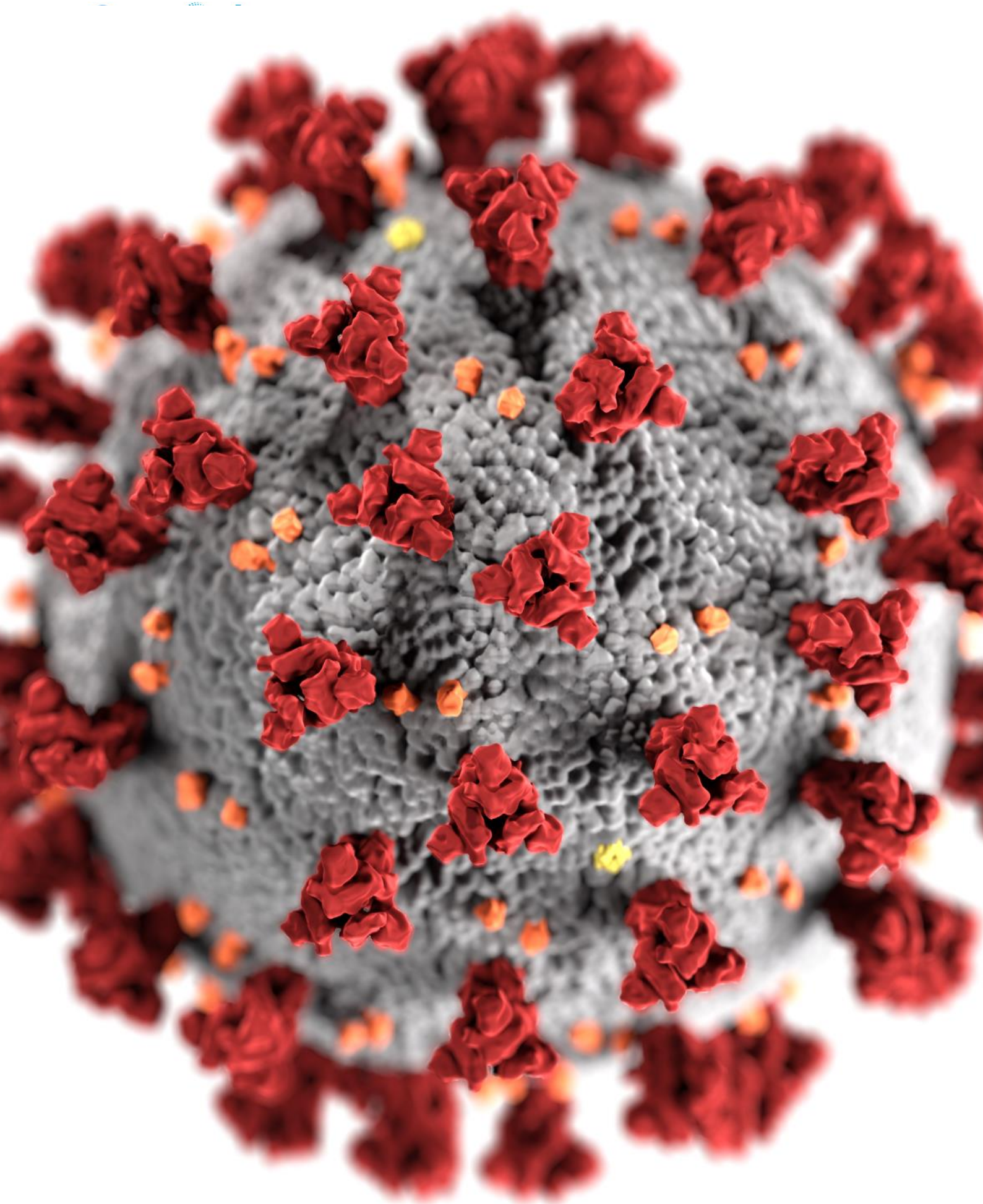

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COVID-19: A 2020-2021 Global Pandemic

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I. ORIGIN OF COVID-19

In early December 2019, several cases of a novel upper respiratory tract infection were reported in Wuhan City, China [1]. On January 12, 2020, Chinese authorities shared the sequence of a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These infections were detected to have been caused by a novel coronavirus SARS-CoV-2 (Small Acute Respiratory Syndrome-CoronaVirus-2) and the disease was named COVID-19 (coronavirus disease 2019) [2, 3]. In the initial months, it spread rapidly to neighboring countries like Thailand, Japan, South Korea, Singapore and Iran, followed by countries like Spain, Italy, USA, UAE and the UK. The World Health Organization (WHO) declared the COVID-19 outbreak a global health emergency on January 30, 2020. Subsequently, on March 11, 2020, WHO Director-General's opening remarks at the media briefing on COVID-19 confirmed that COVID-19 was a pandemic. The medical and scientific community began investigating previously reported coronaviruses which cause severe respiratory diseases in human. They are SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS (Middle East respiratory syndrome coronavirus) [4–7]. The novel SARS-CoV-2 was mostly reported to cause a mild to severe respiratory disease in humans, acute and deadly in some cases, with a mortality rate of 2% [8–10]. This virus has been associated with the ability of leaping between species causing a variety of diseases [11]. The initial cases of COVID-19 reported in Wuhan, China, were thought to be acquired from a zoonotic source from the Huanan wholesale seafood market which sold poultry, snake, bats and other farm animals [12, 13]. The results of a comprehensive genetic sequence analysis among different animal species suggested that SARS-CoV-2 is a recombinant virus between the bat CoV and a CoV from an unknown origin. Bats have also been identified as the most probable wildlife reservoir of SARS-CoV-2 by another study based on relative synonymous codon usage (RSCU) on a variety of animal species [14].

II. STRUCTURE OF THE VIRUS

The term coronavirus (CoV) is itself derived from the Latin word ‘corona’ meaning ‘crown’ and they cause a wide range of mild to severe respiratory tract infections [15, 16]. Coronaviruses belong to the family Coronaviridae and the order Nidovirales (nido Latin for ‘nest’). CoVs are enveloped and non-segmented containing a large positive+sense single stranded, capped and polyadenylated viral RNA genome (27–32 kb) [17]. SARS-CoV first emerged in Foshan, China in November 2002 [16a], and was subsequently transported to Hong Kong in February 2003, from where it spread globally [16b]. The epidemic was finally contained in July 2003 as the transmission chain of SARS-CoV in Taiwan was interrupted [16b]. There were four instances of SARS reemergence that occurred chronologically in Singapore, Taipei, Guangdong and Beijing afterwards [16b, 16c]. The origin of SARS-CoV-2 is more sophisticated. Similar to SARS-CoV, the emergence of SARS-CoV-2 was considered to be associated with

trade activities in a wet market in Wuhan.

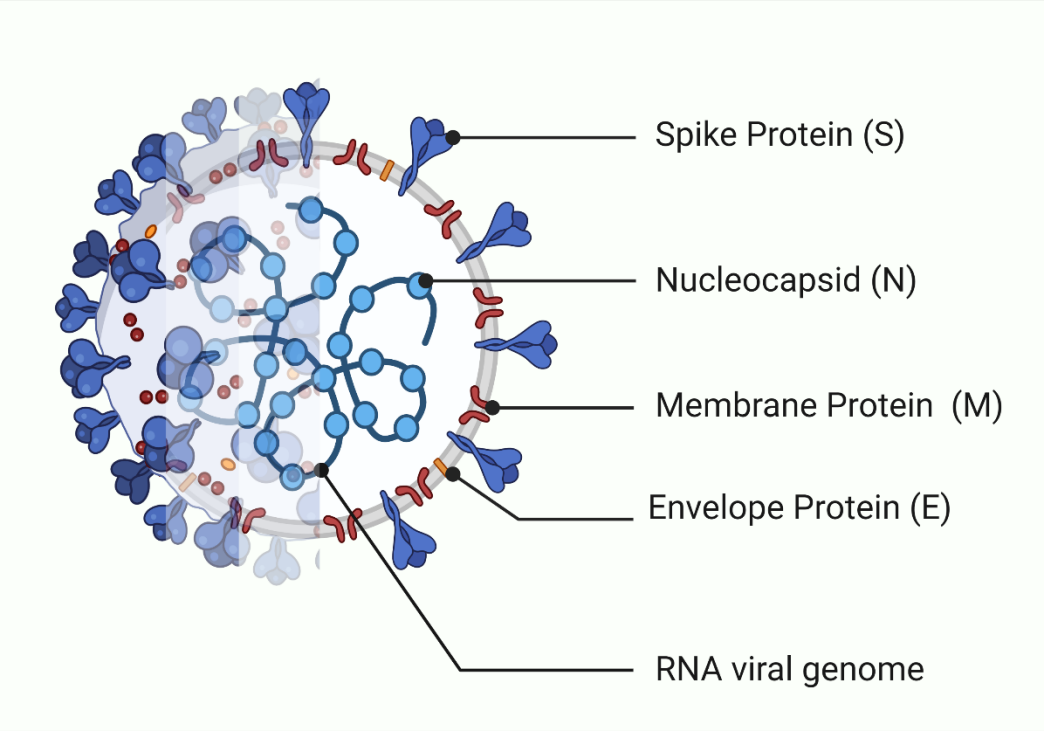

Figure 1: Virus Structure

The entire genome of the SARS-CoV-2 is 29,881 bp in length (GenBank no. MN908947) and encodes 9860 amino acids, which has been characterized using an RNA-based metagenomic next-generation sequencing approach [18]. The 5′ terminal contains the ORF region which encodes proteins responsible for viral replication such as 3-chymotrypsin-like protease, papain-like protease and RNA-dependent RNA polymerase. The 3′ terminal contains the S, E, M and N genes which encode the four structural proteins, namely the spike protein (S), envelope protein (E), membrane protein (M) and the nucleocapsid protein (N) [19]. A large number of glycosylated spike (S) proteins cover the surface of SARS-CoV-2 which divide into two subunits during cell infection: (1) the S1 subunit, which contains two receptor- binding domains (RBDs) that allow the virus to bind to the host cell, and (2) the S2 subunit, which is critical for membrane fusion. The angiotensin-converting enzyme 2 (ACE2), a transmembrane protein located on the cells of epithelial tissue of the human lungs, heart, kidneys and intestine, acts as the host cell receptor for the S1 subunit of the S protein [20]. Following the binding of the S1 subunit to the ACE2 receptor, the heptad repeats 1 and 2 (HR1 and HR2) domains of the S2 subunit combine to form a six-helix bundle core that brings the viral and host cell membranes within close proximity and facilitates fusion [21]. Subsequently, the S protein is activated by the TM protease serine 2 (TMPRSS2), a type 2 TM serine protease located on the host cell membrane, which promotes the entry of the virus into the cell. Once the virus releases its RNA, the host cell machinery replicates and translates the viral RNA and synthesizes and assembles the structural proteins in the host cell itself and releases the viral particles [22].

III. TRANSMISSION OF COVID-19

COVID-19 is primarily transmitted through contact with droplets that contain viral particles, released by infected hosts through coughs, sneezes, and mucous [23]. One study has also reported that the virus was found to remain airborne for three (3) hours under experimental conditions [24]. This disease can also spread if a person touches a contaminated surface and then touches their facial area (fomite-mediated transmission). The virus was found to survive on surfaces for a wide range of time; from several hours on cardboard to three (3) days on plastics or stainless steel [24]. However, over the past year, additional research was done and established that SARS-CoV-2 has varying lifetimes depending on which surface the virus actually resides[24a]. On plastics, the survival time is approximately seven (7) days, but on paper, the survival time is approximately three (3) hours. This ability of SARS-CoV-2 to thrive on surfaces along with attributes of affecting individuals following no immediate symptoms display, has made it difficult to restrain and trace the virus, leading to rapid transmission resulting in the current global pandemic situation.

IV. COVID-19 PANDEMIC DATA

As of March 9, 2021, there have been 117,112,797 cases of COVID-19, with a reported 2,599,046 deaths (2.2% death rate) and 66,303,608 recovered [25]. The chart below shows the number of deaths as a percentage of total cases for selected countries as of early March 2021. Notwithstanding the total number of deaths in the United States, the US currently has the highest fatalities in the world at 531,398 due to this disease as of March 9, 2021. [26]. The data includes confirmed and probable cases.

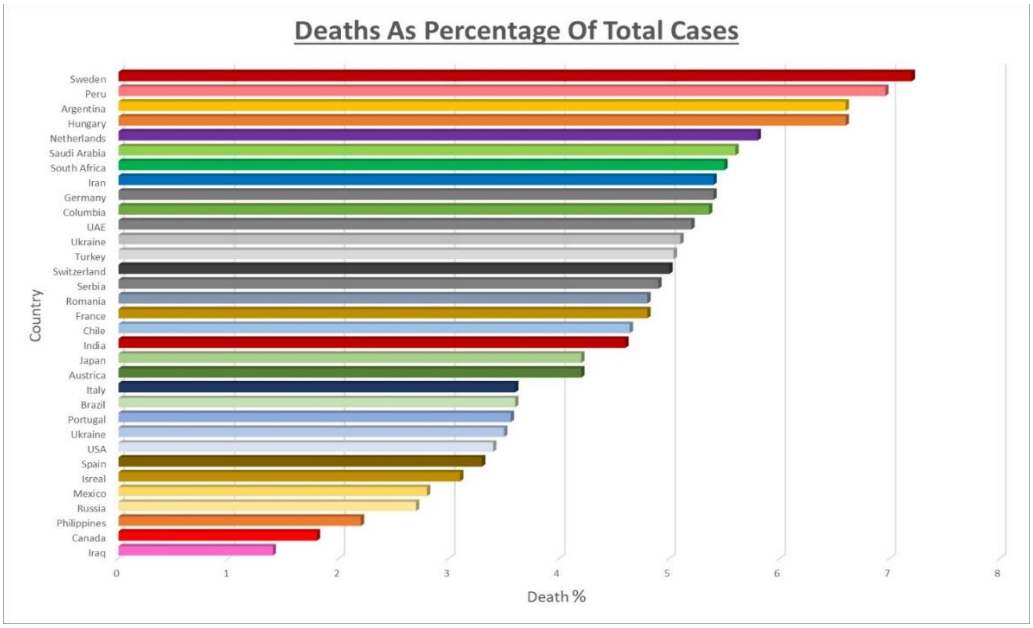

Figure 2: Deaths as a Percentage of Total Cases

By comparison, as of mid-February 2021, there were a total of 108 million cases reported for COVID-19 worldwide. Of those cases, 61 million of them recovered while 2.4 million died. For the latest update click here (Johns Hopkins University Medicine, 2021). Although the mortality rate of COVID-19 is reasonably low and it is more dangerous for older people and individuals with weaken immune system, the experts have advised the individuals of every age and health condition take full precautionary measures against the infection.

Region	New cases in last 7 days (%)	Change in new cases in last 7 days	Cumulative cases (%)	New deaths in last 7 days (%)	Change in new deaths in last 7 days	Cumulative Deaths (%)
Americas	1 129 929 (42%)	6%	50 426 060 (44%)	33 951 (53%)	-1%	1 205 245 (48%)
Europe	1 055 781 (40%)	9%	38 679 334 (34%)	21 302 (34%)	-15%	861 906 (34%)
South-East Asia	171 419 (6%)	9%	13 517 009 (12%)	3 217 (5%)	47%	208 013 (8%)
Eastern Mediterranean	207 177 (8%)	14%	6 388 249 (6%)	2 562 (4%)	5%	144 479 (6%)
Africa	50 324 (2%)	-24%	2840 208 (3%)	1 659 (3%)	-19%	71 991 (3%)
Western Pacific	44 193 (2%)	-2%	1 620 582 (1%)	786 (1%)	-35%	29 006 (1%)
Global	2 658 823 (100%)	7%	113 472 187 (100%)	63 477 (100%)	-6%	2 520 653 (100%)

Figure 3: Newly reported and cumulative COVID-19 confirmed cases and deaths, by WHO Region, as of 21 February 2021

V. SYMPTOMS OF COVID-19

Initially the symptoms of COVID-19 are similar to common cold like fever, cough, fatigue, and shortness of breath in severe cases. Infected person may remain asymptomatic for up to 2 weeks or show very mild symptoms. The incidence of asymptomatic infections is remarkably high. About 60% of all infections may remain asymptomatic or very mild symptoms comparable to common cold. The mild symptoms are generally related to the upper respiratory tract. A person's immunity, genetic makeup and environment can play a major role in the symptoms of COVID-19. Cough and fever are the most common early symptoms. Fatigue and shortness of breath can also occur while pneumonia, respiratory disorders and shocks occur in severe cases. Myalgia, Headache, Homolysis, Sputum production and Diarrhea are some other symptoms of COVID-19 (Saira Baloch, 2020). The symptoms of COVID-19 can depend upon the health of a particular person as well as their genetic make-up. Based on observations made by the Mayo Clinic, the severity of COVID-19 symptoms can range from very mild to severe. Some people may only have few symptoms, while some people may have no symptoms at all. Some people may experience worsened symptoms, such as deteriorated shortness of breath and pneumonia about a week after symptoms start. People who are older have a higher risk of serious illness from COVID-19. The risk increases with age. People who have existing medical conditions also may have a higher risk of serious illness. Certain medical conditions that increase the risk of serious illness

from COVID-19 and include without limitation serious heart diseases, such as heart failure, coronary artery disease or cardiomyopathy, cancer, chronic obstructive pulmonary disease (COPD),

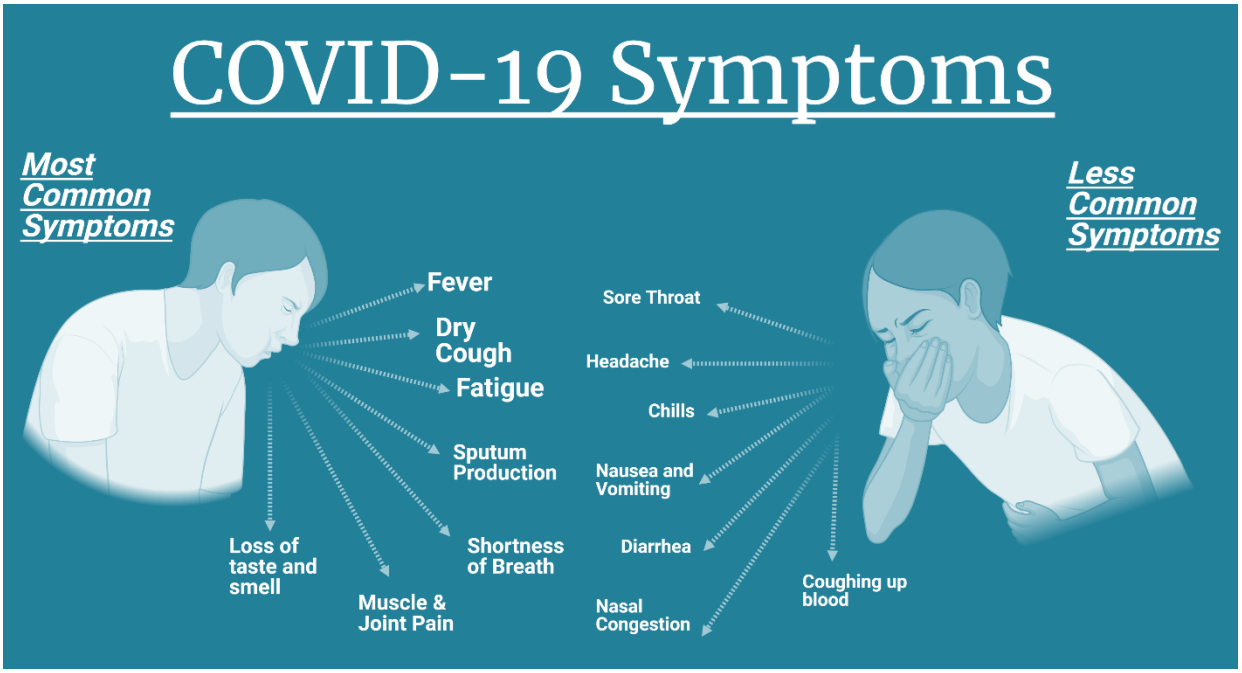

Figure 4: Symptoms

Type 2 diabetes, obesity or severe obesity, smoking, chronic kidney disease, sickle cell disease, weakened immune system from solid organ transplants, pregnancy, chronic lung disease, liver disease, HIV and asthma. This list is not all inclusive. Other underlying medical conditions may increase the risk of serious illness from COVID-19. In addition, non-respiratory symptoms of COVID-19 – such as gastrointestinal (e.g., nausea, diarrhea) or neurologic symptoms (e.g., anosmia, ageusia, headache) – might appear before fever and lower respiratory tract symptoms (e.g., cough and shortness of breath). While COVID-19 is predominantly a lung infection, symptoms have been reported throughout the body, including the central nervous system, eyes, nose and mouth, heart, liver, and gut. These less common symptoms have spurred hospitals to generate new protocols for incoming patients. Indeed scientists began to observe that these non-lung symptoms might also be good indicators of SARS-CoV-2. The mechanism by which the virus invades the host cell includes attachment of the virus to the angiotensin-converting enzyme 2 (ACE2), a protein on human cells. It is not unreasonable to suggest that this early stage infection does not manifest itself symptomatically in other ways. In fact, a cytokine storm is often associated with SARS-CoV-2, causing a severe inflammatory response and concurrent organ damage.

Notwithstanding the foregoing, certain reported symptoms may be unrelated to the actual virus. For example, the American Academy of Ophthalmology has also weighed in on the issue of eye infections cause by the

coronavirus, saying that, “infectious virus has not yet been cultured from the conjunctiva of any COVID-19 patient.” On the other hand, the debate continues regarding the loss of smell and taste. Viral infections often affect our sense of smell, and thus taste, because the infection blocks airways, preventing odorants from interacting with smell receptors. However, in the case of COVID-19, researchers have not ruled out direct infection of smell-sensing cells, or some other mechanism affecting the nerves that conduct smell signals to the brain [28a].

VI. DIAGNOSIS

The SARS-CoV-2 RNA is detected by using reverse-transcription polymerase chain reaction (RT-PCR) method mostly from nasopharyngeal (NP) swabs. The CDC in the United States recommends that specimens from asymptomatic individuals should be collected from NP swabs while specimens from symptomatic patients should be collected from bilateral anterior nares and midturbinate. An oropharyngeal (OP) swab could also be collected if an NP swab is not possible. The CDC also recommends that when patients are mechanically intubated, a lower respiratory tract sample should be collected via a bronchioalveolar lavage (BAL) [28b]. RT-PCR testing for SARS-CoV-2 has been reported to be falsely negative in certain cases either due to insufficient viral load if the specimen is collected too early or too late in the disease course or due to technical errors during handling or shipping. Several cases reported that classic computed tomography (CT) of the chest showed bilateral peripheral distribution with multifocal lower lung involvement combined with high clinical suspicion for SARS-CoV-2 infection in patients who have already tested negative on RT-PCR. Lower respiratory tract samples (i.e., BAL) usually yield a positive result in comparison to upper respiratory tract samples. In a study involving 205 patients, 93% of BAL specimens were found to be positive in comparison to 72% of NP swab specimens [28c]. Consequently, if initial testing is negative but clinical suspicion remains high, the WHO recommends repeat testing, preferably from a lower respiratory tract specimen, if possible.

In serological tests antibodies of IgA, IgM, and IgG isotypes specific to different virus proteins are detected by enzyme-linked immunosorbent assay (ELISA) or chemiluminescence immunoassays (CLIA), and the latter has been shown to be more sensitive. The priority immune response of the host to the virus is related to the cytotoxic activity of NK cells and CD8 + T lymphocytes. The assessment of specific antibodies to N protein is more sensitive but less specific, since this protein is more abundant in all coronaviruses. However, antibodies against S protein are very specific for SARS-CoV-2 as the receptor-binding domain (RBD) is located in the S-protein and their levels presented a good correlation with the virus's neutralization capacity. The available serological tests are different from each other and many factors influence their sensitivity and specificity. Not all patients who have SARS-CoV-2 infection will have detectable levels of antibodies, particularly if they have milder symptoms. The absence of antibodies does not imply the absence of contact or protection against the virus, since there may be an efficient specific cellular immune response. In turn, the

presence of antibodies does not rule out the possibility that the individual is still infectious, as no immediate reduction in the elimination of the virus has been identified [24].

Imaging tests for the diagnosis of COVID-19 have gained relevance, given the unavailability of tests for etiological diagnosis. Chest X-ray is usually inconclusive in the early stages of the disease and might not show any significant changes. As the infection progresses, bilateral multifocal alveolar opacities are observed, which may also be associated with pleural effusion. High-resolution CT (HRCT) is extremely sensitive and the method of choice for diagnosing COVID-19 pneumonia, even in initial stages of the illness. The most commonly seen features are multifocal bilateral 'ground-glass' areas associated with consolidation and a patchy peripheral distribution, with greater involvement of the lower lobes. A 'reversed halo sign' is also seen in some patients, which is identified as a focal area of patchy opacities surrounded by a peripheral ring with consolidation. Other findings include pleural effusion, cavitation, calcification, and lymphadenopathy.

VII. RISK FACTORS

The risk factors associated with the development of severe disease, admission to intensive care unit and mortality are:

Underlying conditions-

- Older age
- Hypertension
- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Diabetes
- Obesity
- Malignancy

Presentation

- Higher fever (≥39°C on admission)
- Dyspnoea on admission
- Higher qSOFA score

Laboratory markers

- Neutrophilia/lymphopenia
- Raised lactate and lactate dehydrogenase
- Raised C reactive protein
- Raised ferritin
- Raised IL-6
- Raised ACE2
- D-dimer >1 μg/mL[30]

VIII. THERAPEUTIC APPROACHES

To manage the proliferation of COVID-19, drug repurposing and host-based targets were primarily employed. Repurposed drugs like Oseltamivir were prescribed in Wuhan due to the presence of fever and other common symptoms of influenza infections but were later found to be ineffective against COVID-19 as the virus does not secrete neuraminidase [27, 28]. Other antibacterials like moxifloxacin, ceftriaxone, and azithromycin showed little therapeutic benefit [29]. Combinatorial drug regimens involving lopinavir and ritonavir were utilized to tackle the SARS-CoV epidemic. These drugs inhibit viral 3-chymotrypsin-like cysteine protease. Ribavirin, a potent inhibitor of the viral RNA-dependent RNA polymerase (RdRp), when co-administered with ritonavir/lopinavir, was found to be effective in controlling the COVID-19 virulence. A profound activation of the bitter taste receptors [taste 2 receptor member 4 (T2R4); taste 2 receptor member 38 (T2R38); taste 2 receptor member 43 (T2R43) and taste 2 receptor member 46 (T2R46)] using bitter taste compounds, including nicotine (as agonists), could attenuate COVID-19 virulence with increased intracellular calcium-dependent nitric oxide (NO) production accompanied by reduced secretion of the proinflammatory cytokines in the upper respiratory system [31]. Although another repurposed drug Darunavir is intended to inhibit viral proteinases, research is still required to prove its significance in case of COVID-19 therapeutics [32]. Moreover, drugs like chloroquine derivatives along with remdesivir showed to effectively control the proliferation of clinically isolated SARS-CoV-2 strain [33]. Although, there is significant controversy regarding the use of chloroquine derivatives. Host-based targets like Convalescent Plasma (CP) therapy may offer an alternative to current regimens. Repurposed drugs and vaccines are being tested and two are on the market. However, in case of COVID 19, some high impact randomized trials did not give a satisfactory answer on the efficacy of convalescent plasma therapy [34]. Among other particulars, bone marrow-derived mesenchymal stem cells (MSCs) have been used successfully to treat patients with respiratory distress [35]. Cytokine IL-6-specific monoclonal antibody tocilizumab was used in one ongoing clinical trial (ChiCTR2000029765) to reduce the inflammatory burden for symptomatic relief. Likewise, observation of twenty one Chinese COVID-19 patients showed symptomatic relief of body fever after treatment along with respiratory functions [36]. Furthermore, a monoclonal antibody tagged ‘CR3022’, in the presence of S membrane glycoprotein of SARS-CoV-2, could help patients to have symptomatic relief by hindering its colony forming nature in the upper respiratory tract [37]. Although facial masks, hand hygiene and social distancing have been highly effective reducing the spread of virus and in flattening the curve, the best solution to this pandemic was the development of effective vaccine. While the possibility of herd immunity after a certain amount of time has been seen in Sweden, waiting for herd immunity to develop while going about

life activities can be problematic. A vaccine appeared to be the best solution to the current situation.

IX. VACCINES IN PRODUCTION

Adenovirus vectored vaccines

Human recombinant adenoviruses have been previously used to make vaccines against several infectious agents. Ad-vectored vaccines express recombinant proteins, including any post-translational modifications, into functioning replicas of the native proteins capable of eliciting neutralizing antibodies in both abortive and permissive animal models. SARS-CoV-2 can be targeted using this technique of vaccine. In fact, a COVID-19 using human recombinant adenoviruses is currently in phase 3 in several countries. Viral vector vaccines use a modified version of a different virus (the vector) to deliver important instructions to our cells. For COVID-19 viral vector vaccines, the vector (not the virus that causes COVID-19, but a different, harmless virus) will enter a cell in our body and then use the cell's machinery to produce a harmless piece of the virus that causes COVID-19. This piece is known as a spike protein and it is only found on the surface of the virus that causes COVID-19. The recently approved vaccine using this technology is Johnson & Johnson's vaccine.

Inactivated whole-virus vaccines

This is the most common and traditional method of vaccine development. An inactivated vaccine consists of attenuated virus particles, bacteria, or other pathogens that have been grown in culture and then killed to destroy disease producing capacity. This vaccine for COVID-19 is in phase 1/2/3 trial.

mRNA-based vaccines

mRNA vaccines, thus far, have proven to be a better option of vaccine development in this pandemic due to their high potency, capacity for rapid development and potential for low-cost manufacture and safe administration. There are currently two vaccines being developed for COVID-19 using this technique namely mRNA-1273 and BNT162b2. Both vaccines and have been given emergency use authorization in the US, UK, and other countries.

X. DEVELOPMENT OF A VACCINE

Development of a vaccine usually takes somewhere between 10-15 years. The fastest vaccine ever developed was for Mumps which took only 5 years [38]. However, both Pfizer/BioNTech and Moderna received emergency authorization in less than one (1) year.

The first stage in the development of a vaccine involves trying out different candidate drugs which have the potential to be effective against the infection. As discussed earlier, SARS-CoV-2 has S-proteins on its surface

that assists in membrane fusion to a host cell. These S-proteins are primary target for most vaccines being developed to provide artificial active immunity against the infection.

In the preclinical stage the vaccine is tested on cell culture, tissue culture and animal models. This affords information concerning the efficacy, immunogenicity, and immune response of the vaccine. Having proved safe in the laboratory, and IND (US FDA) is submitted requesting human trials which test for same information in human beings.

PHASE I

In the first phase of human trials of clinical trials, the vaccine is administered to a small group of healthy individuals. The purpose here is to evaluate the safety of the vaccine on human body. The appropriate dose of vaccine and immune response of the body upon the administration of vaccine is determined in this initial phase of clinical trials.

PHASE II

In the second phase, the vaccine is given to relatively large number of people often in hundreds. This time these individuals are from diverse backgrounds such race, gender, and nationality. It tests for same parameters as phase 1. It also determines the dosage to be given in phase 3 (Omna Sharma, 2020). If a vaccine passes this phase, it suggests that it is safer on a small population.

PHASE III

In phase III, the vaccine is tested on a large population, typically thousands to evaluate its efficacy. There are two measures of how well a vaccine works. One is called “efficacy,” and that is how well a vaccine works in a clinical trial. That is a perfect situation where everybody in the trial who is getting the vaccine doses is getting them exactly when they are supposed to get, and they are being watched carefully. However, we also look at “effectiveness.” In the real world where for example, what happens when people get that second dose a little bit late, or things are not in such a controlled setting? For both measures, there is a comparison of a group of people who receive the vaccine to a group of people who did not receive the vaccine. A determination is made, preferably under a double-blind placebo study, to determine how many cases of the disease are contracted in one group versus to the other group. Vaccine Efficacy is an important parameter at this stage. It is the percentage by which the rate of infections is reduced in vaccinated individuals in comparison to non-vaccinated individuals. The number of people vaccinated depends upon the Vaccine Efficacy. If many people are infected and VE drops below a certain value, then the vaccine is declared as failure and no further proof is required. The vaccine in this case is not sent to advanced stages. But if the number of infections is low and

the VE is high, then further trials are performed in this phase and more people are given the vaccine. Once a vaccine has passed the clinical trials, the data is sent for approval by the regulatory bodies.

PHASE IV

According to the NIH, Phase IV research serves three major functions:

1. to support pharmacoviligance systems in monitoring the safety of new interventions used in large populations and in specific groups who were not studied adequately in the pre-marketing phases such as children, pregnant women, the elderly, or those with co-morbidities.
2. to determine the effectiveness of an intervention in a routine health system, as opposed to within a carefully controlled trial.
3. to assess new strategies of use of approved products or interventions, such as the evaluation of anti-malarials when used for intermittent presumptive treatment, rather than either for malaria prophylaxis or for treatment of a diagnosed malarial infection.

REVIEW AND APPROVAL

After passing the clinical trials, a vaccine must be first approved by the regulatory authorities before its manufacturing on a commercial scale for public use can begin. The US Food and Drug Administration and European Medicine Agency as well as Japan have comparable regulations for approving drugs and vaccines deemed safe for human use. These regulatory bodies have the power to stop a pharmaceutical company from manufacturing and selling a drug or vaccine if the evidence suggests it is not safe. Notwithstanding that the process can require one to two years of intensive review, several international agencies, given the deadly nature of this pandemic, have conferred emergency use authorization to a few drugs and vaccines.

MANUFACTURING

The approved vaccine is manufactured on a commercial scale under approved guidelines of the particular regulatory agency. In the case of COVID-19, governments around the world and foundations provide financial assistance to manufacture vaccine at a rapid pace while keeping the price affordable for all the population of the world.

POST MARKET SURVEILLANCE

The pharmaceutical company as well as corresponding health agencies worldwide remains active when the vaccine is commercialized. It keeps close watch on the reported side effects and other complications and adverse effects.

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XI. VARIANTS OF SARS-CoV-2

SARS-CoV-2 replicates at a rapid rate after it has entered the host cell. During this the viral RNA is replicated. Random mutations occur in this replication. These mutations translate to viral structural differences. As the body's immune system recognizes the virus by its surface protein, changes in the makeup of the surface protein, can "trick" the immune system. As a result, a person who has already developed immunity against the virus may become susceptible again. Vaccines developed against the virus with a certain surface protein may become ineffective when mutations lead to a different surface protein. Herd immunity becomes a moot point.

In case of SARS-CoV-2 these surface proteins are called spike-protein or S-protein. Mutations in them can allow the mutated form to proliferate (notwithstanding possible immunity conferred by existing anti-virals). Thus far, a few minor mutations are reported in SARS-CoV-2 which have led to a few regional variants. The original SARS-CoV-2 is the one that was first reported in Wuhan and all other forms which resulted from its mutations are called its variants. Different regions of the world seem to have their own variants which slightly differ from the original virus. These are reported to be more contagious than the original virus and they are thought to be deadlier. They are particularly devastating when spread to previously unexposed populations. The current vaccines in trial are reported have slightly less efficacy against these variants. Following are some variants of SARS-CoV-2:

UK Variant

This variant of SARSCoV2 was discovered in the United Kingdom in December 2020. A total of 22 mutations are identified in this variant [39]. As a result of these mutations the viral S-protein is slightly difference which can be tricky for vaccines and body's immune system. It is thought that this strain is 70% more transmittable than the original SARS-COV-2. There is evidence of a 20% increase in cases of COVID-19 in Belgium when this strain reached there [40]. The coronavirus variant B.1.1.7, which was first identified in the United Kingdom, is associated with an estimated 64% higher risk of dying from Covid-19, suggests new research published in the British Medical Journal on March 10, 2021[40a].

South African Variant

This variant has some common mutations to UK variant and Brazil variant. It has most mutations in the coding part of S-protein which makes it particularly dangerous.

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Brazil Variant

It is the fastest spreading variant of SARSCoV2. It has 17 mutations, two of which reduce the ability of an antibody to attach to its surface thus reducing the effect of the body's immune response on the virus [41].

XII. VACCINES APPROVED AND UNDER DEVELOPMENT

Pfizer-BioNTech and Moderna, both with mRNA vaccines are approved in some countries including Switzerland with Emergency use approval in the U.S., E.U. and other countries. Gamaleya based on Ad26 and Ad5 adenoviruses is approved for early use in Russian and Emergency use in other countries. Johnson & Johnson has received Emergency use authorization on its adenovirus variant in the U.S. and in Bahrain. Vector Institute and Novavax are in Phase III clinicals with a protein based vaccine. Sinopharm, Sinovac, and Sinopharm-Wuhan have limited approval in China, U.A.E. Brazil and other countries for their inactivated virus vaccine, all three of which are in Phase III clinical trials.

As previously stated, vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists embarked on a race to produce safe and effective coronavirus vaccines in record time. Researchers are currently testing **75 vaccines** in clinical trials on humans, and 21 have reached the final stages of testing. At least 78 preclinical vaccines are under active investigation in animals.[42]

A group of European nations including Denmark, Norway and Iceland suspended use of the AstraZeneca vaccine and Thailand and Bulgaria also suspended the use of the vaccine on March 10 – 11, 2021. These suspensions arose from allegations that the vaccine caused blood clots in some recipients of the vaccine. However, on March 12, 2021, AstraZeneca defended its vaccine, saying there was "no evidence of an increased risk" of blood clots, and European and UK medicines regulators have each said the link between the vaccine and blood clots has not been confirmed and that rollouts should continue. In fact, the European Medicines Agency (EMA) did not recommend suspending the vaccine.

New Additions and Recent Updates	
March 9	Bavarian Nordic and the PREVENT-nCoV consortium enter Phase 1/2
March 9	China's Academy of Military Medical Sciences moves to Phase 2.
March 9	Vietnam's Nanogen Biopharmaceutical moves to Phase 2.
March 5	Canada authorizes Johnson & Johnson's vaccine.
March 4	A vaccine from BioNet-Asia and Australia's Technovalia enters Phase 1.
March 4	Cuba's Soberana 2 vaccine moves to Phase 3.
March 1	Massachusetts-based VBI Vaccines enters Phase 1/2.
Feb. 27	The FDA authorizes Johnson & Johnson's vaccine for emergency use.
Feb. 26	Canada authorizes the Oxford-AstraZeneca vaccine for emergency use.
Feb. 25	China approves two vaccines by CanSino and Sinopharm for general use.

Figure 5: Recent Updates

On March 15, 2021, Germany, France, Italy and Spain said they would all stop administering the shot, followed by Sweden and Latvia on March 16, 2021. Notwithstanding the growing list of suspensions, the World Health Organization, Europe's drug regulator and the International Society on Thrombosis and Hemostasis have all recommended that countries continue to use the Oxford-AstraZeneca vaccine. The U.K., Canada and Australia, which are continuing to deploy the vaccine, are among some of the countries seeking to reassure citizens about its benefits. Suspension of the vaccine deployment, according to Michael Head, Senior Research Fellow in Global Health at the University of Southampton, "during a pandemic has consequences. This results in delays in protecting people, and the potential for increased vaccine hesitancy, as a result of people who have seen the headlines and understandably become concerned. There are no signs yet of any data that really justify these decisions."

XIII. SOCIO ECONOMIC IMPACTS

COVID-19 has changed life of everyone on this planet. No aspect of life is safe from the detrimental effects of COVID-19. It is dubbed the **Black Swan** incident and is being compared to economic conditions of WW2.[43]

Agriculture

Agricultural industry has taken a big hit due to the pandemic. Demand of agricultural products has reduced due to the closure of hotels and restaurants. It is estimated that there is 20% decrease in prices of agricultural products.

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Petroleum Industry

As normal life activities stopped due to the pandemic, the demand of petroleum has dropped significantly. A disagreement between Russia and Saudi Arabia over the production of oil lead to instability in petroleum market. This translated to general anxiety and uncertainty throughout the world.

Manufacturing

Manufacturing industry heavily depends on large number of workers. COVID-19 forced people to stay indoors and not come to work. As a consequence, the manufacturing industry suffered more than any other industry. British Plastics Federation conducted a survey and found that over 80% people are expecting a drop in turnover manufacturing business in UK.

Education

Educational institutions had to close completely due to the pandemic. From preschool to universities everyone suffered from lockdown. Different countries announced alternative ways of reopening schools or utilizing online teaching. The most common solution adopted by world was remote learning. Remote learning poses a different set of challenges. There is a substantial problem regarding availability of a stable internet connection in most of the world. Teachers as well as students had to adjust to this new medium. According to UNESCO about 900 million students are affected by the pandemic around the world. While the lockdown helped decrease the spread of COVID-19 the valuable time lost by the students will never be recovered.

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