced that it is rolling out free access to advanced features for Hangouts Meet for all G Suite and Education customers until the first of July. This means that we can now host meetings with up to 10,000 viewers, or 250 visitors in a single domain, for free. Plus, there's the option to record and save meetings to Google Drive too. The Google team said that this new rollout was its attempt to "do our part" to keep teams connected.

2.14 LoopUp

LoopUp was founded in 2003 and has entered the conferencing space in 2006. It offers a variety of features that business owners will be able to take advantage of. LoopUp sells direct to the enterprise market and via major distribution partners including Alcatel-Lucent

Enterprise, BT, and Cable & Wireless communications. They offer 24 × 7 global support, Free Administrator tools, Dedicated account management and flexible Pay As You Go plans. This means that many entrepreneurs will be able to ensure that they can keep costs low while scaling up when needed.

2.15 Slack

Slack offers one of the simplest collaboration environments on the market. It was one of the first companies to explore the opportunities that come with having a single space to share files and contribute to conversations. We can drag and drop videos, images, and other files directly into Slack, share crucial details via instant chat, or talk face-to-face with video conferencing.

With Slack, teamwork happens through channels – environments that give were staff members a place to communicate and make crucial decisions with the right people. We can make as many channels as we like, dividing them by team or project depending on our needs. Additionally, team members can even launch video calls to improve the context of their conversations.

For companies with more work to do, there's also the Slack Enterprise Grid, which gives employees unlimited workspaces in which they can organise their work. The Enterprise Grid also ensures that administrators have complete control over the information shared.

Key features of Slack are as follows:
- File sharing and management
- Video conferencing and chat
- Unlimited channels for conversations
- Slack enterprise grid
- Countless integrations with the tools we use each day.

2.16 GoToWebinar

With GoToWebinar, we can easily organize our webinar and just focus on reaching more people and growing our business. If we choose the date to host our webinar, and it takes care of mostly everything else.It also exposes us to a variety of features to improve our webinar experience, ranging from flexible scheduling to the entire event management process. We also have access to several in-built webinar templates that provide the ultimate business environment.

Moreover, with impressive features such as automated email reminders, customizable webinar invitations, and a highly converting registration page, we can now promote our upcoming event and drive massive traffic. Other features include in-built polls and surveys, automatic webinar recordings, and more.

Key features of Google Hangouts are as follows:
- Pre-recorded events
- Robust analytics
- HD video quality
- 24/7 customer support
- Integrations with GoToMeeting
- In-built polls and surveys to engage our audience
- Automatic recording, which can then be shared online

⋈ Seamless integration with tools such as Zapier, Salesforce, Unbounce, etc.
Starter plan costs $89 per month for 100 participants, $199 per month for 500 participants, and $429 per month for 1,000 people, all for annual subscriptions. We can also start a free trial with up to 100 people; no credit card required. Its disadvantages are:outdated software, The Starter plan limits the attendance count to 100, Comes with a hefty price, even the lowest tier plan costs around $900/year.

2.17 BigMarker

BigMarker is known as the #1 video platform for webinars, summits, and virtual conferences. Their live streaming capabilities are where they really excel. We can engage up to 10,000 people at once and create an interactive experience with features like polls, handouts, and live Q and As. There are also no limits on the number of presenters in the webinar – literally anyone can hop in and join the discussion on screen.

To host these live events, we're provided with a suite of marketing tools, including custom email invites, registration landing pages, and helpful reminders. With their automated webinars, we can integrate BigMarker with our CRM software to qualify prospect and generate, nurture, and convert wer leads.

Key features of BigMarker are as follows:
▹ Host Tools. Branding. Allows hosts to add official branding to their webinar.
▹ Collaboration Tools. Screen Sharing.
▹ Attendee Tools. Registration.
▹ Meeting Coordination. Scheduling.
▹ Post-Event Tools. Event Analytics.
▹ Software Type. Mobile.
▹ Integrations. Social Media Integration.

2.18 Dialpad Uberconference

Dialpad is a company offering businesses the tools that they need to work from anywhere, wherever a high-speed connection is available. To help other companies in the current landscape follow suit, Dialpad has started to offer the DialpadTalk and UberConference PRO technology in their communication stacks to any business throughout North America and Japan, for free. This free access will continue for the next couple of months as the concerns around the virus continue to grow, helping companies to adapt more quickly to the changing workforce demands. UberConference Free users and new signups, Dialpad are: Removing the 45-min limit (up to 5-hours, max), increasing the maximum participants from 10 to 50.

Additionally, Dialpad Talk paid users can upgrade to UberConference Business, as opposed to the UberConference Free version included with their accounts. They can therefore enjoy all the benefits of UberConference Business (no cap, up to 100 users, no PIN, Voice Intelligence, etc) at no additional cost. Eligible users will be notified by email and an in-app announcement.

The company is making paid versions of all of its products – Dialpad Talk, Dialpad Sell, Dialpad Support and UberConference – available for free, for two months, to help those impacted by the corona virus work from home.

2.19 TeamViewer

TeamViewer software can connect to any PC or server, so we can remote control our partner's PC as if we were sitting right in front of it. For the remote session to work the partner has to start a small application, which does not require installation or administrative rights. TeamViewer 6 is the latest version of the software and works with Windows, Mac, Linux operating systems and Mobile (Android, Apple iPad, Apple iPhone) devices.

Key features of BigMarker are as follows:
⊖ Permanent access for unattended devices.
⊖ Wake-on-LAN and remote rebooting.
⊖ Black screen for private remote access.
⊖ Secure, flexible file sharing.
⊖ Remote Printing for Windows and MacOS.

2.20 AnyMeeting

This video conferencing software was previously known as Freebinar and is one of the best web conferencing software that allows up to 200 people to join the video conferences. Unlike most of the webinar services, AnyMeeting aims to provide user-friendly intuitive controls, good sound quality and a clean interface. Nonetheless, its PayPal integration feature makes it convenient to charge for webinars.

Key features of BigMarker are as follows:
• Screen sharing and phone conferencing are the key features of the software solution.
• The software has meeting recording and even a follow-up functionality.

3 Comparison of the Video Conferencing Software's

Sl. No.	**Software Service**	**Support end to end encryption**	**Supports self hosting**	**Need to register an account for join meetings**	**Meeting capacity (free version)**	**Recording meeting**	**Screen sharing**	**Duration limit of meeting**
1	Zoom	No	Yes	Required	100	Yes	Yes	40 minutes
2	Google Hangouts	No	No	Required	10	Yes	No in App Version, Yes in Web version	No limit
3	Google Meet (Business)	No	No	Not required	50(claims to increase to 100)	Yes	Yes	No limit

4	Skype	No	No	Not required	10(free) 50(paid)	Yes	Yes	100hrs /month, 10hrs/day, 4hrs/ person
5	Microsoft Teams	No	No	Not required	250 (for paid version)	Yes	Yes	No limit
6	Cisco WebEx	Yes	Yes	Required	100	Yes	Yes	No limit
7	FaceTime	Yes	No	Required	32 (apple devices only)	Yes	Yes	No limit
8	Say Namaste	No	No	Not required	25	No	No	No limit
9	Wire	Yes	Yes	Not required	4	-	-	-
10	WhatsApp	Yes	No	Required	4	Yes	-	No limit
11	Free Conference Call	No	No	Required	100	No	Yes	40 minutes
12	GoTo meetings	Yes	No	Required	26	Yes	Yes	No limit
13	LifeSize	Yes	No	Not required	8(free) 300(paid)	Yes	Yes	No limit
14	Team Viewer	Yes	No	Required	300	Yes	Yes	No limit
15	Slack	No	No	Required	100	Yes	Yes	No limit
16	Uber Conference	Yes	No	Required	50	Yes	Yes	5 hours

4 Conclusion

To conduct online classes during COVID-19, I have analyzed and compared various video conferencing software apps. With the emergence of reliable video conferencing software, it has become simpler to organize online classes with screen sharing and recording. Depending on the strength of our class and analyzing other requirements like screen sharing, chat, single or multiple host, we can choose the appropriate software. Zoom app is having many security flaws. Skype, zoom, whatsapp are easy to use. Namaste app has gained popularity in India after its launch; however it is still in security testing phase. Cisco WebEx and Microsoft Teams are other alternatives. Creating an account takes time in Teams. WebEx is designed for official meetings, it gives best experience. FaceTime has best audio, video quality. After comparing video conferencing software mentioned above, one should be clear about which app to choose. I have concluded WebEx and Teams are best suited to my requirements.

References

[1] N. Earle, S. Prentice et.al, *Top 15 cloud based video conferencing services*, Clout Tweaks, https://cloudtweaks.com/15-cloud-based-video-conferencing-services/
[2] https://www.eztalks.com/video-meeting/cloud-meeting-software-for-business.html
[3] M.H. Dam, *8 Best screen recorders for Windows 10 – Free & Paid*, atmoisystems, 2019, https://atomisystems.com/screencasting/record-screen-windows-10/
[4] https://educationblog.microsoft.com/en-us/2020/03/how-schools-can-ramp-up-remote-learning-programs-quickly-with-microsoft-teams/
[5] https://www.voipreview.org/best-cloud-video-conferencing-software
[6] M. Shelton, *Choosing the right video conferencing tool for the job*, Freedom of the Press Foundation, 2020, https://freedom.press/training/blog/videoconferencing-tools/
[7] https://www.g2.com/categories/video-conferencing/free

Remdesivir as a Potential Treatment to COVID-19

V.R. Vyshnavi
Department of Chemistry, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: vyshu.23vrao@gmail.com

Absract: *Remdesivir is a broad spectrum antiviral agent produced by a pharmaceutical firm, Gilead Sciences in January. It was originally developed to treat viral infections like Ebola and Marburg [1]. Several In-Vitro studies have proved its activity against RNA viruses like SARS-CoV and MERS-CoV. Currently United States has labelled Remdesivir with an Emergency Use Authorization [EUA] to treat COVID-19 as an effective intravenous medication. In-Vitro studies have revealed that Remdesivir is efficient in control of 2019 novel Coronavirus. Therefore it is the need of the hour to assess the efficacy of antiviral agents like Remdesivir to combat its global persistence. This article reviews current literature available on the structural characteristics, mechanism of action and the potential side effects associated with Remdesivir.*

Keywords: *Coronavirus, Nucleotide triphosphate, Remdesivir, Respiratory distress, Treatment.*

1 Introduction

2020 has seen a rapid spread of the novel corona virus pandemic. The disease originated from Wuhan, the capital of Hubei province in central China, and advanced to major cities like Hong Kong, Macao, Taiwan, Thailand and countries like Japan, South Korea, Vietnam, Singapore, Nepal, France, Italy, United States, Australia, Canada and India. The pathogen was identified as novel coronavirus [2019-nCoV] also designated as SARS-CoV-2 due to its close relatedness to SARS-CoV that caused the 2002-2004 SARS (Severe Acute Respiratory Syndrome) outbreak. SARS-CoV-2 belongs to Betacoronavirus of Coronaviridae. Other members of this family include SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome- coronavirus).

Several In-Vitro studies on cell lines, mouse models and Non-Human Primate models have revealed the efficacy of Remdesivir in treating Corona virus infections and related symptoms. Recent In-Vitro study revealed that Remdesivir inhibits viral infections in human liver cancer Huh-7 cell lines that are sensitive to 2019-nCoV [2].

US-FDA has accounted that the benefits of Remdesivir outweigh its associated potential risks in treating COVID-19. The National Institute of Allergy and Infectious Diseases (NIAID) made an official statement, that Remdesivir was better than a placebo in reducing recovery time for people with advanced COVID 19 and related respiratory disorders.

2 Mechanism of Action

The antiviral potential and the mechanism of action of Remdesivir post viral entry can be correlated to its structure [3]. Several studies have shown that the mutant cells or animal mod-

els that lack the proofreading activity were significantly more sensitive to Remdesivir [4].

Remdesivir is a prodrug that exists as an inactive molecule. Remdesivir diffuses into the host cells post viral infection and gets converted to Remdesivir monophosphate by the action of phosphorylating enzymes. The mono-phosphates in turn get phosphorylated to an active metabolite Remdesivir triphosphate by the action of enzymes like nucleoside-phosphate kinases [5]. Remdesivir active metabolite is structural analogue to nucleotide triphosphate such as ATP. Post host entry this active metabolite of Remdesivir gets incorporated into nascent RNA chains of the virus and results in premature chain termination [6]. The Remdesivir triphosphate competes with ATP (Adenosine triphosphate) and binds more effectively to the viral RNA-dependent RNA polymerases (RdRps) that incorporates Remdesivir triphosphate into the nascent RNA chain instead of ATP.

Following the incorporation into RNA chain, Remdesivir triphosphate enables addition of three more nucleotide triphosphates followed by arrest of viral RNA synthesis leading to early Chain termination. This ensures stabilization of Remdesivir and prevents its excision by the proofreading activity of the viral RNA polymerase [7, 8]. This prevents the replication of viral particles and thereby their spread to subsequent tissues.

3 Side effects of Remdesivir

Remdesivir is causes Infusion-related reactions like gastrointestinal distress, sweating, shivering, nausea and vomiting and elevated blood levels of liver enzymes like transaminase [9]. It associated with adverse side effects like low albumin, low Blood pressure, anaemia, low platelet count, delayed clotting and jaundice [10]. It is also viewed to cause impairment of vital organs, inflammation of liver and damage to hepatocytes.

4 Structure of Remdesivir

Remdesivir is chemically 2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f] [1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl] amino] propanoate (refer Figure 1). It has a molecular formula C27H35N6O8P and molecular weight of 602.6 g/mol. Structurally it is analogous to the nucleotide triphosphate ie., adenosine triphosphate [ATP]. Remdesivir is an intravenous formulation and readily absorbs into the body tissue. The plasma Half-life of Remdesivir in its activated state is 20 hours in Human Beings [11, 12].

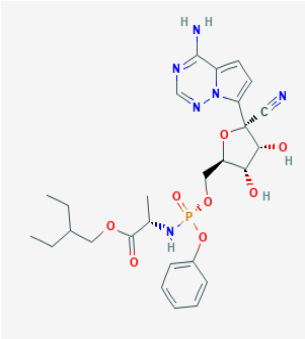


Figure 1: Structure of Remdesivir

5 Conclusion

Remdesivir is a broad spectrum antiviral pharmaceutical used to treat viral infections like SARS, MERS, Ebola, Nipah, Marburg and now COVID-19. Several In-Vitro studies have proved its efficiency against members of viral families like Filoviridae and Coronaviridae. The currently prevailing pandemic caused by SARS-CoV-2 which has no specific established treatment requires the use of such broad spectrum antiviral drugs like Remdesivir. Clinical studies have been undertaken globally to establish safety profile of Remdesivir. However use of Remdesivir faces conflicting ideas due to lack of sufficient scientific data validation and potential risks associated with it. This review highlights the greater requirements to gather more information through clinical studies worldwide and establish Remdesivir as the new face of treatment for COVID-19.

References

[1] C. Scavone, S. Brusco, M. Bertini, L. Sportiello, C. Rafaniello, A. Zoccoli, and A. Capuano, *Current pharmacological treatments for COVID-19: What's next?*, Br. J. Pharmacol. (2020).

[2] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang and H.D. Chen, *A pneumonia outbreak associated with a new coronavirus of probable bat origin*, Nat. 579(7798) (2020) 270-273.

[3] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu and G. Xiao, *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro*, Cell Res. 30(3) (2020) 269-271.

[4] M.L. Agostini, E.L. Andres, A.C. Sims, R.L. Graham, T.P. Sheahan, X. Lu, and A.S. Ray, *Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease*, MBio 9(2) (2018) e00221-18.

[5] T.P. Sheahan, A.C. Sims, R.L. Graham, V.D. Menachery, L.E. Gralinski, J.B. Case, and R. Bannister, *Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses*, Sci. Ttransl. Med. 9(396) (2017).

[6] T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva, and N. Larson, *Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys*, Nat. 531(7594) (2016) 381-385.

[7] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, and E. Nicastri, *Compassionate use of remdesivir for patients with severe Covid-1*, N. Engl. J. Med. (2020).

[8] J.A. Al-Tawfiq, A.H. Al-Homoud, and Z.A. Memish, *Remdesivir as a possible therapeutic option for the COVID-19*, Travel Med. Infect. Dis. (2020).

[9] N. Mehta, M. Mazer-Amirshahi, N. Alkindi, and A. Pourmand, *Pharmacotherapy in COVID-19: A narrative review for emergency providers*, Am. J. Emerg. Med. (2020).

[10] Y. Wang, D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, and Y. Hu, *Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial*, The Lancet (2020).

[11] R.T. Eastman, J.S. Roth, K.R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik, and M.D. Hall, *Remdesivir: A Review of its discovery and development leading to human clinical trials for treatment of COVID-19* (2020).

[12] *Remdesivir*, PubChem Database, NCBI, CID=121304016.

Hydroxychloroquine - Potential treatment to a wide spectrum of diseases

V.R. Vyshnavi[1] and S. Rizwana[2]
[1,2]Department of Chemistry, M.E.S. College of Arts, Commerce and Science,
15th cross, Malleswaram, Bengaluru - 560003.
Email ID: [1]vyshu.23vrao@gmail.com, [2]shamsiya.rizwana@gmail.com

Absract: *Hydroxychloroquine is a US-FDA approved antimalarial agents associated with reducing the manifestations of inflammatory disorders, prevention of disease and prevention of treatment-induced complications. Hydroxychloroquine In-Vitrostudies show activity against viral strains belonging to Coronaviridae such as SARS-CoV-1 (SARS- related Corona Virus strain 1), that caused the 2002-2004 SARS (Severe Acute Respiratory Syndrome) outbreak and SARS-CoV-2 that has caused the 2019-2020 COVID 19 pandemic. The present scenario compels critical care physicians and researchers worldwide to undertake several studies emphasising the role of Hydroxychloroquine as a potential drug. In this review, we discuss the role of Hydroxychloroquine as a treatment to each disorder and the potential side effects associated with its administration.*

Keywords: *Hydroxychloroquine, Immunomodulatory, Novel, Treatment.*

1 Introduction

Hydroxychloroquine, commercially called 'Plaquenil' administered as a sulphate salt, has been in use to treat wide range of inflammatory diseases and intracellular infectious diseases like malaria since its approval as a potential drug in 1950 [1]. Studies have proved that the administration of Hydroxychloroquine leads to improvement of clinical parameters with their slow onset of action [2]. Though hydroxychloroquine is effective, it is associated with the potential of causing numerous side effects, like headache, loss of appetite, nausea, vomiting, skin rash and in severe cases vision loss due to retinal toxicity. Uncertainty in the mode of action, specificity and risks of Hydroxychloroquine questions its viability as a potential treatment. In this review we discuss the use of Hydroxychloroquine with respect to its novel applications.

2 Mechanism of Action

There are many proposed mechanisms of action of Hydroxychloroquine such as alkanisation of the subcellular components like lysosomes [3], interference with physiological processes of immune system such as chemotaxis and phagocytosis, intervention with DNA stabilisation and cell signalling, activation of immune cells and inhibition of proteases and metalloproteinases [4, 5], antagonising prostaglandins [6], blocking subcutaneous reactions by preventing the absorption of UV radiations and down-regulating the production of autoantigenic peptides or their precursors [2]. Hydroxychloroquine has also a strong binding to melanin. This reflects the ocular toxicity and dermatological properties Hydroxychloroquine. The occurrence of any ocular adverse reactions can however be minimised by paying close attention to the dose (based on a body weight) with regular retinal examination [7].

However the specific mechanism and role of hydroxychloroquine in individual disease is not very well established and requires scientific data validation through In-vitro, In-vivo and Clinical studies.

Diseases and Complications treated using Hydroxychloroquine

MALARIA: Malaria is one of the most wide spread parasitic disease in the world with about 3 million deaths being attributed to this disease [8]. The causative agent for malaria is a unicellular eukaryote called Plasmodium. There are four species of plasmodium that cause malaria namely P. falciparum, P. malariae, P. ovale and P. vivax. Qunine and Chloroquine were used to treat malaria until 1960. With the onset of resistant plasmodium strains to Quinine and Chloroquine, its N-ethyl substituted analogue Hydroxychloroquine was used as treatment to malaria since then. Hydroxychloroquine actively attacks the heme polymerization process and heme digestion to disrupt the life cycle of plasmodium [9].

RHEUMATOLOGIC / INFLAMMATORY DISEASES: Hydroxychloroquine is associated with blocking inflammatory pathways that correlates with its anti-rheumatologic activity. Hydroxychloroquine is used as most popular treatment for Rheumatologic disorders like Rheumatoid arthritis, Systemic Lupus Erythematous and Osteoarthritis for over seven decades now. Hydroxychloroquine reduces the rate of accumulation and specificities of autoantibody in Systemic Lupus Erythematous [10]. Hydroxychloroquine is associated with reduction in cytokine mediated cartilage reabsorption in treating Osteoarthritis [7]. Studies provide evidence that hydroxychloroquine down-regulates the promoter genes and/or decreases the secretion of monocyte derived pro-inflammatory cytokines like TNF α (Tumour Necrosis Factor alpha), IL6 (Interleukins 6) and IL10 (Interleukins 10). The exact mechanism by which these occur need to be fully defined [11, 12, 13]. In combination with Chloroquine and other medications Hydroxychloroquine reduces the risk of Type-2 Diabetes Mellitus in patients suffering with Rheumatologic conditions.

VIRAL INFECTIONS: Hydroxychloroquine and its structural analogue Chloroquine have long since proved their efficacy on members belonging to viral families like Retroviridae, Coronaviridaeand Orthomyxoviridae.It has been used to treat viral infections like HIV, Influenza, SARS and now COVID19. The antiviral effects of Hydroxychloroquine are attributed to the reduction in interleukins, inhibition of glycosylation of viral particles, inhibition of viral genome replication and decrease in the production of viral glycoproteins like sialic acid [14, 15, 16, 17]. The broad spectrum antiviral effects of Hydroxychloroquine deserve particular attention especially at a time like now in which the world is threatened by the possibility of a new Corona virus pandemic, and the availability of effective drugs would be fundamental during evaluation of an effective vaccine.

AUTOPHAGY: Autophagy is a complicated cellular homeostatic mechanism that maintains integrity through degradation of defective subcellular organelles, infectious agents, and misfolded proteins [18]. However under stressed conditions of reduced oxidative stress and limited drug efficacy autophagy is linked to cancer tumour development and maintainence. Hydroxychloroquine is viewed as moderately potential immunomodulatory molecule to target the lysosomes and produce measurable anti-autophagy effect [3]. The mechanism involved needs further scientific validation.

THROMBOSIS / BLOOD CLOTTING: Hydroxychloroquine exhibits antithrombotic effect by inhibition of platelet aggregation and adhesion, increasing endothelium dependent vasodilation and artery elasticity, reducing vascular stiffness and vascular resistance [19]. This can be correlated to its potential effect to treat diseases like haemophilia.

CANCER: Hydroxychloroquine induces apoptosis effect on malignant B-cells, by interfering with the cell signalling pathway such as activating caspase-3 and modifying Bcl-2/bax ratio [20, 21, 22]. Hydroxychloroquine has also demonstrated In-vitro antiproliferative effect on breast cancer cell and mouse colon cancer models [23].

SKIN DISEASES: Hydroxychloroquine blocks UV light absorption by skin inhibiting subcutaneous light sensitive reactions reduces skin symptoms like rash or skin cancer in severe cases [24].

3 Conclusion

Among all antimalarial drugs Hydroxychloroquine since its first use decades ago, has exhibited extended effects on diseases in nearly all major branches of medicine including immunology, oncology, hematology, dermatology, cardiology, and infectious diseases. In-Vitro studies have shown that hydroxychloroquine also inhibits SARS-CoV-2 transmission. Hydroxychloroquine works partially by inactivating the body's immune response like inflammation, oedema, pain, fever and disrupts critical cell processes.

Though hydroxychloroquine is effective, it is associated with the potential of causing numerous side effects, like headache, loss of appetite, nausea, vomiting, skin rash and in severe cases vision loss due to retinal toxicity.

One significant benefit with using these drugs is that they have been on the market and used for a sufficiently long time. Hence a reasonable amount of information regarding contraindications, allergic responses, side effects, and efficacy is available that can kept in mind before using it to treat new diseases like COVID-19. Since they have been around for so long, generic versions are available, which may prove to be cost-effective for use in coronavirus treatment worldwide.

References

[1] J.C.S. Yam and A.K.H. Kwok, *Ocular toxicity of Hydroxychloroquine [HCQ]*, Hong Kong Med. J. 12(4) (2006) 294.

[2] R.I. Fox, *Mechanism of action of Hydroxychloroquine [HCQ] as an antirheumatic drug*, In Seminars in arthritis and rheumatism, 23(2) (1993) 82-91 .

[3] S. Ohkuma and B. Poole, *Fluorescence probe measurement of the intralysosomal pH in living cells and the perturbation of pH by various agents*, Proc. Natl. Acad. Sci. U.S.A. 75(7) (1978) 3327-3331.

[4] H.K. Ziegler and E.R. Unanue, *Decrease in macrophage antigen catabolism caused by ammonia and chloroquine is associated with inhibition of antigen presentation to T cells*, Proc. Natl. Acad. Sci. U.S.A. 79(1) (1982) 175-178.

[5] A. Lesiak, J. Narbutt, A. Sysa-Jedrzejowska, J. Lukamowicz, D.P. McCauliffe and A. Wozniacka, *Effect of chloroquine phosphate treatment on serum MMP-9 and TIMP-1 levels in patients with systemic lupus erythematosus*, Lupus 19(6) (2010) 683-688.

[6] B.M. Loffler, E. Bohn, B. Hesse and H. Kunze, *Effects of antimalarial drugs on phospholipase A and lysophospholipase activities in plasma membrane, mitochondrial, microsomal and cytosolic subcellular fractions of rat liver*, Biochim. Biophys. Acta, Lipids Lipid Metab. 835(3) (1985) 448-455.

[7] K.D. Rainsford, A. L. Parke, M. Clifford-Rashotte and W.F. Kean, *Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases*, Inflammopharmacology 23(5) (2015) 231-269.

[8] J. Sachs P. Malaney, *The economic and social burden of malaria*, Nat. 415(6872) (2002) 680-685.

[9] A.F.G. Slater and A. Cerami, *Inhibition by chloroquine of a novel haem polymerase enzyme activity in malaria trophozoites*, Nat. 355(6356) (1992) 167-169.

[10] J.A. James, X.R. Kim-Howard, B.F. Bruner, M. K. Jonsson, M.T. McClain, M.R. Arbuckle and J.B. Harley, *Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus*, Lupus 16(6) (2007) 401-409.

[11] S.M. Weber and S.M. Levitz, *Chloroquine interferes with lipopolysaccharide-induced TNF-α gene expression by a nonlysosomotropic mechanism*, J. Immunol. Res. 165(3) (2000) 1534-1540.

[12] A. Wozniacka, A. Lesiak, J. Narbutt, D.P. McCauliffe and A. Sysa-Jedrzejowska, *Chloroquine treatment influences proinflammatory cytokine levels in systemic lupus erythematosus patients*, Lupus 15(5) (2006) 268-275.

[13] P. Lopez, J. Gomez, L. Mozo, C. Gutzerrez and A. Suarez, *Cytokine polymorphisms influence treatment outcomes in SLE patients treated with antimalarial drugs*, Arthritis Res. Ther. 8(2) (2006) R42.

[14] A. Savarino, M.B. Lucia, E. Rastrelli, S. Rutella, C. Golotta, E. Morra and R. Cauda, *Anti-HIV effects of chloroquine: Inhibition of viral particle glycosylation and synergism with protease inhibitors*, J. Acquir. Immune Defic. Syndr. 35(3) (2004) 223-232.

[15] D.K. Miller and J. Lenard, *Antihistaminics, local anesthetics, and other amines as antiviral agents*, Proc. Natl. Acad. Sci. 78(6) (1981) 3605-3609.

[16] J.J. Kwiek, T. A. Haystead and J. Rudolph, *Kinetic mechanism of quinoneoxidoreductase 2 and its inhibition by the antimalarial quinolines*, Biochemistry 43(15) (2004) 4538-4547.

[17] S. Olofsson, U. Kumlin, K. Dimock and N. Arnberg, *Avian influenza and sialic acid receptors: More than meets the eye?*, Lancet Infect. Dis. 5(3) (2005) 184-188.

[18] H. Yin, H. Wu, Y. Chen, J. Zhang, M. Zheng, G. Chen and Q. Lu, *The therapeutic and pathogenic role of autophagy in autoimmune diseases*, Front Immunol. 9 (2018) 1512.

[19] C. Tang, T. Godfrey, R. Stawell and M. Nikpour, *Hydroxychloroquine in lupus: Emerging evidence supporting multiple beneficial effects*, Intern. Med. J. 42(9) (2012) 968-978.

[20] L. Lagneaux, A. Delforge, S. Carlier, M. Massy, M. Bernier and D. Bron, *Early induction of apoptosis in B-chronic lymphocytic leukaemia cells by hydroxychloroquine: Activation of caspase-3 and no protection by survival factors*, Br. J. Haematol. 112(2) (2001) 344-352.

[21] L. Lagneaux, A. Delforge, M. Dejeneffe, M. Massy, M. Bernier and D. Bron, *Hydroxychloroquine-induced apoptosis of chronic lymphocytic leukemia involves activation of caspase-3 and modulation of Bcl-2/bax/ratio*, Leuk. Lymphoma 43(5) (2002)

1087-1095.

[22] E. Mansilla, G.H. Marin, L. Nunez, H. Drago, F. Sturla, C. Mertz and C. Raimondi, *The lysosomotropic agent, hydroxychloroquine, delivered in a biodegradable nanoparticle system, overcomes drug resistance of B-chronic lymphocytic leukemia cells in vitro*, Cancer Biother. Radiopharm. 25(1) (2010) 97-103.

[23] I. Ben-Zvi, S. Kivity, P. Langevitz and Y. Shoenfeld, *Hydroxychloroquine [HCQ]: From malaria to autoimmunity*, Clin. Rev. Allergy Immunol. 42(2) (2012) 145-153.

[24] R.S. Lester, T.K. Burnham, G. Fine and K. Murray, *Immunologic concepts of light reactions in lupus erythematosus and polymorphous light eruptions: I. The mechanism of action of hydroxychloroquine*, Arch. Dermatol. 96(1) (1967) 1-10.

MES BULLETIN OF APPLIED SCIENCES

AUTHOR GUIDELINES

MES Bulletin of Applied Sciences (MESBAS): It is a peer-reviewed biannual journal that publishes both theoretical and experimental quality papers in any applied field. Aim is to promote research culture in teachers and students of UG, PG and higher. Scope of the journal includes: Biology, Chemistry, Physics, Mathematics, Statistics, Computer Science, Social Sciences, Economics, Business, Environmental Science, Food Science, Geology, Medicine, Engineering.

GUIDE FOR AUTHORS

The following categories will be considered for publication:

Original Research Papers, Original Research Reports, State-of-the-art Reviews, Short Communications / Technical notes.

PREPARING MANUSCRIPT:

Ensure that the following items are present:

- One author has been designated as the corresponding author with contact details:
  i. E-mail address ii. Full postal address
- Paper should be in English.
- Enclose a covering letter.
- The papers for Mathematics, Physics, Computer Science and Engineering should strictly be in LaTeX. LaTeX template will be provided. Others can be in Docx format.

STRUCTURE OF THE PAPER:

Title, Authors details, Abstract, Key words, Introduction, Text, Conclusion, Acknowledgment, References, Figures and Tables.

PAPER SUBMISSION:

Please send your paper as attached file to mail id: mesbas.rcam@gmail.com

Subscription: Rs. 1200.00 per year (2 issues)

MES BULLETIN OF APPLIED SCIENCES

CONTENTS

Volume 3, Issue C-19 **June 2020**