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Online Special Issue on

COVID-19

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- Will a coronavirus vaccine stop the present wildfire of misery?
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Press Statement on the AYUSH Advisory on Coronavirus

Dated 30 January 2020

The Breakthrough Science Society expresses shock and anguish that the Press Information Bureau (PIB), Government of India has released a statement recommending members of the public to use untested Ayurveda, Homoeopathy and Unani medicines to prevent and treat the illnesses caused by Coronavirus . Even as the World Health Organisation (WHO) has only advised the public to stick to basic preventive measures like avoiding contact with people suffering from cold, washing hands, staying away from crowded places, farm or wild animals etc, Indian government after giving similar hygiene recommendations has also advised people to take to ayurvedic practices, homoeopathic drugs and Unani medicines . A homeopathic drug namely Arsenicum album30, or Unani medicines like Sharbat Unnab or Ayurvedic preparations like Shadang Paniya are advised to be taken either as preventive medicines or for symptomatic management against Coronavirus infections. But there are no supporting evidence that these medicines are effective against the virus. How are these drugs even relevant in the fight against novel Coronavirus (2019-nCov), which is itself a new organism is not clear. In the absence of proper studies on the effectiveness of these medicines the government advisory on Coronavirus is irresponsible, misleading, dangerous to the public health and against medical ethics.

The Coronavirus (2019-nCoV) has already claimed 132 lives. It has affected over a dozen of countries. According to the Health Ministry, 9150 passengers have been screened for the Coronavirus. Health ministry has asked travellers from China to report to the nearest health facility in case they do not feel well. It is essential to take adequate preventive measures against Coronavirus and issue proper advisories to the people. We expect that these advisories should go through scientific validation before being publicly communicated.

Open Letter sent to the President of India

Dated 20 March 2020

To
The Honourable President of India
New Delhi

Subject: Request for taking effective steps to contain COVID-19 infections in India

Respected Sir,

We are writing to request your urgent intervention to prevent an impending public health emergency in the country. India is currently in Stage 2 of a COVID-19 pandemic where cases are being reported in those with travel history and those who have been in contact with them. The government must heed the advice of health experts the world over, who tell us that progression to 'Stage 3', community transmission, should be avoided at all costs.

This requires urgent action by the Central and State governments, working together, in the following directions.

1. The foreign nationals and Indians returning from the affected countries need to be mandatorily tested and, if any suspicion arises, should be quarantined.

2. Since this has not been done effectively over the past two months, it is highly likely that many infected individuals are out in the open, mixing with the public and passing on the infection to others. Detection and containment is the only way to control the outbreak. This requires a far larger number of testing facilities than is available at present.

3. The government should rapidly enhance the facilities for treating large numbers of patients, set up large number of critical care facilities equipped with life-supporting equipment like ventilators. Isolation wards should be created in all government hospitals at the state, district, and subdivision levels.

4. Private and corporate hospitals should be requisitioned to give service to the public at this hour of crisis.

5. The government should ensure availability of masks, hand sanitizers, medicines, etc., free of cost to prevent exploitation of people by unscrupulous profiteers, who should be severely dealt with.

6. The government should take effective measures to provide essential commodities to people who are not able to earn their livelihood because of the situation created by Covid-19.

7. Most importantly, effective steps must be taken to impose social distancing by avoiding gatherings of large number of people for religious occasions, marriage parties, and other social events. In this regard we would like to bring to your notice that the Ram Navami celebrations being planned by the UP government in Ayodhya and other places from 25 March to 2 April will be a certain recipe for disaster. Lakhs of people are expected to congregate in various places. Such large gatherings, which can hasten the uncontrolled spread of the epidemic,

must be banned to prevent the potential pandemic.

Finally, we are dismayed that the AYUSH Ministry, without any supporting evidence and clinical trials, has prescribed a homeopathic drug Arsenicum album 30 and an array of Ayurvedic and Unani drugs as preventive medicines against the Coronavirus infection. Such unscientific and misleading advisories should immediately be withdrawn. In addition, the superstitious practices of drinking gomutra and dunking in cow-dung, claiming them as cures for COVID-19, should be banned as these animal waste products are harmful for health.

We are hopeful that you will take the much-needed steps to ensure proper handling and management of the threat posed by the COVID-19 virus.

Thanking you,
Yours truly,

Prof. Dhrubajyoti Mukhopadhyay
President

Prof. Soumitro Banerjee
Secretary

Letter from India March for Science to the Prime Minister of India

Dated 21 April 2020

To
The Prime Minister
Government of India

Sir,

We welcome the measures the government has taken to ensure physical distancing to arrest the COVID-19 pandemic. However, the experiences of Singapore, South Korea, and Japan have shown that social distancing by itself does not suffice; it is necessary to embark on testing on a very large scale to identify and isolate not only the symptomatic patients but also the infected asymptomatic individuals. Moreover, the country also has to prepare the healthcare system to be able to treat millions of patients, if the situation arises. In this context we would like to put forth a few concrete proposals to deal with the crisis.

1. Whenever anybody tests positive, extensive testing has to be done covering the whole neighbourhood, the nearby market area, and the places that the individual visited over the past few days, at least by random sampling. That will require increasing the rate of testing to a substantially higher level compared to what is being done presently. This will require not only a larger number of test-kits, but also a large number of trained personnel. We propose that unemployed science graduates be specially recruited for this purpose and should be trained on a war footing.

2. Most biology departments in research institutions and universities have RT-PCR machines in BSL2 facilities which can be used for COVID-19 detection. Faculty and students of many of these institutions are prepared to offer their services in this crisis period. Effective steps should be taken to utilize these facilities to enhance the testing capability of the nation.

3. India is lagging way behind in genetic sequencing of the novel coronavirus. We do not have sufficient data on which mutated variants of the virus are there in India, neither do we know anything about the rate at which it is mutating—all of which are crucial for effective management of the pandemic. Therefore, we request you to increase the number of genomic sequencing of the coronavirus isolated from Indian patients, and to make the results publicly available.

4. Isolation wards should be created in district and subdivision-level hospitals, and even in the primary health centres, equipping them with the necessary infrastructure to treat COVID-19 patients. The government should use the facilities in private hospitals to create special wards to provide free treatment to COVID-19 patients. All indoor stadiums and similar indoor spaces should be turned into COVID field hospitals. Private doctors, nurses, and semi-skilled helpers should be recruited to serve these makeshift hospitals. Complete safety should be ensured for the people serving in these hospitals.

5. The emerging situation will require large-scale production of PPE gear for health-care personnel, and masks and sanitizers for common people. The government should initiate planned production of these essential items by requisitioning closed factory spaces and by engaging workers rendered jobless by the lock-down.

6. The nation needs to produce a large number of ventilators in a short time. Many relatively inexpensive designs of ventilators (including mechanized Ambu bags) have been proposed by Indian investigators. Some international companies have also made their ventilator designs public. Indian pharmaceutical companies and other manufacturers should be requisitioned to mass produce such ventilators to meet the nation's requirement. Building an Indian innovation-development-production infrastructure is the need of the hour.

7. Migrant labourers are stuck in different states due to sudden announcement of the lock-down. Most of them are living in crowded places and it will not be possible for them to maintain physical distancinga practice necessary to prevent the spread of COVID-19. The Central Government should initiate a dialogue with the states to provide transit of these helpless people to their home states by means of special trains. Once they reach their respective subdivisions, they should be quarantined in primary health centres or school buildings for 14 days before allowing them to go home. Adequate financial and material support should be provided to daily wage labourers and poor people who have lost their livelihood due to the lock-down.

8. The expenses of the above programmes should be raised by levying taxes on the super-rich, and by using Corporate Social Responsibility (CSR) funds of all national and multinational companiesnot by taxing the common people. Since health is a state subject, the Union Government should allocate adequate funds to the states for combating this critical situation. Since research scholars are losing valuable research time due to the lock-down, their tenure of fellowship should be extended by at least 6 months.

We hope that the government will give due consideration to the above proposals.

Signed by

Soumitro Banerjee	IISER Kolkata
Alladi Sitaram	Indian Statistical Institute (Retd.)
Jayant Murthy	Indian Institute of Astrophysics
Debashis Mukherjee	S N Bose National Centre for Basic Sciences
Debabrata Ghosh	All India Institute of Medical Sciences Delhi
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Pranab Roy	Institute of Child Health
Siddhartha Sen	IIT Kharagpur
Pabitra Banik	Indian Statistical Institute
Debabrata Bera	Jadavpur University
...	And 800 others.

Press statement on the Vizag Gas Leak tragedy

Presently the people all over the country are passing through a very critical situation due to lockdown and Covid-19 pandemic. During this lockdown period, the horrific incident happened at L.G. Polymers Ltd. at Vizag, Andhra Padesh, on 7th May morning, where the styrene gas leak caused death of 11 persons and thousands of people have been hospitalized falling seriously ill. In this situation, the Breakthrough Science Society has issued the following press statement:

The Breakthrough Science Society expresses severe shock and concern over the death of 11 persons and severe illness of more than a thousand people in Vizag (A.P.), due to inhalation of styrene gas leaked from the L.G. Polymers Ltd factory. This poisonous gas leakage incident in Vizag reminds us of the Bhopal gas tragedy where thousands of innocent people of neighboring localities and labourers of this industry died due to methyl isocyanide (MIC) gas leakage from Union Carbide factory in1984. This Vizag incident again proves that the central and state governments of our country do not take any lesson from the gas leakage tragedy in Bhopal, the deadliest in industrial history. The Vizag gas leak incident is but a mini Bhopal gas tragedy and neither the neighboring inhabitants nor the respective government authorities were aware about the hazardous chemicals used in such factories and their impact on people if any accident occurs. Breakthrough Science Society demands that the harmful effects due to gas leak from L.G. Polymers Ltd. should be combated on a war footing and the government has to provide free and quality health care for the affected and suspected victims of the gas leak. We also demand a high level scientific enquiry on causes of the styrene gas leak and to bring the guilty to the book.

Lastly, the Breakthrough Science Society draws attention to the fact that in recent years many investors (foreign as well as Indian) are establishing hazardous chemical industries in different places of India. Many of such chemical industries are already banned in developed countries due to their dangerously toxic waste materials which cause environment pollution and destroy biodiversity. These investors do not get permission from the government and designated authority to establish such chemical industry in developed countries like USA, Japan, Germany, England, etc., while in India the investors get quick clearance and license from our government to establish such hazardous chemical industries without proper verification. The effort of chemical hub formation in Nandigram,West Bengal by Salem Group and Dow Chemicals was such an example.

We demand that hazardous Industries must be situated at a safe distance from habitation as per the Hazardous Chemical Amendment Rules, 1989, and the environmental norms prescribed by the state and central Pollution Control Bureaus should to be strictly enforced. We also demand that appropriate compensation must be given to the bereaved families and the people whose health was adversely affected.

A Primer on SARS-CoV-2 and the Evolving Covid-19 Pandemic

Subramani Mani*

Abstract

In this article we first provide a primer on SARS-CoV-2 and Covid-19 delineating the etiopathogenesis, epidemiology, clinical manifestations and the natural history of the disease. We then trace the evolution of the Covid-19 pandemic highlighting the characteristics of the epidemic in China where the pandemic originated, select countries of Europe which peaked during April, and Brazil, USA and India where the pandemic has taken serious turns recently. We also project some possible trajectories for the mega cities of India based on the demographic characteristics of these cities in comparison to New York city. This is an updated version of the article from mid-April published online [2].

Introduction

Corona virus disease 2019 (Covid-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) originated in the city of Wuhan, China in late 2019. After infecting tens of thousands of people in Wuhan and the province of Hubei where Wuhan is located, the disease spread to various other cities of China and internationally. It peaked recently in many countries of Europe (Italy, Spain, France, Germany, United Kingdom) and Asia (Iran, South Korea), is changing course in the United States and currently raging in Brazil, Peru, Russia and India. It has spread to more than 200 countries and is challenging the healthcare resources of both the developed and the developing world. With a global case count in excess of 6 million, and with a mortality of more than 360,000 over a five-month period, the Covid-19 pandemic has become the most dangerous global infectious disease of the 21st century [3].

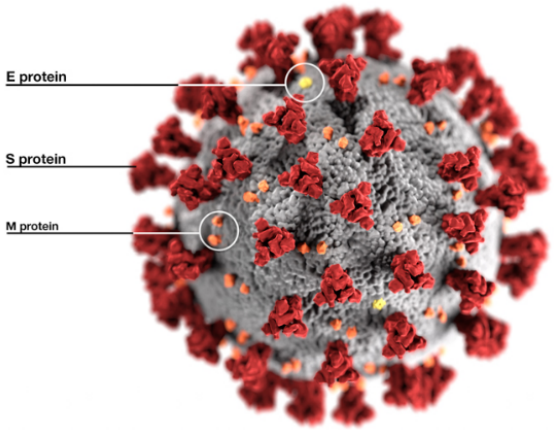

Figure 1: Eckert and Higgins illustration of SARS-CoV-2, Centers for Disease Control and Prevention, USA.

Humans are susceptible to a range of microbes which include parasites, bacteria and viruses. However, most of the newly identified emerging pathogens are viruses

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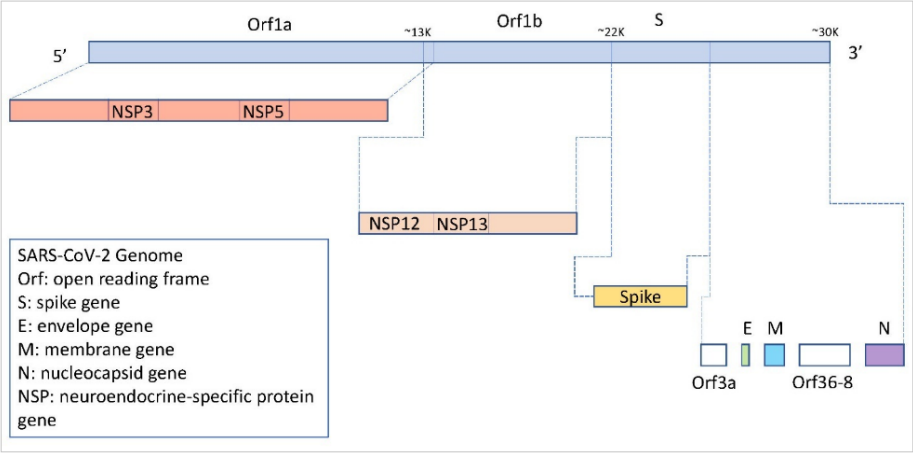

Figure 2: SARS-CoV-2 Genome.

that are carried by vectors, or cause primary disease in animals and then jump to humans (zoonotic). These are opportunistic viruses that mutate at high rates, easily adapting to the new human host, thereby enabling human-to-human transmission. The most prominent of these emerging pathogens are the Zika virus and the newer zoonotic respiratory coronaviruses [4, 5] which also include the current pandemic-causing virus SARS-CoV-2.

The first SARS-CoV outbreak occurred in late 2002 and soon became a pandemic in early 2003, resulting in the death of more than 700 people with a large cluster of fatalities reported from Hong Kong. This SARS-CoV virus is thought to have originated in a single or multiple species of bats [4]. A more recent coronavirus (CoV) pathogen is the Middle Eastern respiratory syndrome (MERS) CoV, which first emerged in 2012 in Saudi Arabia, and spread to many countries in the region. By 2018 MERS-CoV had infected more than two thousand people, causing 803 deaths, the majority of them in Saudi Arabia. Camels and bats are considered to be reservoirs of this pathogen [6].

Before the emergence of SARS, human coronaviruses typically caused only mild upper respiratory infections, resulting in the common cold. All this changed with the emergence of SARS-CoV, MERS-CoV and the newest member SARS-CoV-2, the causative agent of the Covid-19 pandemic.

Etiology

Covid-19 is caused by the recently identified respiratory tract virus SARS-CoV-2, which belongs to the viral family coronaviridae, also referred to as the coronavirus family [7]. Other prominent members of the respiratory tract group of viruses are the rhinovirus, the respiratory syncytial virus (RSV) and the influenza and parainfluenza viruses. The coronaviruses are single-stranded RNA viruses, containing an RNA inner core with an outer oily lipid envelope from which crown-like spikes of proteins project outwards. These characteristic crown-like projections on their surface give the virions the appearance of a solar corona in electron micrographs and hence the nomenclature corona. See Figure 1. The corona viruses are heat sensitive

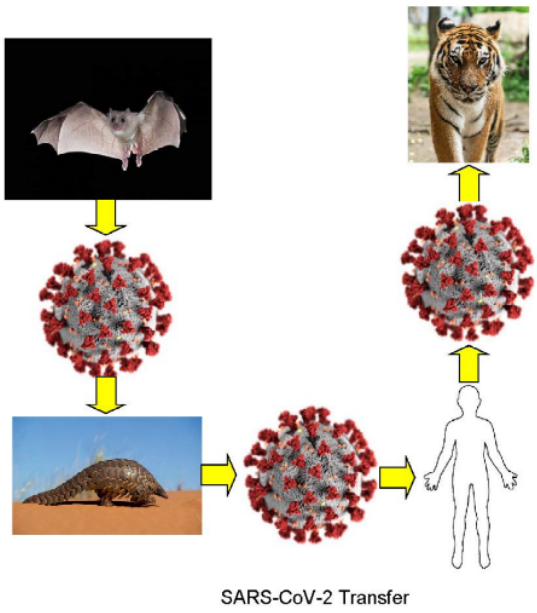

Figure 3: A transmission model from bat to man with pangolin as reservoir.

and are susceptible to lipid solvents such as acetone, ether, and vinegar (which contains acetic acid). The lipid envelope of the virus also breaks apart on contact with soap.

The viral sequence of SARS-CoV-2 identified by Zhu etal. contains 29,892 nucleotides [7] and the viral genome reported by Wu etal. contains 29903 nucleotides [8]. See Figure 2 for additional genetic details.

Phylogenetic analysis revealed the close relationship to SARS-like coronaviruses previously found in bats in China. The pangolin is also likely to be an intermediate host and a natural reservoir of SARS-CoV-2-like coronaviruses [9]. Recently, a jump from human to a tiger in New York city has also been demonstrated when a tiger in the Bronx zoo turned positive. See Figure 3. There are also recent reports of domestic pets such as cats and dogs becoming susceptible to SARS-CoV-2 infection [10].

Isolation period	Missed Symptomatic Infections per 10,000 Monitored Persons			
	Low risk (1/10,000)	Medium risk (1/1000)	High risk (1/100)	Infected sample (1/1)
14 days	0	0.1	1	101
28 days	0	0	0	1.4

Table 1: Expected number of symptomatic SARS-CoV-2 infections missed during active monitoring using 14-day and 28-day protocols with varying risks for infection following exposure (modified from [18]).

Laboratory diagnosis

The lab diagnosis of SARS-CoV-2 infection is performed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay for a genetic sequence matching the genome of SARS-CoV-2. This is accomplished by SARS-CoV-2 specific primers and probes. SARS-CoV-2 is a respiratory virus which is shed in respiratory droplets. A swab taken from the deep nasopharynx is used to isolate the virus from an infected person. Figure 4 provides additional details of the SARS-CoV-2 RT-PCR test.

Epidemiology

This description is based predominantly on the following studies—the first 425 confirmed cases in Wuhan, China [11], the second reporting data on 1099 patients admitted to various hospitals in mainland China [12], the third on 138 hospitalized patients in Wuhan [13], the fourth a review article based on 19 studies (18 from China and 1 from Australia) which also included the three primary studies [14], the fifth a retrospective cohort study of 191 hospitalized patients in Wuhan with follow-up [15], the sixth a retrospective study of 1591 consecutive patients admitted to ICU in the Lombardy region of Italy [16] and the seventh a study of 5700 hospitalized

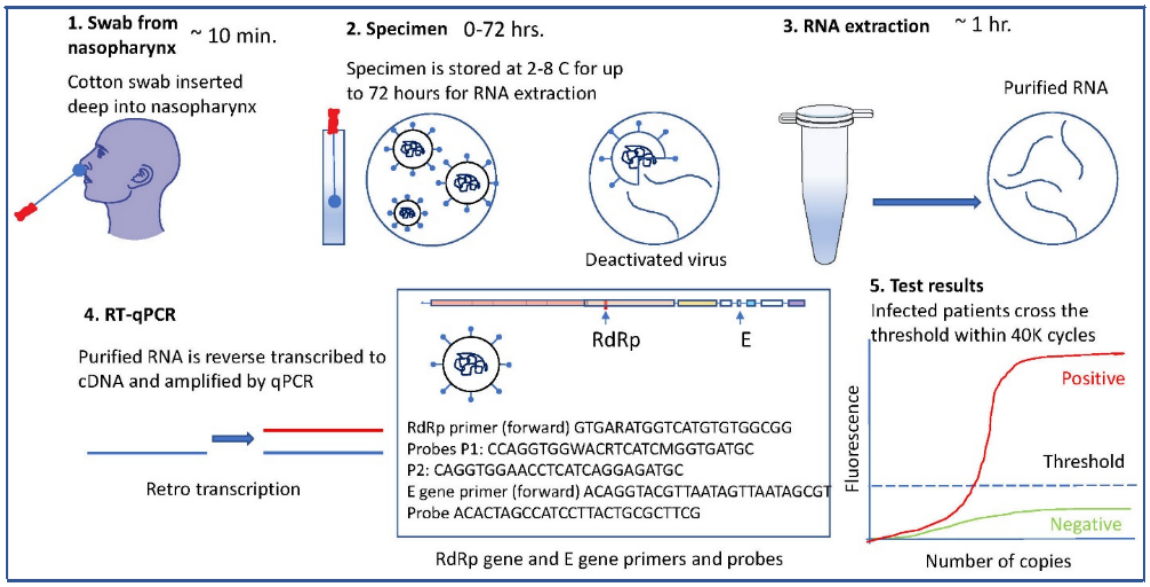

Figure 4: SARS-CoV-2 Diagnostic Test Using RT-PCR.

patients in New York city [17]. Covid-19 is a highly contagious disease, that is, it is easily transmitted from one person to another. The transmissibility factor, also called the basic reproductive number R0, is defined as the number of new cases an existing case is likely to generate on average. The R0 of Covid-19 is estimated to be 2.2.

Incubation period

The incubation period is the duration from the time of exposure to the manifestation of symptoms of the disease. The mean incubation period is 5.5 days with a range of 2 days to 12 days. But there could be outliers and the following table adapted from [18] shows the number of positive cases which could be missed using a 14-day and 28-day protocol of isolation (see Table 1).

The mode of transmission is by respiratory droplets but the virus has also been isolated from the stools of patients. Both symptomatic patients and asymptomatic persons infected with SARS-CoV-2 can transmit the virus [19]. The virus can remain suspended in aerosols for 3 hours raising the possibility of transmission through the air in closed spaces and in a crowded and congested environment. The virus can also remain viable for up to 72 hours on different surfaces as varied as plastic, steel, copper and cardboard [20].

Figure 5 provides the dynamics of infectiousness, susceptibility to infection and disease manifestation. The top panel shows how a person could get infected, remain asymptomatic and be contagious. The bottom panel shows how a person can be contagious during a part of the incubation period when the symptoms have not manifested.

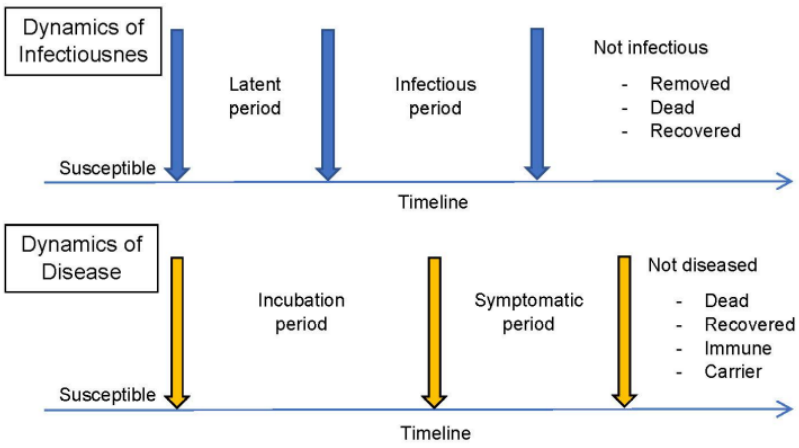

Figure 5: Dynamics of infection and disease (modified from [1])

Demographics

The median age of patients in different studies varied between 47 and 63 years. Males were disproportionately affected ranging from 50-82 percent. Among the first 425 confirmed cases in Wuhan there were no children below 15 years of age [11]. In the study of 1099 patients, the number of children below 15 years was 9 [12]. Out of the 5700 hospitalized patients in New York City only 26 were children below the age of 10 years [17]. About 15% of the hospitalized patients were categorized as severe who were on average older by 7 years, and were more likely to have co-existing medical conditions compared to the less severe hospitalized group of patients.

Pathogenesis

The SARS-CoV2 virus enters the human body via droplets through the nose, mouth or eyes. The virus enters the cells in the airway by binding the viral surface spike protein to the human angiotensin converting enzyme 2 (ACE2) receptor. This follows activation of the spike protein by transmembrane protease serine 2 (TMPRSS2). ACE2 is expressed in the alveolar cells of the lung, heart, vascular endothelium and the kidneys but the main portal of viral entry seems to be the lung alveolar cells [21, 22].

Clinical characteristics

Fever was present in 40% of the patients on admission and in 80% of patients during the hospitalization period. Cough was the second most prevalent symptom and was reported by 70% of the patients. Half of the patients also reported feeling fatigued. Breathlessness was also observed in 30% of the patients. Nausea, vomiting, sore throat and headache were uncommon (less than 10%). A third of the patients had one or more co-existing conditions such as high blood pressure, chronic obstructive pulmonary disease, diabetes, or coronary artery disease and this was more pronounced among patients with severe disease.

Cardiovascular manifestations

There have been some reports of patients presenting with chest pain and showing

ST-segment elevation in the EKG without any evidence of coronary artery disease. In these patients, echocardiography revealed LV dysfunction with reduced ejection fraction and elevated cardiac biomarkers such as troponin. Patients with SARS-CoV-2 infection can also present with myocarditis, stress cardiomyopathy, cardiac failure or they may present with palpitations and chest pain without fever and cough. Patients can also present with shortness of breath, supra-ventricular tachycardia and cardiogenic shock [23]. The exact mechanism of cardiac pathogenesis is not clear [22] but it could be a consequence of systemic hyperinflammation, lymphocytopenia and elevated cardiac stress due to respiratory failure and hypoxemia [24].

Neurological manifestations

Patients have presented with dizziness, headache, ataxia, altered sensorium and other clinical features suggestive of brain inflammation [25]. A small subset of patients developed stroke and seizures. There are also reports of acute necrotizing encephalopathy in Covid-19 patients. Some patients develop tingling and numbness in the upper and lower limbs referred to as acroparesthesia. Patients have also presented with loss of smell and taste suggesting involvement of the olfactory, facial and glossopharyngeal nerves [26]. In a study of Covid-19 patients in Wuhan, based on a sample of 113 patients who died and 161 patients who recovered, the researchers found that 20% of deceased patients developed hypoxic encephalopathy while among the recovered group of patients it was observed in only 1% [27].

Cutaneous manifestations

In a study of 88 patients in the Lombardy region of Italy skin lesions were found in 20% [28]. The cutaneous manifestations reported are erythematous rash, urticaria, and chickenpox-like vesicles mainly distributed in the trunk. There has also been a report of erythematous chilblain-like lesions on feet and hands in asymptomatic corona virus positive patients [29].

Children and Covid-19

Compared to adults, children in general have been found to be less susceptible to serious manifestations of Covid-19. Worldwide, patients under eighteen years have so far accounted for only 2% of severely affected patients even though they can be carriers and transmit the virus [30]. Based on an analysis of 2135 pediatric patients (728 lab-confirmed and 1407 suspected) Dong etal. reported that more than 90% were asymptomatic, mild, or moderate cases. The distribution was similar in both sexes and they found that younger children, particularly infants, were more vulnerable [31]. Researchers have hypothesized that this disparity in the susceptibility to Covid-19 between adults and children could be due to differences in the ACE2 receptors in the renin-angiotensin system (which are used by the SARS-CoV-2 virus to enter the respiratory epithelial cells), and altered inflammatory responses to the pathogen [30, 32].

There have also been recent reports of a multisystem inflammatory syndrome in children due to SARS-CoV-2 infection in the UK and USA [33, 34].

Radiology and lab features

Eighty percent of the CT scans of patients with non-severe disease and 96% of the scans of patients in the severe disease category revealed abnormal findings. The typical patterns on chest CT were ground-glass opacity and bilateral

patchy shadowing. These abnormal patterns were also visible in chest X-rays. Less frequent findings found towards the later stages of the disease include septal thickening, bronchiectasis and thickening of the pleura. Other infrequent CT findings reported with disease progression were pleural effusion, pericardial effusion, lymphadenopathy, lung cavities, CT halo sign and pneumothorax [35].

More than 80% of patients had a low lymphocyte count. About a third of patients had low white cell counts and another third had low platelet counts. Most patients also showed reduced albumin, high levels of C-reactive protein and elevated ESR. The laboratory findings were more pronounced in patients with severe form of the disease. In a study of 2874 SARS-CoV-2 positive patients RNAemia, that is, detection of viral RNA in blood was found in 97% [14].

Treatment, clinical course and outcomes

No specific anti-viral treatment is currently available broadly for Covid-19. A majority of the patients (60%) were given intravenous antibiotics, and oxygen was administered to about 40% of the patients. Twenty percent of the patients typically needed admission to the intensive care unit, out of whom half had to be put on ventilators. More than 90% had pneumonia, 10% of patients developed acute respiratory distress syndrome and five percent of patients went into shock. The median duration of hospitalization was 12-20 days in different studies with the mortality rate varying from 2 to 20 percent in various studies.

Drug pipeline

Three drugs that are undergoing studies for effectiveness in the treatment of Covid-19 are Remdesivir, Hydroxychloroquine and Chloroquine. There is some preliminary evidence that these drugs have the potential to inhibit SARS-CoV-2 [36]. Remdesivir is an antiviral compound originally developed as a potential drug for Ebola, and Hydroxychloroquine and Chloroquine are time-tested drugs used in the treatment of malaria. Hydroxychloroquine is also indicated in the treatment of discoid, systemic lupus erythematosus and rheumatoid arthritis. A recent placebo-controlled randomized trial of intravenous Remdesivir in hospitalized Covid-19 patients reported a reduction in recovery time by 4 days (from 15 days to 11 days) [37]. An observational study of more than 1300 hospitalized patients did not find any benefit resulting from Hydroxychloroquine administration [38]. A multinational retrospective study of the efficacy of hydroxychloroquine and chloroquine for Covid-19 found higher mortality and increased occurrence of ventricular arrhythmias in both the hydroxychloroquine treated group and chloroquine administered group compared to the control group [39]. Another drug Tocilizumab, an interlukin-6 receptor antagonist used in the treatment of rheumatoid arthritis is also being tested for the treatment of Covid-19 [22].

Recently, a small study involving ten seriously sick Covid-19 patients, who were administered a single dose of 200 ml of convalescent plasma (CP) from recently recovered donors, showed that CP therapy was well-tolerated with resulting improvement in clinical symptoms. CP holds promise for improving clinical outcomes by neutralizing the virus circulating in blood [40].

Vaccine trials

There are various candidate vaccines based on RNA, DNA, recombinant protein, viral-vector-based, as well as the time-tested inactivated, and live attenuated versions

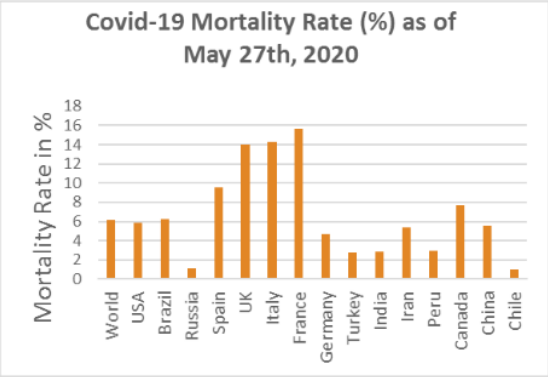

Figure 6: Covid-19 mortality rate.

under pre-clinical evaluation. Currently, there are no existing licensed human vaccines using RNA and DNA platforms [41]. Two candidate vaccines, one from University of Oxford/AstraZeneca, and another from CanSino Biological Inc./Beijing Institute of Biotechnology, based on non-replicating viral vector platform are currently in phase II trials. Two candidate vaccines based on RNA being developed by Moderna/National Institute of Allergy and Infectious Diseases (NIAID) and BioNTech/Fosun Pharma/Pfizer are also moving into phase II trials. Six other candidate vaccines are also undergoing clinical evaluation.

However, availability of a safe and effective vaccine for SARS-CoV-2 on a mass scale is at least 12-18 months down the road.

Covid-19 pandemic story so far

Here we present the story of the Covid-19 pandemic from an analytical perspective based on the numbers available from the worldometer website as of May 27, 2020 [3]. In this analysis we include the top fifteen countries based on the reported number of cases, which includes India and the global figures. A total of 6 million cases and more than 360,000 deaths have been reported worldwide. The United States tops the list with a reported total caseload approaching 1.75 million with more than 100,000 deaths. India has reported more than 158,000 cases and 4534 deaths through May 27th. Brazil has counted close to 400,000 cases with total deaths approaching 25,000, and Russia is close behind with a caseload exceeding 370,000 but with a much lower reported death toll approaching 4,000. Spain, United Kingdom, Italy, France and Germany together have reported more than 1.1 million cases with a combined death toll exceeding 134,000. USA also leads the countries in the total number of tests with more than 15 million tests followed by Russia with more than 9.4 million tests. But the testing rate (number of tests per million people) is highest in Spain with more than 76,000 people tested per million inhabitants.

The number of new cases reported daily is an indicator of the evolution of the pandemic on a daily basis in each country. In this measure, USA and Brazil top the list with more than twenty thousand new cases in one day. Figure 6 provides the mortality rate of Covid-19 for the various countries. The worldwide mortality rate is 6.2% with a range of 1.0% for Chile to ¿14% for Italy and the UK. The mortality rate for India stands at 2.9%. For an epidemiological comparison, the fatality rates and reproductive rates of common and emerging virus infections are shown in Table 2.

Discussion

The pandemic continues to spread and evolve on a global scale. It has overwhelmed the healthcare capabilities and capacities of various cities and countries including Wuhan (China), Italy, Spain, France, UK and New York, causing fatalities in the

Virus	Fatality rate (%)	Transmissibility Factor (R_0)	Deaths
SARS-CoV-2 (2019)	3	2.2	369,000+ (till May 30th, 2020)
SARS-CoV (2002)	10	2-5	700
MERS-CoV (2012)	40	< 1	800
H1N1 (2009)	0.03	1.2-1.6	18,600-300,000
H1N1 (1918)	3	1.4-3.8	17-50 million (1918-1920)
Measles virus	0.3	12-18	140,000 in 2018
Seasonal flu	< 0.1	1.2-2.4	0.3-0.6 million per year currently
Ebola virus (2014-16)	40	1.5-2.5	11,300 (2014-2016)
HIV	80 (without drug therapy)	2-4	30 million total deaths so far
Small pox virus	17	5-7	300 million in 20th century

Table 2: Fatality rate and reproductive rate (R_0) of common and emerging virus infections (modified from [42]).

thousands, tens of thousands and even one hundred thousand. As countries attempted (and continuing) to block the spread of Covid-19 by proclamations of stay-in-place and lockdown orders in cities, states and nation-wide, the economies of these countries are taking a huge hit and sliding towards recession.

Recall that the transmissibility of a contagion is defined by the reproductive number R0 in epidemiological terms. There are two basic strategies to tackle the spread of Covid-19 referred to as containment and mitigation. When the R0 is two or greater there will be an exponential spread as each case will generate two or more new cases on average and the total number of cases in a community or a geographical region starts doubling every few days. A containment strategy is typically used at the beginning of an epidemic and involves testing persons exposed to the virus, isolating and quarantining them individually, and tracing their contacts if they test positive or develop symptoms. In the containment approach the goal is to keep R0 below one to break the community transmission chain.

To tackle an exponential spread and when the number of cases overwhelms containment approaches, a mitigation approach is taken using various types of non-pharmacological interventions (NPI) with the goal of lowering R0 as much as feasible but not to reduce it to one or below one. The common NPIs involve the steps of extensive testing, isolation/quarantine and social distancing measures for certain population groups such as senior citizens and people with pre-existing medical conditions, or the population as a whole with lockdowns and stay-in-place declarations.

Mitigation steps also involve the closure of schools and colleges, shutting down places of entertainment such as performance venues, religious congregations and places of worship, and sports events. Likewise, a drastic reduction in gatherings such as marriages and funerals are also enforced. Both these approaches may need to be applied in tandem in large parts of a country or geographical region facing the onslaught of Covid-19.

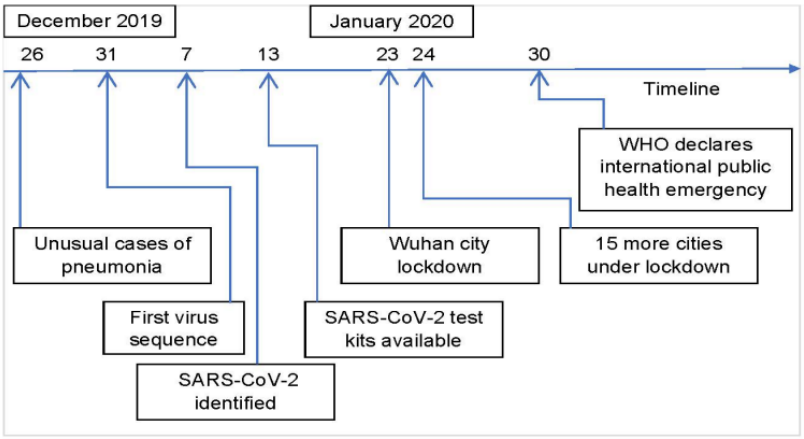

Figure 7: Wuhan Covid-19 outbreak timeline

Covid-19 run in China, South Korea, Europe and USA

China

The novel corona virus originated in December in the city of Wuhan in China and started spreading in the province of Hubei which includes Wuhan. When cases started multiplying and authorities suspected human to human transmission of the new virus, containment measures were instituted. By the end of December, a viral sequence was completed and a week later the novel corona virus was officially announced as the causative pathogen of the outbreak by China CDC [11]. By 13th January a test kit became available for detecting SARS-CoV-2. Within a period of ten days hundreds of people had tested positive for the virus. Moreover, within that timespan more than two thousand people had started showing symptoms of the new disease and visiting hospitals in Wuhan. Even though the authorities hesitated initially, the city of Wuhan was put under lockdown on January 23rd. By that time many other cities in China were also seeded with the virus as more than seven million residents of Wuhan had left the city to celebrate the Chinese New Year. On January 24th, fifteen other cities within Hubei province, in which Wuhan is situated, were also put under lockdown and on January 30th, WHO declared an international public health emergency [43]. Figure 7 provides a timeline of the Wuhan outbreak.

China was able to control the smaller outbreaks that occurred outside Hubei province by initiating effective containment measures. However, in the city of Wuhan, and broadly in the Hubei province, the healthcare facilities were overwhelmed by the outbreak. The lockdown in the city of Wuhan was in place for 76 days, and restrictions on the movement of people put in place during the lockdown were slowly relaxed over the last few weeks. At the time of writing (May 27th), China has reported a total of 83,000 cases and more than 4,600 deaths, mostly in Wuhan and the rest of Hubei province. The country reached the milestone of 80,000 cases in early march which has only increased by 3,000 cases over the last three months.

South Korea

The first case of Covid-19 was reported on January 20th and by February 21st the caseload increased to 346, with the outbreak concentrated in the city of Daegu in the southern part of the country [44]. South Korea cancelled mass gatherings in Daegu and effected containment measures incorporating mass testing, contact tracing, isolation of exposed individuals and quarantining those who tested positive. In late February and early March, the country reported more than 500 cases daily and by mid-March, the outbreak was under control reporting less than 250 new cases. And by mid-April, the number of daily new cases had come down to about 25. It fluctuated between single-digit numbers and forty from 1st through the 27th of May. The total number of deaths through May 27th stands at 269 for a total positive case count of 11,344. South Korea did not institute a countrywide shutdown or social distancing measures applicable to the whole of the country.

Europe

The Covid-19 pandemic opened its account in Europe with the first reported case in France on January 21st and by May 25th, the case count had gone up to more than 1.3 million. As of May 25th, the total number of deaths has exceeded 161,000 in the whole of the European Union (EU) including UK [45]. We consider five countries—Italy, Spain, France, Germany and UK in additional detail here.

Italy

Covid-19 first emerged in Italy on January 31st when two tourists from China tested positive. Three weeks later, a cluster of cases was reported from the Lombardy region of Italy which includes Milan, and by early March positive cases were reported from many parts of the country [46]. By March 1st, the daily case count had increased to more than 500. The epidemic raged in Italy throughout March and the first two weeks of April with the total case count reaching more than 178,000 with a death toll exceeding 23,600 by April 19th. The peak started flattening by mid-April and the daily caseload has started declining from the high three-thousands in mid-April to a few hundred new cases by the last week of May. The total case count tops 231,000 with a cumulative death count exceeding 33,000 as of May 27th, 2020.

Spain

The country reported its first case on January 31st, and by mid-March the disease had spread to all the 50 provinces [47]. By the 10th of March, the daily new case count had increased to more than 500 and the country reached its peak during the last week of March, and the plateau was sustained through the first week of April. As of April 19th, the total case count had reached close to 200,000 with a total death toll exceeding 20,000. Five weeks later, as of 27th of May, the total case count exceeds 230,000 with a total death toll topping 27,000.

France

The epidemic raised its head first in France on January 24th, and the first set of cases was in travelers returning from China. The annual assembly of the Christian Open Door Church attended by 2,500 people was a significant watermark in the spread of the virus, and almost half of the congregants contracted the virus [48]. By March 12th, the number of daily reported new cases had gone up to more than 500 and the country reached its peak in the first week

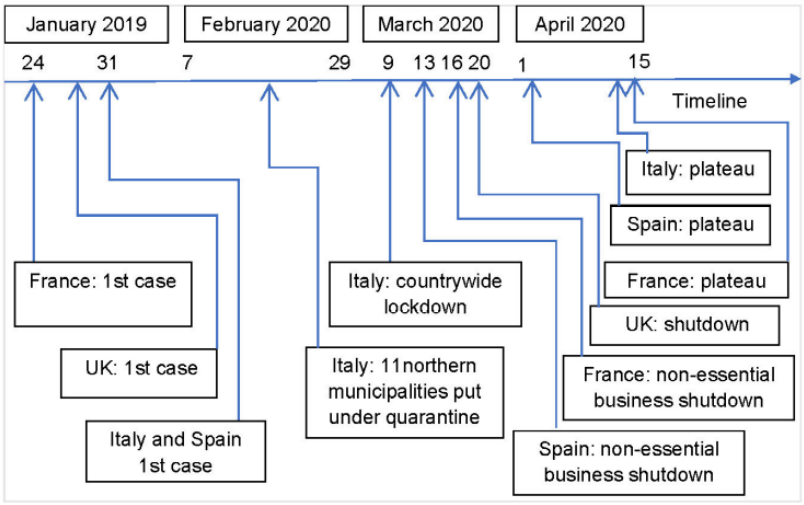

Figure 8: Italy Spain France and United Kingdom Covid-19 outbreak timeline.

of April. By April 19th, the total case count had exceeded 152,500 with a death toll nearing 20,000. On May 4th, retroactive testing of samples in a French hospital demonstrated the presence of Covid-19 as early as December 27th, four weeks before the official confirmation of the countrys first case. As of 27th May, the countrys total case count exceeds 185,000 with a cumulative death toll of 28,600. From a daily new case-count exceeding 5K in early and mid-April the daily case count has come down to a few hundred in the last week of May.

Germany

Covid-19 emerged in Germany in late January, with the first case confirmed near Munich on January 27th. On March 8th, the government recommended cancellation of events with more than one thousand participants and in mid-March, schools and nurseries were closed. Only the state of Bavaria declared a curfew on March 20th, but after two days, the Federal Government decided to forbid gatherings of more than two people. Social distancing measures were also introduced but no formal countrywide stay-in orders were issued [49]. At its peak in late March/early April, the daily new case count exceeded 6,000 but by mid-April it had fallen to about 2,000. As of April 19th, the total case count exceeded 144,000 with a total fatality count of 4,500. As of May 27th, the total case load is nearing 180,000 with a total death toll exceeding 8,300. From a peak of more than 6,000 daily cases reached late March/early April, the daily case count has come down to a few hundred in the last week of May.

United Kingdom

In UK also, Covid-19 was detected first in late January, and by the end of February community transmission within UK was also confirmed [50]. By March 18th, the number of daily reported new cases had exceeded 500. As of April 19th, the total case count was more than 120,000 with a total death toll over 16,000. The epidemic has continued to rage in the country through

April and May and the total case count exceeds 267,000 as of May 27th, with a total death count that tops 37, 400. From a daily new case-count hovering between 4K and 6K during most of April, and between 3K and 5K in the first two weeks of May, the daily case load has declined to 2K in the last week of May.

See Figure 8 for the evolution of the outbreak through mid-April and the interventions instituted by the respective authorities in Italy, Spain, France and the UK.

United States

The first Covid-19 case was reported in the USA on January 20th, when a person who had returned from Wuhan, China, five days earlier tested positive for the virus. Community transmission was first confirmed in late February, when a person without any history of recent international travel or exposure to a known infected individual tested positive [51]. The number of daily new cases exceeded 500 on March 13th. Though a travel restriction was instituted on passengers coming from China on January 31st, no significant intervention measures were instituted during the whole of February or the first two weeks of March. Containment measures such as extensive testing, isolation and quarantine measures lagged behind considerably in the country. Starting mid-March, when the total case count approached 4,000, various states started instituting mitigation strategies to enforce social distancing measures. Stay at home orders were issued in various states starting with California on March 19th, and covered most states of USA by April 7th.

Starting early May the country started opening up in stages. By May 27th, seventeen states have ended stay-at-home orders. Many non-pharmacological interventions such as social distancing measures, restrictions on large gatherings, school closures and wearing of masks in public places are still in place in many regions of the country.

New York has been the most affected state in the United States. The state had a total case count nearing 250,000 and deaths exceeding 18,000 as of April 19th. And as of May 27th, the total case load is nearing 375,000 with a total death count exceeding 29,500. The USA is also the worst affected country in the world. The country had a total caseload exceeding 750,000 and fatalities exceeding 40,000 as of April 19th. This has increased to 1.75 million total cases and a total death count that exceeds 102,000 as of May 27th.

Brazil

The coronavirus was confirmed to have spread to Brazil on February 25th with a Sao Paulo resident who had earlier returned from the Lombardy region of Italy testing positive. It also turned out to be the first positive case in the whole of South America. By March 26th, the country had 2,915 confirmed cases and 77 deaths. By the end of April, Brazil overtook China in the number of confirmed cases and the country has currently emerged as a hot spot for the virus. Brazil has not instituted countrywide lockdown measures to combat the virus but some cities in the north of the country issued lockdown measures in the first week of May. As of May 27th, the total case-load exceeds 411,000 with a cumulative death count in excess of 25,500. Just on May 27th the country added 22,301 new cases and reported 1,148 deaths [52].

Russia

The first cases in Russia were reported on January 31st, when two Chinese citizens turned positive in the Russian Far East

region. Russia was relatively late in experiencing a serious outbreak but currently ranks behind US and Brazil with the third-most number of confirmed cases [53]. As of May 27th, the total case load exceeds 370,000 with a total death count approaching 4,000.

India

Covid-19 raised its head in India in late January with a positive case reported on January 30th, in the state of Kerala [54]. By March 24th, the total case count had exceeded 500 and the same day the government declared a nationwide lockdown for three weeks, which was further extended on April 14th till May 3rd with a phased relaxation of some restrictions expected to occur after April 20th. But the lockdown was further extended by another two weeks through May 17th. Based on the success of containment of spread in various states some relaxation was instituted starting in May but the general countrywide lockdown has been extended through the end of the month. By April 19th, the total case count exceeded 17,600 with a total death count of 559. As of May 27th, the total case load exceeds 158,000 with a total death count in excess of 4,500. For a country with a population of 1.37 billion, the case count appears low but the country has conducted only about 3 million tests with a testing rate of just 2350 per one million people, while the testing rate for Spain and Russia are about thirty times more with a rate of 76K and 64K per one million people respectively.

There are some country-specific trends discernible in the evolution of the pandemic till now, in terms of total number of infected people, hospitalizations, the resulting mortality and the ability of the healthcare systems in coping up with the increased demand on their resources. Let us consider the analogy of a primary and its concomitant secondary metastases to follow some of these trends.

China had a clear source, it was unifocal and the outbreak started in Wuhan and more specifically at the Huanan seafood market there. Even though other regions of Hubei province and the rest of the country got multiple-seeded from this outbreak, containment measures were successful in controlling the epidemic outside Hubei province. In Wuhan, and broadly in Hubei, intervention measures began with containment but the hospitals were soon overwhelmed. So, they had to institute strong mitigation efforts in the city of Wuhan and the rest of Hubei province over a period of 75 days to suppress the community transmission. But the primary source was clear to them.

The South Korea outbreak was seeded by travelers from China but it became concentrated in the southern city of Daegu. The country quickly instituted containment measures with extensive testing of the population, contact tracing, isolation and quarantine. The hospitals were never overwhelmed with a total death toll under 300. Their testing rate stands at 17,000 per million population. The country could prevent a disastrous outbreak in a major population center such as Seoul.

Italy, Spain, France and the UK have some commonalities. They are all well connected globally with extensive travel among them and also with China. It is likely that they were all multiple-seeded and they were slow in scaling up containment measures, starting with extensive testing. These countries were also hesitant in the beginning to initiate strong mitigation efforts. Their health systems, in particular those of Italy, Spain and France were clearly overwhelmed, with a combined death toll which exceeded 65,000 by April 19th. The cumulative death count currently stands at

126,000 as of May 27th. UK had a long plateau stretching from early April to mid-May putting many of its hospitals under pressure.

Germany was much better prepared even though it is one of the most well-connected countries. The country quickly instituted strong containment measures with extensive testing in the early stages. Germany was also able to keep the mortality rate very low initially which then crept up somewhat, possibly because hospitalized people started dying after long stays. But the countrys healthcare system was not overwhelmed.

USA is well connected to China, Europe and most other parts of the world. It is clear from the evolution of the Covid-19 pandemic that the public health infrastructure is lacking in the country. From the start, the country ran into difficulties with its testing strategy. Though initially contact tracing of returning travelers who tested positive was instituted, the machinery for managing and organizing strong containment measures soon broke down, and community transmission started occurring in many population centers in different parts of the country. The tri-state region of New York, New Jersey and Connecticut was severely affected, with hot spots also popping up in Michigan, California and Louisiana. Some hot spots were brought under control by stay-at-home directives, but New York City bore the brunt of the epidemic and many hospitals in the city were overwhelmed exacting a large death toll. Though the first wave of the outbreak is being brought under control, it is not clear how the epidemic will evolve as social distancing measures are relaxed and the businesses open up.

Brazil was in denial about the significance of the pandemic and was late in instituting containment and mitigation measures. Once the country ramped up testing, case counts started to increase and it currently holds the 2nd spot behind USA for the total number of positive cases. In particular, the top political leadership of Brazil has opposed many of the restrictive measures announced by city and state leaders.

India is a large populous country with many dense population centers. However, the health infrastructure lacks considerably when compared with most of the countries discussed earlier. For example, South Korea has 12 beds per thousand people and Germany 8 while India has just 0.5. For Italy, China and US, the number is close to 4.

The first cluster of cases in India was from students traveling back home from Wuhan to the state of Kerala in the southern part of India. Kerala instituted prompt containment measures with isolation of contacts and quarantining people testing positive. Soon other parts of the country also got seeded and dense population centers are now under serious threat. Testing lags considerably with a rate of 2K per million population or 2 per one thousand people.

Though mitigation efforts in the form of a countrywide lockdown have been instituted relatively early, when compared to many other countries, these cannot be sustained for months in the absence of resources to feed and sustain the population. Moreover, the minimal healthcare facilities are likely to be overrun once the lockdown is relaxed. Some relaxation of the lockdown is already happening with a phased opening of businesses and institutions in various states. Domestic flights and long-distance passenger trains have also started to become operational in the last week of May.

Based on the experience of New York City, we provide an outbreak scenario for the

City	Total Population in millions	Population Density/Sq. mile	Beds per 1000 people	Covid cases	Total deaths
NYC	8.7	28,000	3	206,000	21,000
Bombay	21	73,000	0.5	35,485	1,135
Delhi	30	30,000	0.5	16,281	316
Calcutta	15	63,000	0.5	1,895	194
Chennai	11	69,000	0.5	12,761	109

Table 3: Four mega cities of India compared with New York City (NYC).

four major population centers of IndiaBombay, Delhi, Calcutta and Chennai. The projections are based on the total population, population density, the quality of healthcare infrastructure as reflected in the beds per one thousand population and the reported city-specific mortality data. See Table 3 for these parameters and see Figure 9 for the projected cases and fatalities. The lower projections are based on maintaining moderate social distancing measures in place, and the higher range will be reached if mitigation efforts cannot be sustained and compliance is eroded. If mitigation efforts are completely withdrawn, the counts could rise by an order of magnitude.

The demographics of the state of Kerala provide a set of opportunities, while posing some unique challenges. The state has a total population of 35 million, with an average population density of 2,200 per square mile, which is three times the national average. Again, the coastal regions are more than two times denser than the state average [55]. The coastal plains of Kerala, running north to south from Kasaragod to Trivandrum, act as a metropolitan corridor well-connected by trains and long-distance buses. The region also has three major airports with frequent flights to the countries in the Middle East and the rest of India. Kerala also has a high Human Development Index, which informs favorably on the literacy, life expectancy and the public health infrastructure of the state in general. Kerala has managed to contain the spread of Covid-19 by testing travelers, isolating contacts and quarantining people testing positive. However, testing has lagged behind considerably in assessing penetration in the community to get a clear handle on the prevalence of Covid-19. There are four dense metro areas in the state with a population of 1 to 2 million - Kochi, Trivandrum, Calicut, and Quilon, and only by extensive testing can hot spots be quickly picked up and snuffed out in time to prevent flare ups. Extensive testing is critical when social distancing measures are relaxed.

An outlook similar to India is likely in many of the densely populated countries of Asia (for example, Indonesia, Bangladesh, Pakistan, Japan) and most countries of Africa, South America and also Mexico. One worrying common denominator is the number of people tested per million which stands very much under 3 per 1,000 in all these regions.

There is also a line of thinking that opposes social distancing measures by means of shut downs and stay-in orders; they oppose closure of educational institutions, businesses and events. They want the younger working populace to acquire herd immunity, and segregate the older people and others who are at risk of developing severe manifestations with poor outcomes. However, it is becoming clearer that many younger people are also getting hospitalized and losing their lives. Moreover, the USA alone lost more than 37,000 seniors

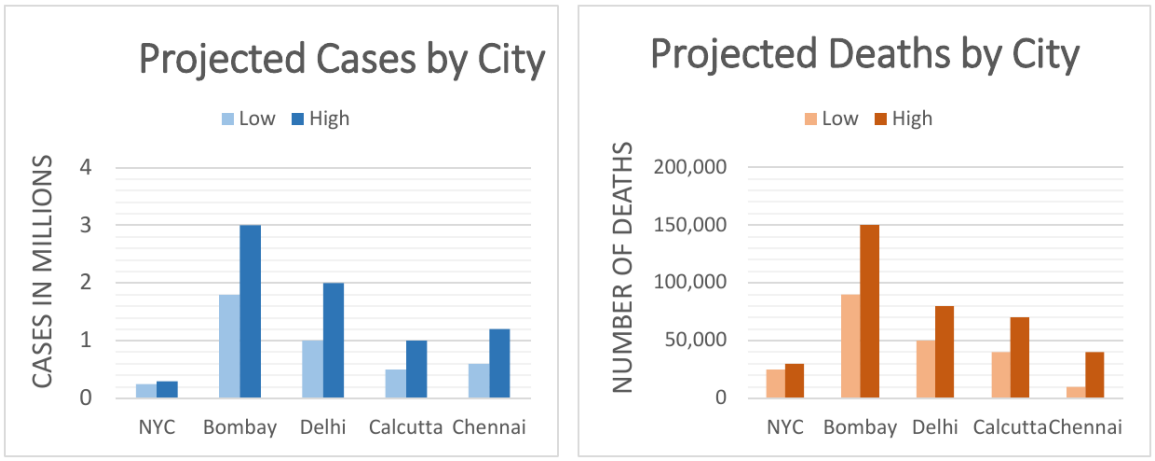

Figure 9: Projected cases and deaths for New York City, Bombay, Delhi, Calcutta and Chennai

and staff members to Covid-19 in nursing homes and other long-term care facilities where they are kept typically separate from the younger population.

In a country such as India, with joint-family households where children, parents and grandparents live in the same household, segregating seniors is not a viable proposition. Riding out the pandemic without instituting containment and mitigation measures will overwhelm the healthcare system, resulting in carnage in almost all population centers. For a contagious disease with a high mortality rate, herd immunity has to be acquired with effective vaccines.

Summary and conclusion

Covid-19 originated in China and within a few weeks, it had infected tens of thousands of people, overwhelmed hospitals, and caused thousands of deaths. It then quickly spread to many other countries in Asia, Europe and the Americas. It has also slowly found its way into many countries of Africa and has truly emerged as a global pandemic. But the magnitude and severity of the spread in different countries varies considerably. Currently Covid-19 is raging in the United States, Brazil, Russia, UK, India and other countries. The virus is like a slow-moving tsunami that has acquired the ability to launch outbreaks at the time and place of its choosing. There are some knowns but many unknowns surrounding the SARS-CoV-2 virus.

An effective vaccine which can confer definitive protection against Covid-19 appears to be at least 18 to 24 months away, though many scientists are in a race to develop such a vaccine and ten candidate vaccines are currently in phase I/II trials. Likewise, there is no definitive drug treatment for the condition though a handful of drugs including the anti-viral drug Remdesivir and the anti-malarial drugs Hydroxychloroquine and Chloroquine are being evaluated in clinical studies for their efficacy. Because of the increased mortality and cardiac arrhythmias reported by one large study [39] and lack of clinical benefit observed in another [38], Hydroxychloroquine and Chloroquine are quickly going out of favor.

In the absence of vaccines and definitive

drugs, the only effective resistance against the contagion seems to be vigorous containment and mitigation efforts to alleviate the onslaught of Covid-19. Effective public health measures, improved public sanitation and meticulous observation of the best practices of personal hygiene will also help in breaking the chain of community transmission of the contagion. The pandemic has reinforced the age-old but often sidelined aphorism that prevention is better than cure.

After providing a primer on Covid-19, we have charted the early stage of the pandemic which started in China and then moved quickly mainly to the countries of the western world, picking through their health systems and decimating many senior living facilities. The pandemic has also laid bare the disparities and inequities in healthcare access and delivery to different segments of the population in all the affected countries. We have also provided a window to the next stage where the pathogen is spreading its tentacles to the developing countries of Asia, Africa and South America. As the pandemic evolves further, the virus is also likely to cycle back during fall into the countries ravaged earlier. Covid-19 is likely to remain endemic and get entrenched in many parts of the world till an effective vaccine emerges to stop the SARS-CoV-2 virus in its tracks.

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Will a coronavirus vaccine stop the present wildfire of misery?

Raju Mukherjee*

Usually, when we visit our friendly neighborhood general practitioner with symptoms for upset tummy, the doctor sends us back with medicines that contain at least two different antibiotics. Upset tummy associated diarrhea is caused by eating food contaminated with waterborne bacteria. The first of the two broad-spectrum antibiotics stop the bacterial genome duplication while the other one targets bacterial protein production, thereby ensuring a quick cure. Most often, the second antibiotic is also prescribed for symptoms of common cold and flu. This is not given to eliminate the influenza virus, which causes the seasonal flu, but on most occasions to satisfy the patient who would not return without an antibiotic and sometimes to prevent a suspected secondary infection by bacteria. One can achieve protection from an infectious or communicable disease caused by bacteria, viruses, and parasites by getting vaccinated. However, when it comes to the seasonal flu that requires yearly vaccination, only a handful can afford to buy.

Vaccination is a method of creating a mild disease like condition in order to allow the human body to train and prepare itself for a future attack by the same infection. Early records of vaccination (then called Variolation) in India can be traced back to the sixteenth century when it was practiced by a mysterious group of Brahmins wandering along the course of the Ganges in undivided Bengal [1]. They vaccinated young children from smallpox, prevalent in the region, by dipping a needle into a dried pustule and puncturing the skin repeatedly in a small circle on the upper arm. A severe smallpox epidemic followed the famine in Bengal in the 1770s that left the victims disfigured and blind if not dead. Its sheer scale and severity saw the re-emergence of "Shitala Devi" the Goddess of smallpox, which received large-scale community worship [2]. All of these were much before Lady Mary Wortley Montague, the wife of the British ambassador, informed the Royal Society of London about the technique of Variolation being practiced in the Turkish countryside [1]. Perhaps, variolation or vaccination against smallpox is one such early medical intervention, which Indians

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can be proud of, rather than the mythicized stories of innovation of ancient India, we often get to read. This article on the development of vaccines against COVID-19 is written for readers who love science and for those who fear studying life sciences. It gives a simplified description of vaccination, different types of vaccine and an update on the present excitements and challenges in vaccine development for COVID-19.

What is a vaccine, and why is it helpful to get vaccinated?

A vaccine can be defined as a biological agent derived from the microorganism that causes the infectious disease. It is generally presented as a preparation of the infectious agent or one of its components, that when introduced into our body allows us to experience the symptoms of a mild disease and thus helps to develop protective immunity. Our immune system thus stimulated provides this protection through the two main arms: Innate immunity mediated by few particular types of white blood cells that have the non-specific ability to kill infected cells, and Adaptive immunity mediated by the generation of some more specific killer cells and production of neutralizing antibody directed against the invading microorganism. This protective immunity also has a memory and once developed, can last throughout the lifetime, sometime with the help of repeated vaccination (booster doses). Vaccination during an epidemic has multiple benefits and can be efficiently used to i) reduce disease severity among the infected individuals, ii) control transmission of the agent by reducing its release into the environment and iii) lastly to prevent infections during future outbreaks.

Hundred years back, wildfires of misery burnt the whole world, with millions of deaths caused by measles each year. The famous Spanish flu, which also reached India, wiped away nearly 5% of the human population. Until decades ago, polio used to leave many children with life-limiting disabilities. We cannot imagine a world without vaccination, which has managed to save millions of lives. Therefore, it can be quite astounding to see the anti-vaccination movement gaining support from the educated parents and leaders of the developed nations, leading to the resurgence of measles fifty years after a vaccine was developed. Today, we have vaccines for most of the infectious diseases that can be taken at a specified age during one's lifetime or during travel to a country where a disease is prevalent [3]. Research is actively being pursued to also have vaccines to prevent cancers, but we will not discuss it here.

What do we need to know about the coronavirus to make the best vaccine?

It is necessary to know as much as possible about the causative agent of the disease, in this case, the new coronavirus (SARS-CoV-2) to design a vaccine. This virus is the seventh member of the coronavirus family that caused the severe acute respiratory syndrome (SARS) epidemic of 2002-04 and the rather colonially named Middle East respiratory syndrome (MERS) that is still prevalent since 2012. This coronavirus is believed to have originated from the bats, its natural reservoir, in Hubei province of China and spilled over to humans or first to pangolins before reaching the humans [4, 5]. This conclusion is made by identifying similarities in the genetic material to that of the bat and the pangolin coronaviruses.

Like other microbial entities, viruses have their own genetic material, which is either made of DNA or RNA, packed together with some proteins inside a shell that is again made from proteins. Most of the time this shell is decorated with proteins (in this

case, spike protein) projecting outwards, giving a look of a corona, but whose main function is to dock at its receptor (in this case, ACE2 protein), another protein present on the surface of the human cell,

very politely called as the host. This encounter with the host cell becomes the first step towards establishing an infection, so if one can prevent this interaction between the two proteins, one can achieve protection from the infection. However, we must understand that not much is known about the mechanism of coronavirus infection and all of our assumptions on how our immune system will react to SARS-CoV-2 proteins is based on the large number of similarities that were observed between the proteins present on SARS-CoV and SARS-CoV-2 viral surface [6].

The viral genome also undergoes changes (mutation) to adapt to the environment provided by the new host, the humans. In case of viruses like this, the genetic material (RNA) usually has higher mutation rates $\sim 10^{-4}$ substitutions per position per year, so it becomes very important to continuously monitor these changes that generate variability in the genetic material [5]. This information is crucial in identifying the best strain or the variety (Chinese, American, Italian, or Iranian) of the new coronavirus to develop a good vaccine.

A vaccine candidate is chosen from the several options available as per the level and type of protection required. The simplest way to vaccinate is to introduce the virus into the body after inactivation using chemicals, ultra-violet or gamma rays, or simply heat. Proteins present on the dead viral surface will serve as antigens and induce the production of neutralizing antibodies, as seen in the case of the early polio vaccine.

Another method involves introducing a weaker version of the virus that grows slowly inside the host cell but produces enough antigens to induce an immune response that finally eliminates the virus. This procedure is practiced for the oral polio vaccine, rabies vaccine, or the BCG vaccine given at birth to protect from childhood tuberculosis. Administering a weaker virus is less safe than a dead virus and has been the cause for a few disease outbreaks but they are superior in terms of mimicking an infection that is necessary for mounting a successful immune response [7]. Developing this live-attenuated vaccine in a short time is challenging, as it requires isolating the weak virus through rounds of time-consuming culturing in the laboratory.

One each of the above type is currently under development to estimate their efficiency. Formaldehyde inactivated formulation is being developed by Sinovac Biotech in China while a genetically modified growth deficient coronavirus is being developed in a partnership between Codagenix, USA and the Serum Institute of India [8]. A relatively newer method of introducing the surface proteins (spike protein) or its fragments to induce the production of neutralizing antibody constitutes the "subunit based vaccines", like in the case of the hepatitis-B vaccine. A virus being an obligate intracellular entity, meaning it requires the host cell for its multiplication, all vaccine strategies are aimed at preventing attachment and fusion of the virus to the host cell surface. However, choosing the right vaccine candidate is as much an art as a science since finding the viral component that won't trigger severe inflammation but can provide a protective immune memory is not so easy. This is more difficult in case of COVID-19 when nothing much is known about how much damage is caused during the disease and how and where the virus hides itself to escape from the body's immune army.

Is there any quicker way to develop a vaccine?

Based on the popular concept of *"plug-and-play,"* several new methods have been developed that can be used to prepare a vaccine against multiple agents and in a short time, although they largely follow the same principles as mentioned above. This is possible only because the safety features of modern vaccines are determined predominantly by the technology used in the method of preparation rather than on the virus of interest.

The viral protein in subunit vaccines, when injected into the body, might not be stable and can lose their three-dimensional shape, which might result in a sub-optimal immune response. To circumvent this problem, a new method called *"Molecular clamps"* was devised at the University of Queensland, Australia, in which short segments of known protein can be stitched at several places on the viral protein to help retain its original shape [9]. In another method, which is based on nanotechnology and is quite popular, viral proteins were genetically modified such that when mixed with other structural protein can self-assemble into a nanostructure, enclosing the viral protein inside a *"virus-like particle."* They are non-living particles and do not cause infection, but because of their virus-like structure can stimulate strong immune protection [10].

Further, with rapid advances in understanding the life cycle and the damage caused by a wide variety of viruses, along with the development of tools required for manipulating the viral genome, it has now been possible to generate safer vaccines expressing viral proteins using a proxy infection [11]. This technology involves using *"viral vectors,"* which have the backbone of harmless viruses that can be used as vehicles for delivering the gene of interest (in this case, the gene corresponding to the spike protein). This new piece of DNA will eventually give rise to the required protein of interest, and as this harmless virus multiply, it mimics the natural infection cycle without causing any damage. To make this process completely safe from any rare events of the harmless virus becoming hostile, the genome of the virus can be modified to stop from multiplying inside the body. Viral vectors based on measles virus have been used to prepare safe vaccines against HIV-AIDS, SARS, Ebola and Zika.

Nucleic acid (DNA and RNA) based vaccines have emerged as a better alternative to live and inactivated vaccines for treatments against emerging viruses as the DNA coding for the viral protein can be produced in a short time. This does not involve growing the virus in the laboratory and gives equivalent protective immunity as other vaccines. In case of "DNA vaccines", the DNA is introduced directly into the human body and once they make their way into the nucleus of a host cell, the viral surface protein production is outsourced to the cell's natural machinery [12]. "mRNA vaccines" represent the new generation therapies, and unlike DNA vaccines it avoids the risk of being integrated into the human genome. The RNA can produce the spike protein of interest in the cytoplasm in high numbers but cannot package itself into a functional virus [13]. All of the above innovations are being rapidly utilized to develop multiple vaccines against the new coronavirus.

Do we need multiple vaccines for COVID-19?

Vaccine development is as challenging as developing a new drug, and in case of COVID-19 this is even harder due to the presence of so many unknowns associated with the disease and unavailability of an animal model to test the vaccine. Despite

all of these difficulties, the scale and severity of the current pandemic has attracted around 65 companies, both multi-national pharmaceuticals, small biotechnology firms and even university spinoffs, to develop a vaccine for COVID-19 [8]. Thanks to the attractive funding from the government of the USA, work has been initiated on multiple candidates, which are currently in clinical trials and in the laboratory. In addition to this, the Coalition for Epidemic Preparedness Innovations (CEPI), a global alliance based funder for vaccine development, co-founded in 2017 by the governments of India and Norway, with support from several philanthropic organizations including the Bill and Melinda Gates Foundation of Microsoft fame, has enabled several small biotechnology firms and academic institutions to join this global effort.

The new candidates are not only based on traditional approaches, they are also being built on the existing vaccines and leveraging on platforms used to develop the SARS vaccines. It is important to note that vaccines for COVID-19 do not have to be similar to the ones proposed against other coronaviruses. Pasteur Institute, France, has proposed to use the measles vaccine virus backbone, earlier used to prepare vaccines for Ebola and Zika, to develop a vaccine specific to new coronavirus [8].

Clinical trials were started on healthy adult volunteers with funding from CEPI, for a nanoparticle encapsulated mRNA vaccine co-developed by the National Institute of Health, USA, and a company named Moderna. Another frontrunner in starting the clinical trials is CanSino Biologics in partnership with China's Academy of Military Medical Sciences' Institute of Biotechnology. This candidate is based on a viral vector used earlier for Ebola. The University of Oxford's Jenner Institute has started trials for another viral vector based vaccine backbone. Among others, prominent candidates that are undergoing testing are mRNA based vaccines from two German companies that are re-using their cancer vaccine technology and the molecular clamp based protein subunit vaccine from the University of Queensland. A very ambitious DNA vaccine candidate that will be injected through the skin is being developed by Inovio Pharmaceuticals, USA, with funding both from CEPI and Bill Gates, though DNA based vaccines have not received any regulatory approvals in the past [14].

It is hard to predict when and which candidate might see a dead end and success finally depends on the results of the human clinical trials which has been started directly for the first time in the history of vaccine development. For the first time, an unprecedented amount of government funding has been sanctioned for multiple vaccine candidates. This is being done with a single hope of hitting one success that can make it self-reliant in protecting its citizens. Since it might take a while until the results of the clinical trials are published, the famous BCG vaccine that is given for protecting children from tuberculosis has found some interest among scientists. This is due to the non-specific protection that BCG gives against viral infections [15]. Although not scientifically proven yet, large-scale trials have started in Australia where nurses and healthcare workers are receiving BCG vaccines with the hope of getting protected from COVID-19 disease [16].

Will the battle be won by developing a vaccine?

Usually, it takes more than 10 years to develop a vaccine following the classical path of inactivated or live-attenuated vaccines,

after collecting safety and efficacy data over a long period. This involves first testing in laboratory cultures and on animal models for its efficiency in producing the required antibodies and absence of any toxic side effects. Once it clears this stage, the same tests are repeated on healthy human volunteers (Phase I of clinical trials) before being given to a small number of infected persons (Phase II). Based on the results of this, a larger phase III trial is initiated to check for long term protection among different age groups, genders, ethnic populations, children and expecting mothers. Safety data from all of these studies are absolutely required by the regulatory bodies to approve a new vaccine.

One cannot short circuit these procedures but can perform the last two steps somewhat together as were done during the Ebola emergency in 2014 when timelines were brought down to 5 years. As the COVID-19 contagion rapidly spreads across all the continents except Antarctica, Inovio Pharmaceutical has ambitiously placed a timeline to complete human clinical trials within a year [14]. This is understandable, keeping in mind that there may not be enough volunteer patients available later to participate in the trials, though it is not clear how one will collect information on vaccination-induced severe illness that happens in a vaccinated patient upon re-exposure to coronavirus later in life.

When it comes to manufacturing and delivery, the process will face a number of new challenges. Large quantities of the vaccine preparation are generally required to start full scale phase-III trials, which also needs to be produced quickly. Moreover, each product will require a customized scale-up technology that will have to be developed. In a market driven economy, more and more companies have shifted focus to the safer lifestyle disease business and has resulted in losing the skillset and expertise required for vaccine development. These units need to be re-built with continuous financial commitments, with no guarantee for the best rewards. Furthermore, the manufacturing units will have to be ready before the success of the human trials, raising the most challenging question of choosing the best candidate vaccine for production.

More than the technical challenges, a strong long term international political commitment will be required to convince big pharmaceuticals to forget worrying about the plummeting future demands after the pandemic is over, foolish anti-vaccine campaigns and the lack of prospects of creating wealth. These have been the foremost reasons for reluctance to develop cures for neglected diseases that are prevalent in countries with poor socio-economic conditions and high global health equity. However, since no single company will be able to supply the billions of doses required for worldwide deployment allowing several different versions to be produced, an advance purchasing commitment will certainly motivate them to come forward.

Another important question that may arise and needs some clarity is selecting the target population for delivery. Will we vaccinate the healthier individuals who might be naturally protected and the older people who might show problems of a poor immune response? Certainly, healthcare workers need them the most in our preparedness for the next wave of infection and perhaps also the traders in Chinese live animal markets.

Once we have the vaccines and hopefully, after the peak of the pandemic is over, an effective policy needs to be carefully written to develop a global access framework for equitable distribution of the coronavirus vaccine in the developing world while at the

same time protecting intellectual property and marketing rights of the innovator. We may not be able to solve this global crisis if we fail to eliminate the virus from its last reservoir. Distribution of the vaccines should be made strictly based on humanitarian benevolence, and centrally through agencies like the Global Alliance for Vaccines and Immunization (GAVI) and WHO. The global leadership should not permit the vaccine manufacturers to sell to the highest bidder, nor should the vaccine producing countries and the richest economies be allowed to stockpile the doses for their citizens in the absence of a national emergency [17]. History has seen this happening during the H1N1 influenza virus epidemic in 2009, and such acts will ensure our defeat in this global fight against COVID-19. However, there has been some recent development with world leaders pledging to raise 8.3 billion dollars to support creating a "development and manufacturing cooperative" to deliver available, accessible and affordable vaccines for the world [18].

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SARS-CoV-2 and COVID-19: Where from and whither to?

Mahipal Sriram

The first reports of atypical pneumonia (COVID-19) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) from Wuhan, Hubei province, China came into light on 30th November, 2019 [1, 2, 3]. Since then, COVID-19 infection is now widespread and the WHO (World Health Organization) declared this infection as a pandemic on 11th March, 2020; as of 19th May, 2020 more than 48.94 lakh cases have been confirmed in more than 213 countries, with more than 3.2 lakh deaths [4]. In 2002, an epidemic mediated by SARS-CoV-1 (Severe Acute Respiratory Syndrome Corona Virus 1, another coronavirus which originated in China) occurred and infected 8098 people causing 774 deaths before the end of the epidemic [5]. Thereafter, in 2013, infection mediated by another coronavirus, MERS-CoV (Middle-East Respiratory Syndrome Corona Virus) occurred in the Middle East and this virus infected 2521 people causing total 866 deaths, as of today, this disease is still prevalent [5].

As per available data, SARS-CoV-1 was much more fatal than SARS-CoV-2 but its infectivity was not as high. SARS-CoV-1 transmission occurred predominantly in hospital settings (hubs), transmission occurred only 24-36 h after the appearance of symptoms, and lack of asymptomatic cases were reported, leading to effective implementation of barrier nursing. In contrast, COVID-19 displays widespread community transmission and patients remain asymptomatic but infective for the first 7-10 days of infection.

As it is highly contiguous in nature, most parts of the world are under lockdown at present with people staying at home and maintaining physical distancing to contain the infection in the absence of any available therapy. In these worrying times, people are uncertain about their future and the duration of this pandemic, and significant anxiety exists regarding the origin of this virus.

In the midst of the global COVID-19 public-health emergency, it is reasonable to wonder why the origin of the pandemic matters; it matters because detailed understanding of the origin of this virus will help to mitigate further spread and to prevent future outbreaks. Scientific data has confirmed that SARS-CoV-1 and MERS-CoV originated from bat coronaviruses with civet cats and camels, respectively, as the spillover reservoirs. Such knowledge is useful in culling the chain of infection, but in the case of COVID-19, *the spillover reservoir is unknown*.

There are many theories being discussed regarding the proximal origin of this virus. Conspiracy theories regarding the virus being human-made arose primarily because it was first reported in China which has been engaged in coronavirus-related research in a BSL4 (Bio Safety Level 4) laboratory near the Wuhan market. Another school of

thought is that like other SARS coronaviruses, this novel human virus SARS-CoV-2 also originated from bats through natural selection followed by adaptation and then jumped the species boundary of animals and subsequently infected humans.

In this article, these theories will be analyzed on the basis of published biological data and scenarios by which they could have arisen will be discussed.

SARS-CoV-2 is a super-virus

The SARS-CoV-2 virus has an oily lipid membrane packed with genetic instructions to make millions of copies of itself (Figs 1A and 1B). The instructions are encoded in 30,000 'letters' of RNA comprising A, C, G, and U (adenine, cytosine, guanine and uracil), which the infected host cell reads and translates into several kinds of viral proteins. Like other coronaviruses, SARS-CoV-2 contains a spike protein to gain entry into host cells but differs from them in that the SARS-CoV2 spike protein (S) has distinct characteristics which enhance its rate of infectivity making it a super virus (Fig. 1B) [6].

SARS-CoV-2 performs the following actions: 1) attaches to the host cell membrane 2) binds to a human cell 3) enters the host cell 4) transfers its genetic material into the host cells and 5) makes millions of copies of itself (Figs 1B and 1C).

When a COVID-19 patient sneezes, the water droplets carrying viruses enter the mouth, nose, and throat of a nearby person. Then, the sticky and oily lipid membrane of the virus attaches to the membrane of the host lung cells. Next, the virus binds to a cellular receptor called ACE2 (Angiotensin-converting enzyme 2). These ACE2 receptors, which stick out from the surface of lung cells act like little antennae and are designed to sense signals that change our blood pressure; our lungs are involved in the fine adjustment of blood pressure. (Fig 1C). These receptors are also present in the arteries, heart, kidneys, and intestine.

The above sequence of steps is only the beginning of the infection process. Once SARS-CoV-2 is stuck to a cell, it needs to get in. SARS-CoV-2 is covered in spikes. The spike protein acts like a key to open the lock and enter cells. For unlocking, the correct key needs to be inserted into the groove of the lock, the key turned in the right direction, and sufficient pressure exerted (this step is known here as the trigger). However, this pressure cannot be exerted randomly; if it is too early or too late, the lock will not be opened.

The spike protein consists of three subunits namely S1, S2 and S3. The virus binds to the cell receptor through the S1 subunit of the spike protein very tightly and then the spike protein pulls the surface of the cell and the virus together. Now, the trigger has to act. The junction of the S1 and S2 subunits of the viral spike protein contains a signature motif of a trigger sequence. To trigger the spike protein at just the right time, viruses rely on a human protein enzyme in our blood called Furin. Furin cleaves this trigger sequence and allows both the membranes to fuse, thus playing the role of a perfect trigger. Our bodies produce large amount of Furin. "Basically, you can work out if a virus is going to be highly pathogenic or not if it is activated by Furin", according to Prof. Turner [7]. After fusion, the genetic material of the viral genome is transferred into the host cells. The virus then makes millions of copies of itself exploiting the host's ingredients (Figs 1B and 1C).

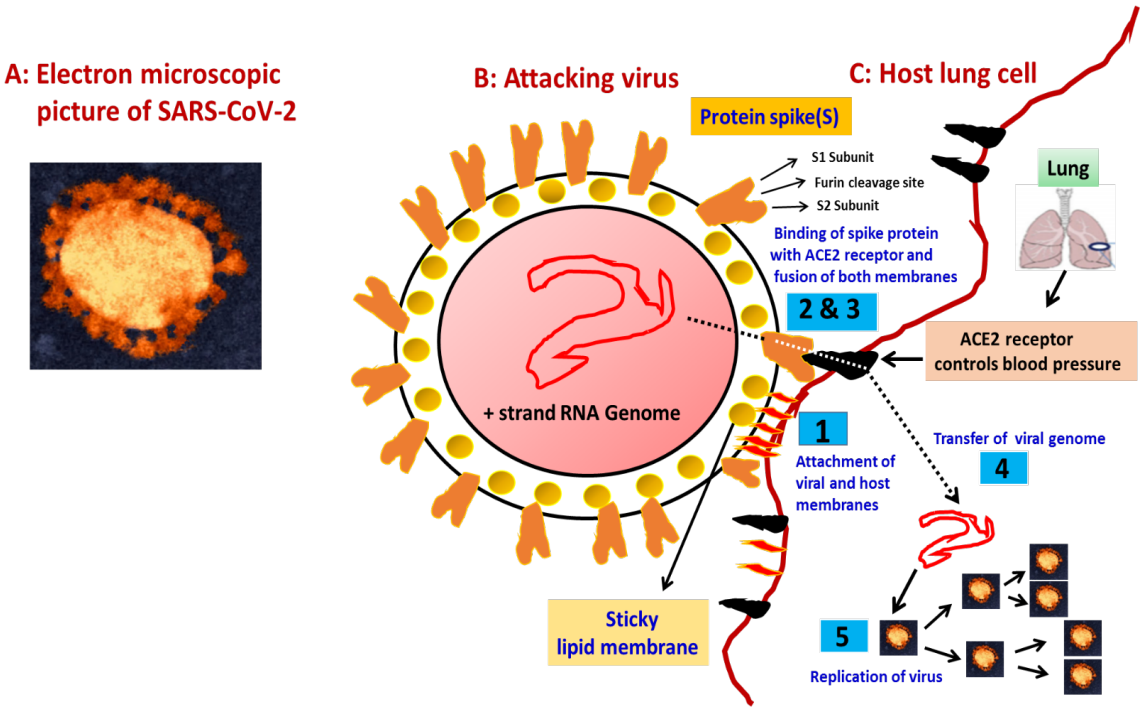

Figure 1: How does virus enter the cells and replicate? A) An electron-microscope image of the COVID-19 virus, isolated from the first Australian coronavirus case.Note the bubble in the centre surrounded by spikes. Credit: CSIRO (7) B) Schematic diagrams of SARS-CoV-2 and C) a host lung cell. Representation of the five sequential steps of viral entry into the host cell and its replication. 1) The viral sticky lipid membrane attaches to the host cell membrane; 2) S1 subunit of the viral spike protein binds to the ACE2 receptor protein of the host cell; 3) Furin cleaves the S2 subunit of the viral spike protein causing fusion of the viral membrane with the host cell membrane; 4) the viral genome is transferred into the host cells; and 5) the virus replicates and makes many copies of itself.

Notable genomic features of SARS-CoV-2

The genetic material of SARS-CoV-2 is a plus-stranded RNA molecule. This RNA encodes information to make viral proteins ($\sim$ 30), each of which is involved in a different step of the synthesis and assembly of millions of new virus particles (virions). The key first step is to make copies of the viral RNA. How does the virus copy its genetic material? An enzyme called RNA-dependent RNA polymerase (RdRP) copies the genetic instruction from this plus-stranded RNA and thus helps in its replication. The characteristic feature of this virus is that the same plus-stranded RNA is used both for translation (to synthesize proteins) and replication (to make millions copies of its own genetic material).

More than 500 coronaviruses have been identified so far in China with estimates of unknown bat coronavirus diversity reaching $>$ 5000 [5]. There are seven coronaviruses associated with human diseases. Alpha-coronaviruses such as HKU1, NL63, OC43 and 229E are

associated with mild symptoms whereas beta-coronaviruses such as SARS-CoV-1, MERS-CoV and SARS-CoV-2 can cause severe diseases in human. SARS-CoV-2 is the seventh coronavirus known to infect humans (6). Comparative genomic analysis is a scientific tool which identifies variation in genomic sequences among different types and different strains. SARS-CoV-2 viruses have been isolated from infected patients, and their genomes (+ strand RNA) have been isolated and sequenced.

Genomic comparison of alpha- and beta-coronaviruses reveals the following notable genomic features of SARS-CoV-2 (6) (Fig 2):

- Its genome is $\sim$ 96.1% identical/similar to Bat RaTG13 coronavirus genome
- The region of the Spike protein in the S1 subunit, which is important for ACE2 binding, is called the receptor binding domain (RBD). Intriguingly, six important contact amino acid residues of SARS-CoV-2 RBD match 100% with the RBD of the Pangolin coronavirus Spike, but with only one amino acid residue of the Bat RaTG13 Spike! (Figs 2A and 2B)
- The SARS-CoV-2 Spike has a unique Furin enzyme cleavage site at the junction of S1 and S2 subunits and the enzyme acts like a trigger and helps in viral entry in host cells (Fig 2C).
- The SARS-CoV-2 Spike has acquired three O-linked glycans near the Furin-cleavage site and these are used as a mucin shield for immune-evasion so that production of antibodies in the host against viral proteins is delayed (Fig 2C)

Bat RaTG13 coronavirus: $\sim$96% genomic homology with SARS-CoV-2

In 2013, in the province of Yunnan, about 2000 kilometers west of Wuhan, a horseshoe bat was caught in a trap. These bats stay in dark caves and maintain social and physical distancing from humans! If one were to put this bat on one's palm and try to feel its weight, it will be evident that the weight of this small creature approximately equals the weight of a ball-point pen; not significant at all! Scientists swabbed the mouth of this bat and tested it. Surprisingly, they found that this bat contained a virus, named RaTG13 whose genomic sequence had similarity to other isolated coronaviruses. The copy number of this virus in the bat was very low. It is clear that viruses and bats maintain a symbiotic relationship and the viruses do not harm the bats. While such viruses were being found in bats, life moved on, people stayed busy with other things and never worried about these Chinese viruses. Ironically, SARS-CoV-2, which has caused this pandemic and has now infected millions, killed lakhs of people, and continues to terrorize mankind, shares 96.1% per cent of its genetic code with the above virus, RaTG13. This is the main reason for the frequent mention of the RaTG13 bat virus in the news.

Interaction of the viral receptor binding domain (RBD) with the host ACE2 receptor: Used by the virus to enter host cells

SARS-CoV-2 binds to the host cell using the S1 subunit of the spike protein. Its S1 subunit contains the Receptor Binding Domain (RBD) which binds with the host ACE-2 protein; six important contact amino acid residues (-L-F-Q S-N-Y-, Fig 2B) in SARS-CoV2-RBD match 100% with the RBD of a Pangolin (an endangered animal) coronavirus, but with only one amino acid residue (-L-Y-R -D-H-) of Bat RaTG13 (Fig 2B) (6). This is why the pangolin coronavirus may be able to infect humans

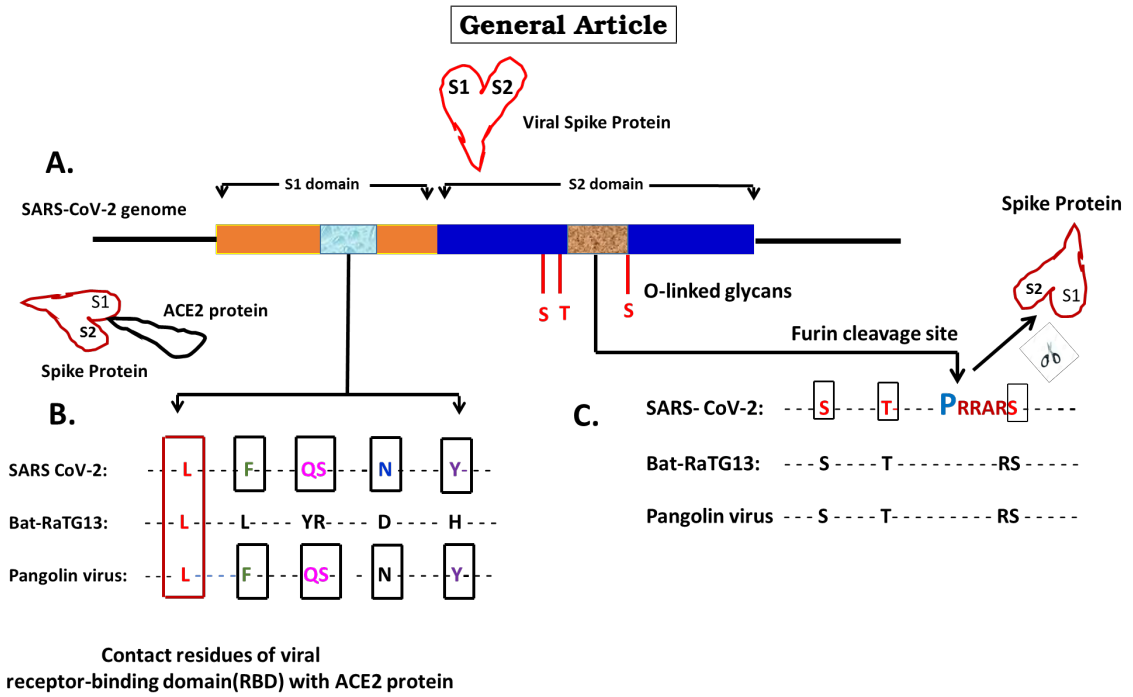

Figure 2: Features of the Spike protein in SARS-CoV-2 and related coronaviruses. A) Schematic diagrams of the S1 and S2 subunits of the Spike protein of SARS-CoV-2. B) Important contact amino acids of SARS-CoV-2 Spike receptor-binding domain (RBD) mediating interaction with ACE2 protein and their homology with that of others coronaviruses. C) A unique Furin-cleavage site (RRAR) of SARS-CoV-2 is located at the S1-S2 junction of the Spike protein but is absent in other coronaviruses; SARS-CoV-2 acquires three O-linked glycans at Serine (S), Threonine (T) and Serine (S) amino acids located near the Furin-cleavage site.

effectively but the Bat RaTG13 cannot. This also suggests that the bat RaTG13 coronavirus might have acquired RBD of the pangolin coronavirus. How is this possible? Could this have occurred through mutation or through gene recombination? A typo (mistake) occurring while writing equals a mutation in genetics, but a group of words being replaced with another group of words equals recombination (insertion and/or deletion).

SARS-CoV-2 has exonuclease activity (proofreading capacity) and may not allow many mutations to occur in the RBD of the S1 subunit (though it is a highly potential mutable region) of bat RaTG13, leading to the speculation that SARS-CoV-2 acquired the main residues in its RBD domain from that of pangolin coronavirus most probably through recombination. However, detailed study is required to confirm this RNA recombination theory.

Furin cleavage site: Helps in viral entry into cells and enhances infectivity

As discussed earlier, Furin (trigger) cleaves its cognate cleavage site at the S1-S2 junction and helps in virus-host cell fusion, impacting transmissibility and pathogenesis. SARS-CoV-2 has an RRAR sequence known as a polybasic Furin cleavage site (named polybasic because three out of the

total four amino acids are the basic amino acid Arginine (R), Fig 2C), but bat and pangolin virus spike proteins have only one Arginine (- - - R); these two viruses thus have incomplete Furin cleavage sites (known as sub-optimal cleavage sites) (6). A consequent question that arises is: If an optimal Furin cleavage site is inserted in the bat and pangolin coronaviruses, could these viruses then act like SARS-CoV-2?

This can only be verified experimentally, in vitro (in tissue culture experiments), and/or in vivo (in animal experiments). Experiments with SARS-CoV have shown that insertion of a Furin cleavage site at the S1-S2 junction enhances cellcell fusion (8). In addition, efficient cleavage of the MERS-CoV spike enables MERS-like coronaviruses from bats to infect human cells (9). Avian influenza viruses encode the hemagglutinin (HA) protein (10), which serves a function similar to that of the coronavirus spike protein. While replicating widely in dense chicken populations, this virus acquired a polybasic cleavage site in HA, either through insertion or recombination. Acquisition of such a polybasic site converts the virus from a low pathogenic to a high pathogenic virus. This fact indicates that acquisition of a Furin site played a role in the crossing of species boundaries. Thus far, data has shown that bat or pangolin viruses do not contain a Furin polybasic site though the analysis has involved under-sampling (6). The question that remains is: From which source did SARS-CoV-2 acquire its Furin cleavage site? Could it be from humans?

Three O-linked glycans: Used for immune evasion and protection against host antibody responses to virus proteins

There is another interesting insertion in the Furin polybasic cleavage site of the SARS-CoV-2 spike protein. The amino acid Proline (P) is present before the arginine and the corresponding sequence is PRRARS (6). This insertion of proline has remarkable significance because proline is known to cause turns in proteins and change their overall conformation. In the present case, such a turn generated by proline might help to acquire three O-linked glycans in SARS-CoV-2. But these glycans are absent in bat and pangolin coronaviruses though these viruses contain the specific Serine (S) or Threonine (T) amino acids to be O-linked glycosylated. In general, these O-linked glycans are used as a mucin shield to hide viral epitopes resulting in delayed responses in eliciting antibody generation in the body after infection (known as immune evasion). While no published data is yet available to assess whether this is in fact the case with SARS-CoV-2, this hypothesis points to explore the asymptomatic nature of COVID-19 for the first 7-10 days after infection.

The birth of a virus

Here is one potential scenario: *Natural selection in an animal host before zoonotic transfer.*

"These bat viruses are, in evolutionary terms, very stable. They do not change much. It is unlikely that RaTG13 turned into SARS-CoV-2 within a bat", according to Baker [7].

However, things change when a bat virus jumps to another animal.

RaTG13 has the ability to bind to ACE2 but not very effectively (Fig 3A). It is possible that RaTG13 jumped from a bat into a pangolin – a small, scaly anteater and highly valued in traditional Chinese medicine [7]. Pangolins have the ACE2 receptor as do other animals like ferrets, and the pangolin may have been infected with RaTG13 and another bat coronavirus

at the same time (Fig 3B). When two viruses infect the same host, they can possibly recombine in a process leading to swapping of their genes; this may represent the first instance of gene tweaking resulting in a virus containing a bat genetic backbone and a pangolin RBD site (Fig 3C). Such a virus could have infected humans but would not be very infectious because it lacks a Furin cleavage site (trigger site).

Then, such a virus could have infected humans at a low level and via human-to-human transmission, could have acquired the Furin cleavage site representing *the second instance of gene tweaking*; in the course of time, the virus could have been O-glycosylated in humans.

This may be one of the potential routes via which this virus originated and gained the ability to both bind to ACE2 and use Furin to quickly enter human cells (Fig 3D).

Another potential scenario:*Natural selection in humans following zoonotic transfer*

It is conceivable that a progenitor of SARS-CoV-2 jumped into humans during short undetected human-to-human transmission and acquired the genomic features described above through adaptation. Once acquired, these adaptations would enable the pandemic to take off in due course of time.

Can this virus be generated by purposeful manipulation in the laboratory?

So far, we have discussed notable genetic features of the SARS-CoV-2 and described the most likely pathway of the origin of SARS-CoV-2 from bat via pangolin through natural selection followed by adaptation. Let us now examine the conspiracy theory of the origin of the virus.

The availability of a viral backbone for manipulation

In a laboratory, scientists use a viral backbone to manipulate viruses. The genome of SARS-CoV-2 has ~96.1% similarity with the Bat RTG13 coronavirus genome. To manipulate all the notable genetic features, some viral backbones closely similar to the genome of Bat RaTG13 should have been available and would have been reported; however, no such reports can be found until the pandemic occurred, suggesting that SARS-CoV-2 has not originated from the laboratory.

Viral Receptor Binding Domain (RBD) which binds ACE-2

SARS-CoV-2 contains the RBD of pangolin coronavirus in the Bat RaTG13 backbone. This RBD sequence binds to the ACE2 host receptor and these two proteins interact with each other through a few crucial amino acid residues. To manipulate this RBD, scientists need to know its exact sequence. What is typically done in such cases? Consider an example. You lost your house key; you call a key smith. He first assesses the shape and mold of the lock. Then he brings a dummy key and conducts many trials by polishing and cutting the key and ultimately, comes up with a duplicate key that works. Similarly, scientists would predict the optimal sequence of the RBD of the viral protein which binds to ACE2 and test several combinations by changing the amino acids in the RBD with the help of a computational method called molecular modeling, and ultimately predict an optimal sequence. This prediction may or may not match with the living system.

However, in the case of COVID-19, the scenario was different. After the outbreak, the genomic sequence of the virus has been determined revealing the viral RBD

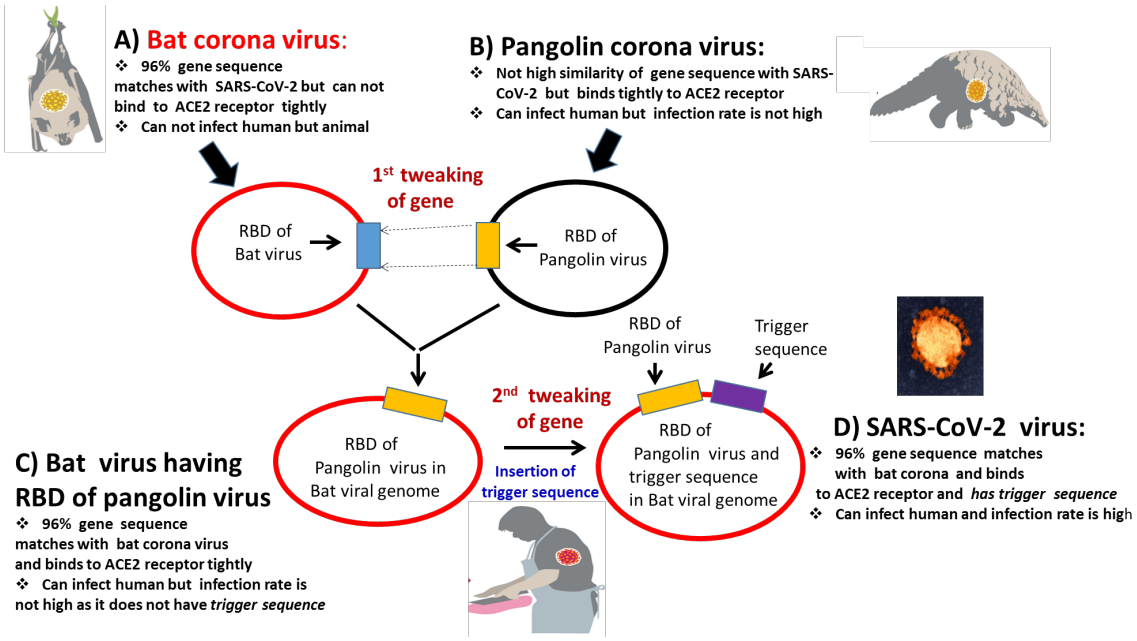

Figure 3: The birth of SARS-CoV-2; the most likely pathway: Tweaking of two genes – natural selection followed by adaptation. A) Bat RaTG13 coronavirus with 96% genome homology to SARS-CoV-2 but unable to bind well to the ACE2 receptor. B) Pangolin coronavirus with low genome homology to SARS-CoV-2 but able to bind tightly to the ACE2 receptor. C) The first instance of gene tweaking occurring when an RaTG13-infected pangolin gives rise to an RaTG13 derivative containing the RBD of the pangolin coronavirus, and D) A second instance of gene tweaking occurring when the above RaTG13 derivative infects humans and acquires the Furin trigger cleavage site, giving rise to SARS-CoV-2. The sketches of bat, pangolin and human have been taken from the article [7].

sequence as well. Scientists subsequently tested this RBD sequence using computer-based molecular modeling and predicted that while it has high affinity for ACE2, it is not the ideal sequence for ACE2 interaction (11). If it was a result of manipulation, why would this sequence be less than ideal?

Thus, the high-affinity binding of the SARS-CoV-2 spike protein to human ACE2 is most likely the result of natural selection with a pangolin or pangolin-like ACE2, or directly with a human ACE2. This is strong evidence that SARS-CoV-2 is not the product of purposeful manipulation.

Acquisition of both the polybasic cleavage site and predicted O-linked glycans

Generation of any manipulated virus needs cell culture-based experiments, requiring several rounds of cell culture in Petri dishes through several passages. It has been experimentally shown that new polybasic cleavage sites arose in avian influenza virus after prolonged passaging; but in that case, the virus backbone was known to the scientists while in the present case, a progenitor virus with high genetic similarity to Bat RaTG13 has not been described. Moreover, generation of predicted O-linked glycans

needs the involvement of the immune system which is not possible in cell culture but is feasible only in vivo (in a whole living organism with the relevant immune system) [12].

Counter arguments

Wuhan wet animal market and BSL4 laboratory

Near the Wuhan wet market, a BSL4 (Bio-Safety Level 4) laboratory was carrying out coronavirus-related research since many years. This type of BSL4 laboratory can house animals for experiments and so manipulations can be done. Of relevance, as per available data, rats and mice are not carriers of COVID-19. There is no evidence of the housing or breeding of Bat RaTG13 and pangolins in this laboratory. As these animals contain low level of viruses, huge numbers of bats and pangolins would be needed at the laboratory for generation of viable number of viruses. Such large numbers of these animals are available only in nature. These facts suggest that SARS-CoV-2 is a product of natural selection followed by adaptation.

Spillover theory of the ready-to-infect-human virusSpillover theory of the ready-to-infect-human virus

The ready-to-infect-human SARS-CoV-2 has been spilled over in the wet market of Wuhan and the infection began. If the virus was ready to infect humans, then what was the necessity to bring it to the wet animal market? It could have been spread in any human groups. The medical journal Lancet published the analysis of the first 41 COVID-19 patients. They found that 27 out of 41 patients had direct exposure to the Wuhan market. But the same analysis also reported that the first known COVID-19 patient did not have any exposure to the Wuhan wet market [13].

Requirement of additional data

More scientific data could swing the balance of evidence to favor one hypothesis over another.

1. The availability of data on patient "Zero" will throw more light on the origin of the virus. This will also give additional information about how this virus crossed the species barrier.

2. Analysis of sufficient serological data of the initially infected patients near the Wuhan wet market is required to know whether unidentified but short durations of human-to-human transmission of the virus occurred. Some data is available in this regard but more is required.

3. More animal viruses are to be sequenced to understand their genetic content and how similar they are with respect to SARS-CoV-2.

Whatever may be the theory behind the origin of SARS-CoV-2, one lesson is we should be extremely careful about the way we deal with nature. Bats and pangolins maintain real social distancing, not only physical distancing with human. They do not come to us rather we go to them. This is very important. SARS-CoV-1 was more fatal than SARS-CoV-2 but infectivity is lower. SARS-CoV-2 is less fatal compared to SARS-CoV-1 but highly infectious. Through natural selection followed by adaptation if a new strain arises, having features of the high fatality and infectivity, then humankind will be in much more trouble. In this such a scenario, humans may not get enough time to respond.

Lastly, in this troubled time, people have realized that only science can save the humankind. They do not believe in the

influence of any supernatural power behind the origin of this virus. Rather, even a palmist who touches the palms of another person is now wearing a face mask on his mouth and gloves on his hands. Is a semblance of scientific temper and approach finally making an appearance in our society?

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Some New Findings to Track the Origin of Novel Coronavirus

Kumar S. K. Varadwaj *

The human species has locked itself down in homes due to the attack of an enemy which, till date, is very little understood. The strategy that has evolved to fight COVID-19 is to avoid human touch or close proximity or even indirect contact through some inanimate object. This behaviour is quite contrary to any mammalian species, including homo-sapiens.

The first COVID-19 patient was detected on 12th December, 2019 from Wuhan in Hubei province in China. The scientists in China realised the devastating potential of the virus and the Chinese Government officially reported the outbreak to WHO (World Health Organisation) on 31st December 2019. Due to high global mobility of the modern day, and highly efficient human to human transmission, the virus spread very quickly to every corner of the Globe. On 30th January 2020, WHO declared the outbreak a Public Health Emergency of International Concern. This devastating pandemic caused by a virus hitherto unknown affected ten lakh people, of which almost fifty thousand died by 5th April 2020.

From where did this virus come from? If it came from some other species, then how did it cross the species boundary? How did it became so efficient in terms of human to human transmission? What is the mode of its transmission? Scientists around the globe are working hard to find answers to these questions which are intimately related to the origin of this new virus. Other studies have gained momentum to understand factors such as how long does the virus stay active outside the human body and on different objects, and what are the chemical formulations that can effectively neutralize the virus. These investigations are essential in the long journey to fight the viral infection by finding medicines, vaccines and technologies to stop its spread. The sheer amount of scientific effort being deployed can be gauged by the fact that more than 900 English language publications have appeared on this new virus till 12th March 2020.

In December 2019, cases of influenza with severe infections in respiratory track emerged in Wuhan, China. Initial investigations showed that the infected people had either visited or were related somehow to a seafood market at Hubei province. Scientists at Wuhan institute of virology took blood and swab samples from the affected patients and tried to detect the microbe responsible for this disease.

The unique character of every life form is encoded in chemical entities in its genes - arranged in particular order called the genome sequence. A group of scientists from China, first did the genome sequencing of this virus and put their findings in public domain [1]. The study of genome sequence from samples collected from dif-

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ferent patients showed that this was a new virus. It belongs to a family of virus known as coronavirus. The chemical backbone of this virus has similarity with that of another coronavirus, which caused epidemics in 2002 to 2003 in southern China. That epidemic is since known as Severe Acute Respiratory Syndrome (SARS). The previously known virus was named as SERS-CoV. The new virus that has started the pandemic in 2019 is named as SERS-CoV-2 by special bodies for naming and characterising viruses. Viruses are named based on their genetic structure to facilitate the development of diagnostic tests, vaccines and medicines. Virologists and the wider scientific community in the International Committee on Taxonomy of Viruses (ICTV) are responsible for naming the viruses.

The coronavirus is a large family of viruses, which causes diseases in mammals and birds. The first corona virus in human beings was discovered in 1960. The earliest one was studied from patients suffering from common cold and it was named as human corona virus 229E. Apart from the presently discovered novel coronavirus i.e SARS-CoV-2, six other corona viruses are known to infect humans. In last two decades, another coronavirus epidemic occurred in 2012, which is known as Middle East Respiratory Syndrome (MERS). But, the other four coronaviruses, namely 229E (alpha), NL63 (alpha), OC43 (beta) and HKU1 (beta) only cause mild symptoms of cold in human.

The viruses do not show any signature of a living body outside a host animal. In fact, some animals such as cattle, horse, pig, mice, dromedary camels and also birds, bats, pangolins and chickens act as reservoirs for different types of viruses. The viruses have gone through a parallel evolutionary process with the evolution of their host animals. Certain viruses stay in certain animals but do not cause any disease in those animals. But when these viruses leave their host animal and enters into the body of some other animal, they cause disease in their new host. It has been established by scientific studies that the dromedary camels found in the Middle East are hosts for MERS-CoV coronavirus. They crossed the species boundary and entered into the human body due to intimate man- camel contact. But the host for SERS-CoV coronavirus which caused the epidemic in 2002 is not exactly known yet. However, studies have shown that different bat species available in China are host for SERS like coronaviruses.[2]

In the present case, therefore just after knowing the sequence for the chemical entities in the novel coronavirus, i.e the genome sequence, it was matched with that of other viruses and a 96% similarity was observed with a particular coronavirus present in bats. Therefore, the Chinese researchers wrote that the virus has a probable bat origin. In this situation of panic and distress, another leading research group in the field of virology from the Scripps Research Institute, from California, USA made a detailed study regarding the origin of this novel corona virus [3]. Before going into details of their study, it needs to be discussed how a virus from its original animal or bird host jump the species barrier and infect the human body.

If any virus from an animal host, by any chance, comes in contact with a human cell, it cannot cause any damage to the cell. The virus needs to have a site, which can efficiently bind to the human cell through some chemical interactions. The Scripps research group studied these binding sites of the novel coronavirus and compared it with that found from the bats and pangolins. They showed that, although there

is 96% similarity in the genome sequence of virus from bat with that of the novel coronavirus, the binding sites for both the viruses are not the same. It has more similarity with that of pangolin. However, the genome sequence of the virus present in pangolin has many differences with that of the novel corona virus. Therefore, at present there is ambiguity in deciding the immediate ancestor of the virus and the host animal from which it has come to human body. However, in their communication to Nature Medicines Magazine the group reported "Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus."

Nevertheless, the authors have proposed two theories for its transfer. The first one is that the virus might have changed its genetic code in the host animal so that necessary changes have been incorporated in their binding sites, which makes it able to attack the human cells, penetrate into it and cause disease. The second one is that the virus first transferred to the human body, stayed dormant there till it underwent required genetic changes for human to human transfer. In both the cases changes occur in the arrangement of basic chemical backbone of the virus by the process of natural selection suggested by Darwin some 150 years ego. However, the primary difficulty in knowing the exact ancestor of the virus and the host animal from which it has come from is that the whole family of coronaviruses present in bats and different species are 'massively under sampled'.

In the last two decades, we witnessed three such events of virus spill overs from their animal host causing massive health hazards. Therefore, a detailed understanding of how an animal virus jumped species boundaries to infect humans so effectively will help in the prevention of such future events. The identification of closest viral relatives circulating in different animals will also be important to understand their action.

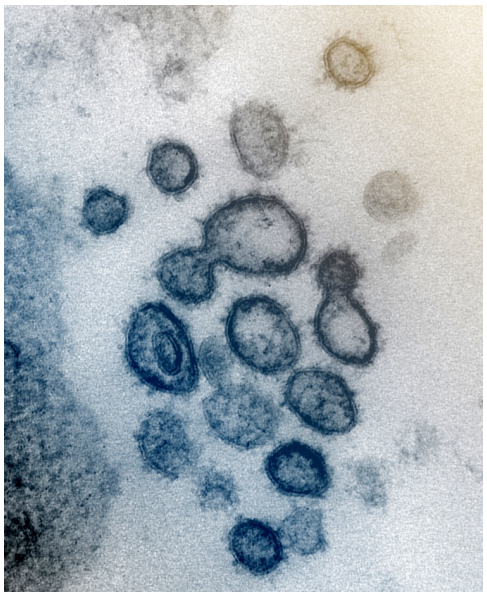

Figure 1: An electron microscope image of SARS-Cov2 particles. Every virus particle shows spikes around it, which looks like a crown. These are the spike proteins covering the surface of the lipid bilayer. The size of each virus particle is around 100 nanometers (1nm = 10^9 meter). These extremely small virus particles can easily float in air along with water droplets, which is one of the modes of its man to man transmission.

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Organizational News

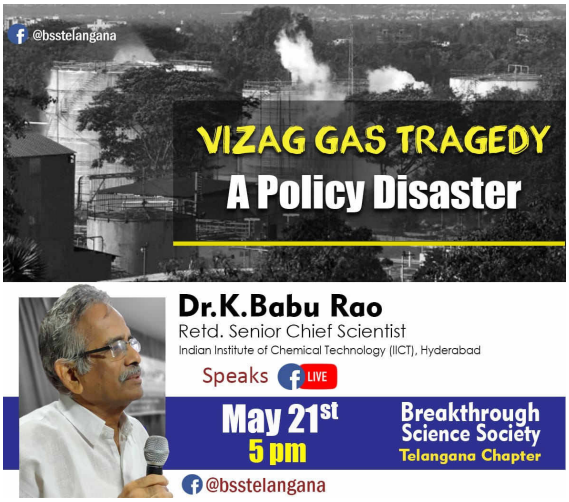
Telangana

A social media protest campaign by holding placards on the Vizag gas leak issue was organized throughout the state of Telangana. The response was overwhelming from different sections of people including the academia. At BSS office, a candlelight program held on May 8.

The protest against Vizag gas tragedy

In the background of COVID-19, an online State level science cultivation program was organized. The program included essay writing, cartoons, poster presentations and short flim making. Students from 9 districts of Telangana participated actively. On May 15, a felicitation function was organized in which the chief guest was Dr Vikas Sharma, Asst Professor of Biotechnology, University College of Science, Osmania University. The winners in various competitions were felicitated.

A webinar was held on the Vizag gas leak



Poster of the webinar on the Vizag gas leak tragedy

tragedy on May 21. Dr Babu Rao, Retd Chief Scientist, IICT, Hyderabad was the speaker.

Odisha

Relief support to migrant workers

Starting from 10th May to 16th May, volunteers of Bigyana Chetana Macha (BCM) affiliated to Breakthrough Science Society provided food and water to distressed migrant workers travelling on the national high way on their way to distant places in Jharkhand, West Bengal etc. Every day scores of men, women and kids were seen travelling on foot, on bicycles, on top of trucks loaded with goods and other vehicles. They were thirsty and hungry. Seeing the plight of those hapless people members of BCM from Cuttack started

Volunteers distributing food and water among the migrant labourers in Odisha

providing relief like food and water.

On 21st May, after the cyclone Amphan made land-fall causing havoc in West Bengal, coastal Odisha including Cuttack. These areas experienced heavy rain and wind. Several hundred labourers were taking shelter below the flyover at Manguli. Trucks loaded with goods and labourers were also ferrying on the road. A youth group from Peyton Sahi, a place in central Cuttack, collected fund and distributed packed dry food to the distressed laborers. The culture of 'Sahi Bhai' that is the living soul and driving force of the thousand year old city, was again at its best. The 'Good Samaritan' was again out on the street.

Kerala

Trivandrum district

Science Orientation Program for school students: An online Science Orientation Program for students in 9th and 10th standards was organized from April 20 to 26. More than 250 students applied for participating in the program.

To ensure the quality of the program, admission was restricted to 50 students. A selection list was prepared by giving preference to the students from Trivandrum district with a limit of four students from one school. Online sessions were conducted from 9:45 am to 12:00 noon every day.

Classes conducted:
Dr. Sarita Vig, 'Wonders of the Cosmos',
Dr. K.B.Jinesh, 'Seeing and Playing with Atoms'
Dr.Sojomon Mathew, 'Microbes and Immunity'
Dr. Umesh R Kadhane, 'Who wants to be the next Archimedes?'
Ms. Medha Surendranath, 'Mendeleev and

periodic table'
Dr. Rajeevan P.P, 'A Brief History of Science and Evolution of Scientific Method'

All lectures were followed by an activity-based session in which the students were advised to do a few activities related to the topic of the session.

Students were grouped into small teams for the ease of management. Each team consisted of 5 students and 3 BSS volunteers. Volunteers played a remarkable role throughout the program. They were keen to help the students in their activities and ensured the active participation of students in every session.

Each day, the session started with presentations by students. One student from each group presented the activity carried out by them based on the previous day's session.

Students were also advised to conduct an experiment using the materials available at their homes to demonstrate or prove a concept in any branch of science based on their interests and present it on the final day. The response was tremendous. Almost all of them performed at least one experiment. Students posted short videos on their experiments in the common Whatsapp group before the final presentations.

In the concluding session Dr. Soumitro Banerjee, Professor in the Department of Physical Sciences, IISER, Kolkata and General Secretary, Breakthrough Science Society delivered a lecture titled 'What actually is science?' and interacted with the participants.

Alappuzha district

The Alappuzha BSS chapter organised a three day science camp for students from 8th class to 11th class from May 11 to May 13, 2020. The timing was from 10.30.am to 12.30.noon. About 110 students including science activists registered. On the average about 30 to 45 students attended the classes. The program was inaugurated by Dr.C.Muraleedharan Pillai, Asst.Director of Health Services and Adv Sajeev T Prabhakaran made a presentation on 'Evolution of stars'. The second day began with a speech by Dr. K. G. Padmakumar, Agricultural Scientist. Shri P. P. Sajeevkumar made a presentation on 'An introduction to sky watching'. On the third day Dr. Godfrey Louis, Former Pro V C, CUSAT gave a talk on 'The method of science'. The last session was on 'Learning science through experiments'. Seven students presented videos of their experiments and explained the science behind the experiments. The participants enthusiastically took part in the discussions on each experiment.

It was also decided to form a whatsapp group of the student participants and continue science discussions and 'learning through experiment' activities.

Idukki district

BSS Idukki chapter in association with the Newman College, Thodupuzha organized a webinar on May 13, 2020. The topic was "Beyond the stars". Prof Joe Jacob, HoD, Dept of Physics, Newman College and a renowned astronomer made the presentation.

The Idukki chapter of BSS in association with the Newman College, Thodupuzha organized a science quiz program for college students on May 15, 2020. 35 students participated in the quiz program.

Thrissur district

BSS Thrissur Chapter organized a series of online talks.
April 5: Talk on 'How man conquered diseases', by Dr. Babu P S.
April 11: Talk on 'History of Astronomy' by Dr. Sheeba, Associate Prof, Dept of Physics, MES College, Kodungallur.

April 22: Talk on 'Earth and the sky seen from the Earth' by Mr Surendran Punnassery, Amateur Astronomer.
April 23: Talk on 'The past and future of the Universe' by Dr.Sheeba, Associate Prof, Dept of Physics, MES College, Kodungallur.

Ernakulam district

BSS Ernakulam chapter organized a series of webinars
April 22: 'Louis Pasteur – life and contributions' by Mr Harikumar K S, Former Safety Officer, FACT, Kochi
April 19: 'Comets – Ice from space' by Adv Sajeev T Prabhakaran , Amateur astronomer
April 25: 'Diseases and treatments in the era of science' by Shri C Ramachandran, Retd scientist, ISRO.
May 16: 'Covid19 – A view from USA' by Mr Martin Kalathungal, Independent researcher of Nutrition and well-being, USA

Science camp for school students: Breakthrough Science Society, Ernakulam chapter organized an Online Science Orientation Program for students of 9, 10 and 11 classes. The camp was conducted in two batches with more than 50 students in each batch. The first batch was from May 2,3 and 4 and the second batch from May 9, 10 1nd 11. Each day there were 2 sessions of one hour duration from 10 am to 12.30pm.

The program schedule for the two batches were as follows.

Batch 1 Day 1
Session 1: 'Evolution of the method of science' – Dr Rajeevan P P
Session 2: 'Evolution of stars' – Shri. Sajeev T Prabhakaran

Day 2
Session 1: Learning through experiments –Chemistry- Mr Alwyn George
Session 2: Learning through experiments – Physics- Smt. Rajani S

Day 3
Session 1: Basics of sky watch – Shri. Sajeevkumar P P
Session 2: 'World of microbes and immunity' – Smt Soniya Mohandas

Batch 2 Day 1
Session 1: Basics of sky watch – Shri. Sajeevkumar P P
Session 2: 'Louis Pasteur and the world of microbes' – Shri. Harikumar K S

Day 2
Session 1: 'Universe in a nutshell' – Prof Joe Jacob
Session 2: Learning through experiments – Chemistry - Smt Lasitha and Smt. Aswathy

Day 3
Session 1: 'Evolution of the method of science' – Dr Rajeevan P P
Session 2: Learning through experiments – Physics - Smt. Rajani S

A whatsapp group of the participants was formed to continue science discussions and 'learning through experiment' activities.

Tamilnadu

In the lockdown situation, a series of webinars were organized in Tamilnadu. 10 May, 2020 : Mr T Pradeep Kumar, a student of M Sc Physics, A V C College Myladumthurai made a presentation on "How to measure the circumference of earth using a stick". It was in fact a re-enactment of the historic experiment by the Greek astronomer Eratosthenes more than 2000 years back.
17 May, 2020: Shri Ilango Subramanian, a science communicator gave a talk on "The wave particle duality of matter".
21 May: Mr Parthasarathy, a student of B Sc Physics, A V C College Myladumthurai made a presentation on 'The history and

use of MORSE code'

24 May: Dr S Jagannathan, Pasteur Institute, Coonoor, Tamilnadu gave a talk on 'Louis Pasteur and Vaccination'. The talk covered a history of the development of vaccines and a life sketch of Louis Pasteur.

29 May: Prof Joseph Prabagar, Dept of Physics, Loyola College, Chennai made a presentation on 'Mountains on Moon – How to measure their heights'. It was a recapture of the famous experiment done by Galileo Galilee in the sixteen hundreds.

Quiz program

May 27: The BSS unit of Coimbatore organized an online science quiz for under graduate students. 260 students took part in the first round. The entire program was visualized and executed by a team of student members of BSS.

Responding to the call of IMFS committee, the members and supporters of the state chapter participated enthusiastically in the Online Campaign on the Pandemic Covid19 situation.

Jharkhand

A two day state level online science camp for students was organized on May 30 and 31. The topics discussed were mainly related to COVID 19. In continuation of the Camp, two webinars were organized on 7 June:

"Can animals think?" by Prof Soumitro Banerjee

"What can we do and how can we develop our society by our power of thinking?" by Sri Debashis Roy

BSS Zonal Workshop in New Delhi

On behalf of Breakthrough Science Society All India Committee, a two day workshop for Central and North zonal activists was held on 14th and 15th of March in New Delhi. Representatives from Jharkhand, Bihar, UP, MP, Chattisgarh, Rajasthan, Uttarakhand, Haryana and Delhi attended the workshop. The main subject matter of discussion was the setting up of 'Breakthrough Science Learning Centres'. A set of experiments was demonstrated and explained by Dr Manabendra Bera and Mr Vijay Kumar. A session on the history of science was conducted by Prof Soumitro Banerjee, General Secretary, BSS. The concluding session on organizational issues was conducted by Shri Debashis Roy, Vice-President, BSS.

The North and Central zonal workshop in Delhi

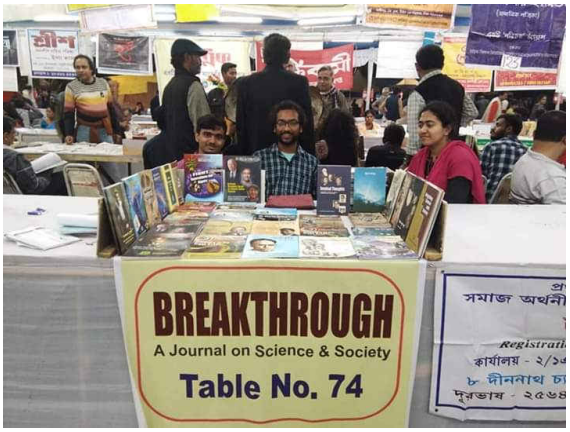
West Bengal

27 January, 2020: At the call of Nazrul Smriti Sangha, Subhasgram, a team of BSS demonstrated several anti-superstation programs and also a few methods for the detection of common adulterants in food.

29 January to 9 February, 2020: BSS participated and put up stall at the 44th Kolkata International Book Fair.

17 February, 2020: Science Martyrs' Day was observed throughout the state. Floral tribute was offered to Giordano Bruno – the first martyr of science by several science clubs and institutional chapters of BSS. Besides, debates and discussions were also organised.

The anti-superstition demonstration at Subhasgram, WB



The stall at the Kolkata Book Fair

Parliament) and local councillors were also present in the fair. More than 130 students demonstrated their models. During the second session of the day two, a seminar was organised on the subject 'Science and Scientific Outlook'. Prof. Amitava Dutta, INSA Emeritus Professor of Calcutta University was the main speaker of the session. Dr. Nirmal Duari, Assistant Secretary, BSS WB chapter, handed over the prizes to the winners of the different groups.

The Science Martyr's Day observation in Kolkata

21st February, 2020: A state level training camp was organised on 'Sky Watching and Telescope handling' at Mourigram, Howrah. Nearly forty members from different Science Clubs participated. The camp was conducted by Dr. Safique Ul Alam, Dr. Tapan Kumar Si and Dr. Radhakanta Konar.

22-23rd February, 2020: In collaboration with BSS, a two day Science Fair was organised by Charu Mohan Dutta Memorial High School, Dumdum. Dr. Debabrata Bera of Jadavpur University inaugurated the Science Fair. Sri Dipankar Dutta (Headmaster), Prof. Saugata Roy (Member of

The telescope handling training camp in Mourigram

Prof Amitava Datta speaking at the Science Fair, Kolkata

Relief work in North 24 Parganas district, WB

Science Cultivation

Since physical gatherings were not possible during the lockdown, the W.B. Chapter of BSS organised an online state level 'Science Cultivation' program. Science essay writing, poster drawing, 'Corona in cartoon' and experiment demonstration were the topics of the Science Cultivation program. The topics were meant mainly for the school and college students. More than 800 students participated in this online initiative.

Corona Relief Work

BSS WB Chapter initiated the Corona relief work from the middle of April. Some of our affiliated science clubs took a leading role during this phase. As the time and situation was really tough in holding the relief camps publicly, our members did their work with all the required precautions.

As our members were unable to collect money directly from public, this time we had to rely fully on the online bank transactions. People responded spontaneously to the call of Breakthrough Science Society. During this time, the IIT Kharagpur Chapter of BSS collected more than One lakh rupees and donated to our relief account. The students from the Physics Department of Calcutta University (Rajabazar Science College Campus) donated their full amount of Eleven thousand nine hundred rupees from their farewell Account of 2nd year students. A free coaching centre, meant for the poor and needy students named 'Adhayan' donated an amount of Fifteen thousand rupees from their collection.

Meghnad Saha Bigyan Sanstha, North 24 Parganas, has been conducting relief work every Sunday to help the people below poverty line in several areas of Duttapukur, Bira, Bamangachi and Chotojagulia.

Panskura Science Centre and Mahisadal Science Centre of East Midnapore district, Marie Curie Science Club of NBU, Boson Science Centre of Birbhum also conducted relief works in their respective areas. Mainly food and sanitizing materials were distributed during the first phase of lockdown.

On 3rd May, 2020, on behalf of India March for Science (IMFS), Kolkata Organising Committee, Gloves and Sanitary Masks were handed over to Calcutta Heart Clinic and Research Centre.

BSS volunteer Dr Nirmal Duari handing over gloves and sanitary masks to the Calcutta Heart Clinic and Hospital

Cyclone 'Amphan' Relief Work

In West Bengal, at a time when the people were struggling hard to fight the Covid-19 pandemic, the super-cyclone 'Amphan' struck and caused large-scale devastation. Telecommunication systems were razed to the ground, trees along with electric poles were uprooted, thousands of dwellings were destroyed, and roads, bridges and embankments were ravaged. It was a massive blow within a short period of time.

In this grave situation, the volunteers of BSS extended their helping hands inspite of many odds and difficulties.

Meghnad Saha Bigyan Sanstha, North 24 Parganas, started Community Kitchen (Acharya Prafulla Chandra Roy Kitchen) at Duttapukur area after the cyclone. Since 23rd May they are continuing their service amid acute fund crisis. Cooked food is served among slum dwellers who are affected due to Amphan.

Our volunteers have removed collapsed trees to clear roads, lanes and streets from 20th to 26th May.

Block No.1 of Barasat is one of the worst affected areas in North 24 Parganas. Meghnad Saha Bijnan Sanstha is working directly here.

BSS unit of Kanchrapara and Basirhat are also doing relief work.

The Progressive Science Forum of Habra has already conducted a relief camp.

30th May, 2020: At Nalgora of Joynagar Block 2, South 24 Parganas relief work along with medical camp was organised by Breakthrough Science Society along with Medical Service Centre (MSC), India March for Science (IMFS) Committee and Relief and Public Welfare Society.

On the same day, sanitary masks along with gloves were handed over to South Joynagar Health Centre on behalf of the IMFS Committee.

31st May, 2020: Relief Camp was organised by BSS East Midnapore district chapter at Nandigram. Food material along with soap and detergent were distributed to one hundred families.

Besides, a representative team visited the several households of Tengua, Chowrangi and Kanchannagar. The situation is still very bad even after ten days. There is the crisis for drinking water. Most of the villages are without electricity. The uprooted trees have still not been cleared. The polluted ponds are spreading foul smell.

2nd June, 2020: Relief Camp was organised at Bhubaneshwari of Kultali Block and Ghatiharaniya of Joynagar Block 2 by BSS South 24 parganas Chapter. In

Cyclone relief work at Joynagar, South 24 Parganas district, WB

Bhubaneshwari two hundred families were benefitted and in Ghatiharaniya, relief materials were distributed to seventy affected families.

3rd June, 2020: On behalf of Kolkata District BSS, relief work was conducted at Jadavpur area. It was assisted by the members of C.V. Raman Science Society. Nearly 85 cyclone affected families were served with food material and soap.

6th June, 2020: Relief Camp was organized at Daktargheri of Kankandighi (Mathurapur Block), South 24 Parganas on behalf of S N Bose Science Society (BSS affiliated) and DRSO jointly. Nearly 150 families were supplied with relief material.

7 May, 2020: A webinar was organised on the Covid-19 pandemic Prof. Partha Pratim Majumdar, founder Director, NIBMG Kalyani and President, Indian Academy of Science, Bangalore was the speaker. The webinar was in the form of question and answer, with questions like 'How dangerous is the Coronavirus?', 'What is the view of science regarding this Pandemic?', 'What precautions are needed to be taken?', etc. More than 500 people participated directly in the webinar, more than 600 others watched through Fb and Youtube live streaming.

Relief work at Panskura, East Midnapore district, WB

Cyclone relief work at Bhubaneswari, South 24 Parganas district, WB

Online Campaign

At the call of the India March for Science, the members and supporters of the state chapter participated enthusiastically in the Online Campaign on the Covid-19 Pandemic situation. The campaign started on 9th May and continued till 14th May. During this period nearly 800 supporters of BSS came up with colourful, printed as well as hand written posters and placards and presented on several platforms of social media. Besides, scientists from different institutes came up with advocacies in the form of short videos.

Movement to save AJC Bose Indian Botanic Garden

Super cyclone 'Amphan' has caused severe damage to the rare collection of trees in the 233 year old AJC Bose Indian Botanic Garden. This garden is the richest, oldest and largest of its kind in whole of South East Asia and is a National Heritage.

From various news sources, it is clear that around one thousand trees and plants were partially or fully uprooted due to the cyclone. The 260 year old Great Banyan Tree suffered 20 to 25 percent damage. Many rare species were destroyed completely.

The programme in front of the Botanical Garden, Howrah

From BSS Howrah district chapter, a memorandum was submitted to the Director of Botanical Survey of India, with copy to the District Magistrate of Howrah, Central and State Ministries of Environment, and The Governor of WB. We requested the authorities to take quick measures to save the damaged trees.

The BSS Howrah chapter gave a call to observe 5th June as "Save AJC Bose Indian Botanic Garden Day".

Karnataka

Bangalore

28 March: *Webinar on 'Going to space without money'.* Speaker: Dr Jayanth Murthy, Senior Professor, IIAp. This talk was to show the what is the minimum cost required for space exploration and the difference in the space research carried out by ISRO and IIAp and in the funds by the two organisations, along with the different research that is carried by IIAp. The webinar was conducted and presided by Dipti.B and Amjad Syed.

27 April: *Sending quotes of scientists to contacts in the state.* So far 21 quotes have been shared and published on our social media.

5 May: BSS members and contacts, along with members overseas participated in the online campaign with various demands of the India March for Science on COVID-19.

8 May: Vizag Styrene Gas Tragedy online protest State level online protest was held standing in solidarity with the victims of Vizag Styrene gas leak victims, with BSS members holding slogan placards demanding justice for the victims and publicized them on social media with the #SaveVizag #BSSwithVizagVictims.

State level Online Science Fest

Online poster making, cartoon and science poetry writing fest was held from 10th to 31st May 2020. Participants had to register for the events and submit their work by 31st May. Submission evaluation is under progress. Online Certificates for all participants and prizes for winners will be given in the month of June. 300 participants registered across Karnataka.

A whatsapp group consisting of all members made during various programs conducted across the states was formed, as a way to further consolidate those who have signed for membership.

An online membership campaign was carried out during the month of April-May. A good number of scientists, teachers, professors, IT professionals, engineers, students of colleges and schools have joined as

Online protest in solidarity with the Vizag gas leak victims

members. A few from overseas also joined.

Dharwad

BSS Dharwad raised funds from contacts and made ration kits. More than 25 ration kits were distributed to migrant and slum area people during the COVID-19 pandemic.

Relief distribution among migrant workers and slum dwellers in Dharwad

Mysuru

BSS Mysuru raised funds from contacts and distributed relief material to migrant and slum dwellers during the COVID-19 pandemic.

Davangere

May 2 and 3: Webinar on *'Immune system vs corona'*. Speaker: Dr. D.S. Shihupala, Professor, Department of Microbiology, Davangere University.
7 May: *'Relevance of Louis Pasteur: Then and Now'*. Speaker: Rajani .K.S, Secretary, BSS Karnataka State.
9 May: *'Snakes and Science'*. Speaker: Dr. D.S. Shishupala, Professor, Department of Microbiology, Davangere University.
16 May: *'Important lessons humans can learn from honey bees'*. Speaker: Dr. B. E. Rangaswamy, Dean, Research and Development, Professor and Head, Department of Biotechnology,Bapuji Institute of Engineering and Technology, Davangere.
17 May: *'Beautiful World of birds'*. Speaker: Dr. D.S. Shishupala, Professor, Dept. of Microbiology, Davangere University.

Gulbarga

15 May: Webinar on *'Relevance of scientific thinking in the era of social media'* Speaker: Satish Kumar.G, President, Breakthrough Science society, Karnataka State.

In midst of various wrong information and news coming from various platforms, it has become very much necessary to find out what is right and how to find out what is right. The talk addressed these questions and was well received by the people who attended. Around 70 contacts attended and all were given participation certificates.
24 May: Webinar on *'Relevance of Louis Pasteur: Then and Now'* Speaker: Rajani.K.S, Secretary, BSS Karnataka state. The talk covered the life of Louis Pasteur and his contributions in the field of Biology. Apart from this she also discussed about viruses and immunity.

Programmes on National Science Day

The National Science Day this year was dedicated to the struggle of the women scientists in the country. Breakthrough Science Society observed the day with the objective of taking the life struggles and contributions of the great men and women in science to the people at large to foster a scientific bent of mind and to cultivate scientific temper in the society. A detailed account of the programmes can be found here. https://breakthroughindia.org/national-science-day-feb-28-2020-women-in-science/

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