


COVID-19 Vaccine

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Abstract

A number of companies have announced the vaccines for COVID-19 pandemic that has caused extreme poverty, famine, and more than a billion people have lost livelihood all across the globe. Mass production of vaccine Sputnik V is underway at different locations to inoculate population in Russia, Philippines, Vietnam, Brazil, Saudi Arab, and United Arab Emirates (UAE), and India. mRNA based vaccine of Pfizer-BioNTech after passing phase 2 trial is ready for testing on thousands of volunteers. Oxford University-AstraZeneca vaccine is also under phase 3 trial in US, Brazil, and India. In September, Novavax Inc.'s vaccine will be ready for phase 3 trial. By early next year, two billions of doses will be ready of Novavax. Moderna Therapeutics conducting vaccine trial on 30 thousands volunteers, results will be known soon. Hundreds of thousand volunteers have registered already for vaccination in US and other parts of the world. SinoVac Biotech Ltd. has prepared a vaccine "CoronaVac" and inoculating volunteers in Indonesia and Brazil. CanSino Biologics Inc. in phase 2 trial on 508 volunteers found a satisfactory immune response to COVID-19 virus. Apart from vaccine preparation and availability, we provided data for therapy and treatment for COVID-19 and transmission and stability aspect of COVID-19 SARS-Cov-2 virus. The data and results presented in this article are very important and useful in containing, treating, and eliminating the pandemic COVID-19.

Keywords

COVID-19 Vaccine, Plasma Therapy, COVID-19 Transmission, SARS-Cov-2 in Feces, COVID-19 in Pets, Community Transmission, Super Spreader

1. Introduction

As of August 10, 2020, a total number of COVID-19 cases reached 20,002,577 and 733,842 deaths were recorded [1] since the airborne outbreak occurred. The lockdown and easing have been in rotation to slow down the spread of the virus. Easing the lockdown is necessary to keep work and social life in place until a proper workable vaccine is developed. All over the world governments, doctors, health care works, and other administrative staff are controlling the pandemic by employing a number of methods and techniques.

Some countries are more successful and others are less in keeping people healthy and economic activities rolling. Testing, treatment, isolation, quarantine, wearing face mask, social or physical distancing, and sanitization are the methods and tools being used so far to contain the pandemic. Till now treatment using anti-flu Avigan, remdesivir, dexamethasone, asthma steroid inhalant ciclesonide have been employed. Critically ill patients are being kept on ventilators and in intensive care units (ICU) and treatment is being given case by case to save the lives from COVID-19. After the emergence of SARS-Cov-2, a more lethal strain, researchers turned [2] to data they accumulated for previous virus SARS-Cov-1 and MERS (Middle East Respiratory Syndrome) to develop vaccines. For SARS-Cov-1 and MERS, vaccines were not developed as the pandemic stopped of their own. SinoVac was the only company that conducted [3] phase 1 vaccine trial for the SARS-Cov-1 outbreak in 2002-2003. When the pandemic disappeared suddenly, the company did not proceed to develop a vaccine. SinoVac now using data of earlier (2003) research which was for SARS-Cov-1 to develop vaccine for COVID-19. Both virus are coronavirus and have similarities. Therefore, the company taking advantage of earlier data they had for SARS-Cov-1 to develop a vaccine for COVID-19 which reduced the time for SinoVac's vaccine development. Russians claimed the concept used to develop the "Sputnik V" vaccine was being developed for the last 20 years to make a vaccine for other virus such as Ebola. The concept which Russian vaccine maker Gamaleya used is similar to the coronavirus prototype vaccine of CanSino (Chinese company). In our earlier published article [4] we described the testing, treatment, and vaccine development in the preliminary stage. There are difficulties in keeping the population healthy using limited treatments and therapies. The plasma therapy has the following limitation. Study shows [5] people infected with SARS-Cov-2 lost immunity to the virus in a few months explains the importance of developing a vaccine which can keep a person immune for at least 1 - 2 years. Antibodies remained only in 16.7% of infected people after three months of the onset of symptoms. Antibodies do not last long in asymptomatic person or mild infection. This is a big challenge for vaccine makers to keep antibodies' level very high to neutralize the incoming coronavirus. It is not yet clear what level of antibodies is sufficient to keep a person healthy against the infection. Antibodies level only in SARS-Cov-2 declined fast. In SARS-Cov-1, appeared in 2002-2003, antibodies remained [5] much longer up to 18 years. However, hope may come from T cells in the blood which are also part of the immune system. T cells with the aid of B cells produce

antibodies based on the memory of previous infections. The development of an effective vaccine is the only way for putting the world's economy back on track. The drug companies and governments have challenges of manufacturing and distributing 5 billion doses of vaccine to protect all the people globally. Development of world's first vaccine for COVID-19, as announced by Russia, is the big hope which not only contributes to the containing the pandemic but also started a strong competition for rapid development of the vaccine by more companies around the world. Russian vaccine has two adenovirus strains, there is high chance that vaccine will be a success but real data are needed to justify it. The dependence on the recommended drug such as remdesivir is also not wise. Remdesivir treatment could not stop mortality. Moreover, serious side effects were noticed leading to death by organ failure [6]. In this article, we describe COVID-19 vaccines' details: updates of mass production, names of companies and location, type of vaccine, side effects, and cure. Methods of novel coronavirus SARS-Cov-2 containment have also been described.

2. Results and Discussion

2.1. COVID-19 Vaccines: Ready to Inoculate and under Clinical Trials

To overcome the COVID-19 pandemic world leaders, organizations, and banks, in a video conference organized by European Union, pledged [7] \$8 billion (7.4 billion euros) for vaccine research. Leaders suggested sustained efforts must be made to meet the goal. The amount remained a little less than targeted 7.5 billion euros. This amount does not include the money which Russia and the US have put to develop the vaccine. The United Nations' Secretary-General Antonio Guterres said the money will be used for vaccine development, diagnosis, and treatments. Efforts will be made to make sure the tools needed to fight the pandemic must reach to everyone and everywhere. In future, more money will be made available. People in many countries in Europe are returning to work cautiously. The fear of the second wave of spread remained. In this situation finding a vaccine is the only hope to resume normal life and economic activities. European Commission President Ursula von der Leyen said the collection of 7.4 billion euros in just one meeting is historic global cooperation.

The targeted amount was 4 billion euros for vaccine development, 2 billion euros for treatment, and 1.5 billion euros for testing. Head of government from Canada, Australia, Israel, Japan, Jordan, South Africa, Turkey, and China's EU representatives attended the summit. Emmanuel Macron, the President of France donated 500 million euros and warned the world community is racing against time to stop COVID-19. Boris Johnson British Prime Minister told "the race for vaccine" is not a competition among the countries rather combined lifetime efforts by the entire world. Japan is the largest donor to pledge \$800 million whereas Germany contributed 525 million euros. Italy and Spain the two hardest hit European countries by novel coronavirus gave more than 100 million euros.

Switzerland, the Netherlands, and Israel gave 378 million euros, 192 million euros, and 60 million dollars, respectively. The vaccine must be available to everybody, not just wealthy nations to end the pandemic. One hundred research teams developing the vaccine and a dozen have entered human trials. It is difficult to predict which will be successful. Some makers are already preparing tons of doses they don't mind wasting millions of dollars if their vaccine does not work but it will save time to inoculate the large population if they succeed. The US in the separate process has pledged \$2.4 billion for global health, humanitarian, and economic assistance for the COVID-19 crises.

President Trump has funded [8] several research projects in the US and abroad for securing vaccine for US citizens. EU and US also have mutual agreements for vaccine production avoiding troublesome and lengthy trials and testing. Japan's response to procure vaccine is usually quick as Japan procured enough swine influenza vaccines well in time in 2009. Also, Japan domestically produced tens of millions of doses. Japan either should manufacture a domestic vaccine for COVID-19 or collaborate with foreign drug makers to give vaccine shots to its citizens in time. For measles, a person needs two-doses of a vaccine in childhood that gives lifelong immunity. Coronavirus is like influenza. It mutates and requires a yearly shot. There are several challenges to develop the COVID-19 vaccine. An individual who was treated for COVID-19 may get infection again, yet to be established. If the person need to take a vaccine every year, is not clear yet. The possibility of novel coronavirus keeps changing strain by mutation can not be ruled out. There are different types of virus strains causing the COVID-19 disease. Does a person develop antibodies is immune to all the virulent, must be known? A successful vaccine must have cross-reactive antibodies to protect against all strains of the virus. The other concerns about the vaccine development are efficacy, safety, and side effects. Vaccines developed in the past by Japanese companies were very safe. Japan can develop an effective and safe vaccine by next year but production capacity will be a challenge.

Japanese drug maker Daiichi Sankyo Co. has a schedule [9] in March 2021 to launch its genetic vaccine for novel coronavirus. The company tested its prototype formulation on animals and noticed antibodies formation against the virus. A synthetic mRNA was injected inside the body that produced proteins similar to the COVID-19 virus and in response, antibodies were formed. More clinical tests are awaited, if successful the company will supply the vaccine as early as possible. US biotech Moderna Inc. is ahead in the race conducting large scale clinical testing of its mRNA vaccine. In Japan startup, Angen Inc. is currently undertaking DNA based final vaccine trial. In a record ¥31.91 trillion extra budget, Japan government has approved, the amount ¥205.5 billion is for vaccine development. Japan will get [10] 120 million doses of the COVID-19 vaccine from BioNTech and Pfizer, the two companies in collaboration developing the drug. The price of one hundred million shots will cost around \$2 billion. The first shipment is expected to arrive in Japan in the first half of next year. Com-

panies all over the world are in the race to develop a vaccine for COVID-19 which has taken lives of more than half a million people and damaged livelihoods of millions. About 200 drug makers are working to develop the vaccine, several of them have reached human trials. The vaccine (BNT162b2) developed by BioNTech and Pfizer combined are most promising. Mass trial on 30 thousand volunteers is underway. By the end of 2020 one hundred million of doses will be available for inoculation. In the year 2021 more than 1.3 billion more will be prepared. The pandemic in Japan is not so devastating, Japan's infection reached 32,500 and one thousand mortalities so far. The worry of increasing cases every day remained.

The Coalition for Epidemic Preparedness Innovation (CEPI), a very influential foundation group is supporting nine potential coronavirus vaccine manufacturers and targeting to produce 4 billion doses [11]. Britain's Prince William visited Oxford's laboratory where the novel coronavirus vaccine is being produced. CEPI planned to make 2 - 3 manufacturing plants for each vaccine. The group is also making ten distribution sites and shipment facilities to send vaccines around the world. The Oslo based group has the support of fourteen governments. Bill and Melinda Gates Foundation and Britain's Wellcome Trust are also giving full support to the group. The total amount of money available to the group is \$829 million with the involvement of 9 vaccine candidates. Hopefully, some of them will be successful. The following companies are participating in the Group's project: Inovio Pharmaceuticals Inc, the University of Queensland with CSL Ltd., CureVac, Moderna Inc, Novavax Inc., University of Oxford-AstraZeneca, Clover Biopharmaceuticals, University of Hong Kong, Institute Pasteur-University of Pittsburg-Themis Bioscience (now Merck&Co.). From these nine candidates, three of them are developing more advanced mRNA-or DNA-based technology.

Gavi, the Global Alliance for Vaccine and Immunization has predicted [12], the COVID-19 vaccine availability in the fall of this year. At least one potential effective vaccine will be known in October-November 2020. Much effort is needed until an approved compound is available in large amount to immunize the global population. Coordinated efforts across the globe are essential to produce and share the vaccine formulation. An international agreement is needed to install manufacturing facilities for rapid production once a product is developed. Whichever vaccine is effective to keep long term immunity against the virus will get the attention. There are possibilities some vaccine will work for younger people and others for the aged population. The vaccine must be made available equally to the rich and poor.

Big biotechnology and pharmaceutical companies around the globe are in the race to develop the vaccine for the world's first pandemic (COVID-19) in modern history. The effective vaccine will put the devastated economy on the right path again. As reported by WHO a total of 142 vaccines is in the different developmental stages. The vaccines developed by AstraZeneca (British) and Moderna

Inc. (US) are leading in the race and hopefully will come in the market by 2020-end. In Japan AnGes Inc. and Takara Bio Inc. with the help of Osaka University are the first to launch the vaccine in the first quarter of next year. Shionogi & Co. is another Japanese drug maker following closely the above two companies. AnGes vaccine is a DNA vaccine whereas the Moderna vaccine is mRNA type. The complete data of both DNA and mRNA vaccines are awaited. Oxford University's vaccine (AstraZeneca) shot will be ready [13] in August, Johnson & Johnson will follow in September and Novavax in October. Prime Minister of Japan Abe told [14] in the Upper House Audit Committee that a COVID-19's vaccine may arrive in Japan at the 2020-end. Once the production has started, Moderna-AstraZeneca PLC vaccine will supply the product.

Russia's President Vladimir Putin on August 11, 2020, announced [15] [16] [17] [18] [19] world's first vaccine against the COVID-19 pandemic which Russia prepared successfully after two months of human trial. Putin said Vaccine has completed all the trials and testing. Moscow hailed the move as Russia's scientific prowess in the world. The vaccine is ready for mass inoculation of the Russian population. Moscow has won the global race for an effective vaccine product. In a televised address, Putin said the vaccine is safe and effective and his daughter has received the vaccine shot. The vaccine was developed by Gamaleya Institute in Moscow. The vaccine is named "Sputnik V", a reference to the first orbital satellite which was launched by the Soviet Union in 1957 and set off the global space race. There is skepticism about the vaccine's efficacy and safety that Russia has to address. The data and results of the vaccine have not been reported yet in any form of publication is the concern of the people. Russian health ministry claimed the vaccine is good enough to provide immunity against the COVID-19 SARS-Cov-2 virus for up to 2 years. Two shots of the vaccine are needed. The vaccine is prepared on the pattern of adenovirus which causes common the cold. The vaccine has human adenovirus characteristics carrying S-antigen of the SARS-Cov-2 virus which makes the person immune to COVID-19. Sputnik V vaccine is a viral vector vaccine, it uses a virus to carry the DNA for encoding the immune response against the SARS-Cov-2 virus. Russians claimed the concept used to develop the Sputnik V vaccine was being developed for the last 20 years to develop a vaccine for the virus such as Ebola virus. The concept which Russian vaccine maker Gamaleya used is similar to the coronavirus's prototype vaccine of CanSino (a Chinese company). In this summer and fall, several thousand teachers and frontline health care workers will be inoculated. Mass production will start to make the vaccine available for the general public by October. In October, the Philippines will start a vaccine trial for phase 3. Vietnam will buy 50 - 150 million of Russian vaccine, doses such a contract has been signed. Some of the doses will be given as a donation. Phase 3 trial is scheduled to start in Russia, Saudi Arabia, and the United Arab Emirates. In July, Russia has also begun clinical trials for a second vaccine developed by Vector laboratory in Novosibirsk and two more vaccines will be tested soon [20] [21].

Messenger RNA (mRNA) based COVID-19 vaccine developed [22] by Pfizer-BioNTech has reached phase II/III trials after it gave promising results in pre-clinical trials. The vaccine will be tested on 30,000 volunteers. The prototype tested has no side effects and developed a strong immune response against the virus. The company will produce “BNT162b2” vaccine doses enough for the US population. The trial is being conducted at one hundred research centers in the US and Germany. The final product will be available by 2020-end at the price per dose in the range of \$20 - 30. Much talked Oxford University-AstraZeneca vaccine is also under phase III trial in the US, Brazil, and India. Volunteers have received the vaccine shots and data are satisfactory so far. Mild side effects noticed in some volunteers can be cured by harmless paracetamol. For timely large scale procurement, AstraZeneca pharma has signed an agreement with Chinese Shenzhen Kangtai Biological Products company. In India, Serum Institute of India (SII) will do marketing of the Oxford Vaccine. Novavax Inc. is another company making the COVID-19 vaccine and planning to conduct phase III trials in September. The company reported a large amount of antibodies formation in healthy volunteers when two shots of vaccine were given in experimental trials. As early by next year, the company can prepare up to two billion doses. SII of India will also produce Novavax’s vaccine enough for millions of people.

Another mRNA based vaccine of Moderna Therapeutics is also in phase III trials. The testing on 30,000 volunteers is underway, results are expected soon. The company said the price of the vaccine will be reasonably affordable to meet the pandemic crises. Moderna Inc.-NIH jointly developed the vaccine. Moderna (US firm) claimed its mRNA vaccine generated antibodies in phase 1 trial to assess the safety and tolerance but the result if the vaccine can protect against the virus still awaited. Older adults with poor health, African-Americans and Latinos have also been selected for vaccine shots to certify if vaccines work on all the groups of the population. At present 150,000 US citizens have registered for vaccination. Many more volunteers will be needed for phase 3 trials. National Institute of Health (NIH, US) is selecting healthy and younger people from the area most affected by COVID-19 for vaccine trials. Another COVID-19 vaccine prepared [23] by Chinese company CanSino Biologics Inc. induced the immune response in 508 volunteers after receiving one shot. Only mild side effects were noticed like a fever.

SinoVac Biotech Ltd. has started [24] phase 3 trial in Indonesia for its “CoronaVac” COVID-19 vaccines. In the presence of President Joko Widodo vaccine shots were injected to 20 volunteers. Until December all 1620 volunteers in age 18 - 59 will receive the inoculation. Indonesian company PT Bio Farma and Padjadjaran University Medical School are collaborating in the inoculation program. Food and Drug Supervisory Agency of Indonesia is monitoring the safety and ethical aspects of the vaccination. The formulation of the vaccine is “Halal” keeping in the mind of Indonesian Muslims’ religious aspect. Bio Farma company’s CEO told the company has a manufacturing capacity of 100 million doses. By December the capacity will increase to 150 million and finally 250 million

doses will be made available. Hopefully, this vaccination program will finally end the COVID-19 pandemic in Indonesia. Indonesia has 127,000 coronavirus cases, and mortalities of 5760 were recorded till now. Sinovac Biotech is also conducting a simultaneous trial in Brazil.

Sinovac Biotech Ltd. has received [25] the approval of Brazilian health care surveillance agency (Anvisa), to conduct the phase 3 trial in Brazil to test the efficiency and safety of the product COVID-19 inactivated vaccine. In Latin America Sinovac Life Sciences, a subsidiary of Sinovac Biotech Ltd. has developed the vaccine. In Brazil, there is no scarcity of volunteers as it is the second most country with positive COVID-19 cases. According to Anvisa the COVID-19 vaccine which is being tested in Brazil has the composition of inactivated strain of the SARS-Cov-2 virus. The vaccine will be tested on 9000 volunteers selected from different locations of Brazil. Anvisa conducted a study of Sinovac's vaccine in animals, the results were within the safety limit. The other Chinese companies are also conducting trials abroad. Sinopharm Group is conducting trial UAE. Cansino is the third Chinese company targeting several other countries around the world for phase 3 trial in the second half of the year 2020.

The sequence of trials is following. Phase 1 trial check side effects, phase 2 justifies side effects and efficacy of the vaccine and phase 3 is the same as phase 1 but involves several thousand participants. Usually, a vaccine development takes up to 10 years, mumps vaccine was the fastest developed in four years. Experts feel the development of COVID-19 in a few months time is not fast considering the damage COVID-19 has caused around the world in 2 - 3 months. SinoVac was [3] the only company that conducted phase 1 for the SARS-Cov-1 outbreak way back in 2002-2003. When the pandemic disappeared suddenly, the company did not proceed to develop a vaccine then. After 17 years SinoVac built earlier research which was for SARS-Cov-1 for COVID-19. Both virus are coronavirus and have similarities. Therefore the company took advantage of earlier data to develop a vaccine for COVID-19 that reduced the time for vaccine development. Apart from vaccine development production and streamlining will be a big challenge. SinoVac currently has the capacity to make 100 million shots but it is increasing the capacity to make 300 million every year. The company said a person will need at least two doses to develop immunity to the virus. But how to immunize 7.6 billion population of the world is a big challenge for the world community to put the economic activity back to normal. US biotech company Moderna along with the National Institutes of Health developed a vaccine that showed enough antibodies in 45 volunteers for the COVID-19 virus and this vaccine will enter in phase 3 trials. Moderna vaccine is mRNA based product. mRNA tells cells to build SARS-Cov-2 specific antibodies thus stops the virus in the body. mRNA vaccines are faster to produce but the vaccine must be stored at below zero temperature making distribution difficult. SinoVac a Chinese company earlier developed mRNA based vaccine later shifted and produced finally to a more common inactivated virus vaccine instead of mRNA type. The com-

pany found good results with inactivated virus based products (CoronaVac) which is also under normal conditions is good up to 3 years to use. The Chinese government has invested [3] \$140 million in CoronaVac.

The cargo industries using ships, planes, and trucks said they are not prepared to carry billions of doses from makers to the people around the world. The cargo companies already affected by the COVID-19 pandemic, the business have already shrunk. Making effective vaccines in a short time is difficult and facing several challenges. Similarly, worldwide ferrying and distribution of an unprecedented amount of a large number of fragile vaccine vials are also challenging. Handling this huge amount of a cargo is a challenge in modern history. Logistic companies are working [26] to undertake this task. The supply chain is already overloaded in handling PPE cargo worldwide. If extra arrangements, for proper handling of vaccine, are not made in advance then the distribution chain can face failure. Emirates SkyCargo has estimated airlifting the vaccine vials for half of the world population will need 8000 Boeing Co. 777 cargo planes. Refrigeration is another difficult issue. The vaccine needs a temperature 2°C - 8°C in storage and shipping before it is injected in an individual. Some vaccine products even need more severe cooling of -80°C. If proper cooling is not done, it can destroy the whole consignment.

2.2. Plasma Therapy

An important aspect that needs to be investigated is how long a person recovered from the COVID-19 virus remains safe from reinfection. According to studies [27] [28] patients may lose immunity to reinfection within months after recovering from COVID-19. COVID-19 patients with mild symptoms were also found to have some immune response to the SARS-Cov-2 virus as detected in blood analysis. The study was conducted in 90 COVID-19 patients to examine the existence of antibody level over a period of time. In the first few weeks of infection strong antibody response was noticed in 60% of patients. After 90 days only 16.7% of individuals were found having strong antibodies neutralizing capacity and in many patients, no antibodies were detected. The findings are important to suggest the possibility of reinfection by novel coronavirus as antibodies wane in three months' time. For vaccination against the COVID-19 virus, the present study shows that people will need antibodies boosting by multiple shots as one shot may not be enough to keep people healthy. This is the scenario at present, but the number of shots needed will depend on the type of vaccine developed. Researchers must work out the possibility of developing a single shot vaccine that can make durable long lasting and in large number antibodies to come out of the pandemic COVID-19. It is a difficult and challenging task for any researcher.

2.3. Role of T Cells against COVID-19 Virus

The role of antibodies in keeping at bay the novel coronavirus is well known. But

the new study shows the antibodies produced against novel coronavirus COVID-19 wane quickly in patients with mild COVID-19 infection do not give lasting immunity solution. The hope in fighting with novel coronavirus and better vaccine development is the presence of white blood cells, T cells noticed in the vaccine recipients by the researchers of major vaccine developing companies: CanSino Biologics Inc., Pfizer Inc. and partner BioNTech SE, and AstraZeneca Plc. In the data report [29] the companies expressed achievement and satisfaction by the presence of T cells, the experimental shots developed, and a success in controlling the pandemic apart from the antibodies the vaccine produced in the blood against the pathogen SARS-Cov-2. It is well known that the body's defense relies on the antibodies and the role of the immune system to new coronavirus has been studied in the light of antibodies formed which do not last long. Researchers have a strong opinion that T cells remember past diseases for decades and work to rouse fresh antibodies again after the first one disappeared. It was reported that people infected with SARS-Cov-1 in 2003 still have T cell response to the virus even after 17 years. The existence of the COVID-19 virus recognizing T cells was confirmed in the persons who had no detectable antibodies. The T cells generated by common cold coronaviruses can give some immunity to the newly COVID-19 virus though detectable antibodies were not found in those patients. The presence of T-cells may be the reason that some patients are hardly affected however many get infected and may die when exposed to the SARS-Cov-2 virus. Another research [30] suggests antibodies produced by the immune system to neutralize the novel coronavirus lasted for a short time of a few months. The fading of antibodies not necessarily means that an effective vaccine can not be developed. Fresh antibodies can be prepared by the immune system when needed that can neutralize the new virus attack. The immune system has memory to activate the production of new antibodies when necessary once it is trained. In the above report [30], the half-life measured of antibodies formed in COVID-19 infected patients mentioned was 36 days. But in case of antibodies have gone, T cells are also able to attack the virus when the next virus attack occurs. The nature of vaccine developing antibodies must be stronger and durable than naturally produced antibodies.

2.4. COVID-19 Transmission Dynamics

We describe the transmission aspects of the virus by taking the example of Diamond Princess cruise ship quarantined in January-February 2020 at the port of Yokohama, Japan when the coronavirus outbreak happened. There were 3711 passengers and crew members on the cruise ship. Researchers [31] in Aichi Prefecture, Japan have worked out the data of COVID-19 SARS-Cov-2 infection that occurred on the cruise ship in January-February 2020 that shows a typical pattern of the pandemic in an isolated place. There were 3711 passengers and crew members on the cruise ship. Out of 712 infected passengers, 410 were asymptomatic. On the cruise ship, 96 persons infected with COVID-19 virus were

positive and asymptomatic whose tests were conducted and 32 of their colleagues on ship tested negative. The above cases were shifted to the hospital for observation. Of 96 persons 11 became symptomatic in 4 days suggested they were pre-symptomatic already instead of asymptomatic. 8 of 32 negatives became positive in 72 hours but did not show the symptoms. In 8 and 15 days, 48% and 90% showed resolution to infection, respectively. The time taken (days) for resolution was found to increase with the age of the infected person. From the above findings, we can know the majority of infected asymptomatic persons remained asymptomatic. The shedding or resolution time of 15 days was justified. In a separate report [32], data collected from the same Diamond Princess cruise ship, authors wrote the chances of asymptomatic patients becoming symptomatic are dim until a patient is already pre-symptomatic. The finding confirmed nearly half of the coronavirus positive patients shed the virus in 9 days and in 15 days 90% of people recovered. In easy transmissible environment when people stay with asymptomatic infected patients then symptoms will develop in other people. Here comes the role of testing to stop people from developing symptoms and avoiding healthier people from getting infected. The positive patients who completed the resolution in 6 days before the appearance of the first positive report and tested negative twice in successive tests can be discharged from the hospital. The viral particles may take 6 days to appear and to clear the infection it may take 8 - 10 days. These numbers of days can be considered to declare if patents are safe to bring them back in a healthy society. This has justified a quarantine period of 10 days reduced from 14 days that was used before. The amount of virus decreases in these days which makes the transmission odd. The asymptomatic healthy carriers can infect the people is “the Achilles” heel (weak point) in controlling the COVID-19 pandemic. The chances of asymptomatic COVID-19 patients developing symptoms later are very slim but can not be ruled out completely.

2.5. Stability of SARS-Cov-2 Virus in Waste Water and Feces

The COVID-19 virus is very much stable in water medium under difficult conditions of pH and the presence of other materials in sewage water. Viable virus was detected [33] in sewage drainage in Yamanashi Prefecture, Japan. Testing sewage water is helpful to understand a second wave of spread. A total of 13 samples were collected from sewage treatment facilities and rivers by Professor Eiji Haramoto (University of Yamanashi) and Masaaki Kitajima (Hokkaido University) for five days in the time March 17-May 7, 2020. PCR (polymerase chain reaction) test was conducted of concentrates. The sample collected from sewage on April 14 was found the COVID-19 positive. The number of infected persons was many around this date. The number of positive samples will depend on the number of infected people. The findings of Haramoto and Kitajima were published in a research article [34]. Such research was published the first time in Japan. It was found in France, the US and other places also that coronavirus

COVID-19 originates from the waste of infected persons. Another research group in Japan from Toyama Prefectural University and Kanazawa University have found COVID-19 virus SARS-Cov-2 in sewage but the results were not published in the journal.

Kitajima *et al.* in a review article [35] of investigation SARS-Cov-2 in waste water have reported the gastrointestinal symptoms due to the COVID-19 virus and surprisingly the viral RNA was reported in waste water as well as in the feces of the COVID-19 patient. The findings have suggested quantitative microbial risk assessment of SARS-CoV-2 exposure from feces and waste water must be addressed to avoid second and future waves of the infection. There is the need to study the SARS-Cov-2 virus from the purpose of occurrence, persistence, and removal in wastewater. Methods must be established to conduct research for waste water surveillance and the effect of virus contamination in spreading the disease.

2.6. Pets Susceptible to COVID-19 Virus

Keep your pets cats, ferrets, and mink isolated from an infected person. The study [36] showed among cats, dogs, pigs, chickens, ducks, and ferrets, only cats and ferrets were found susceptible to airborne SARS-Cov-2 virus infection. One more study [37] shows the virus spread among cats. Seven farm workers and 87% of the mink tested positive for the COVID-19 virus in a mink farm in Spain [38]. There is a reason to believe that an infected person passed coronavirus to the mink. From humans to mink transmission was possible but there are chances of *vice versa* were not denied. Mink were culled using the same method gassing by carbon monoxide and dioxide gas. Culled fur did not enter the fur market industry. Globally the fur farming was already in a decline due to bans at some places. A pet insurance company in Japan reported [39] two pet dogs, of coronavirus positive owners, were found infected with the virus. Dogs did not show any symptoms and one of the dogs became negative when tested again. Until now only cats and mink were found infected with COVID-19. Dogs are the recent addition to the pet list. The insurance company has not found if any of the employees looking after the pets had health problems. Though it was not confirmed if the virus found in the dogs was of the owner's body or produced in the dog. To confirm if the COVID-19 virus can multiply in dog's body more tests are needed.

2.7. A Recent Example of Community Transmission of COVID-19

The community transmission of the COVID-19 virus in two coastal settlements (Poonthura and Pulluvila) occurred [40] in Thiruvananthapuram capital city of Kerala state of India around the time July 17, 2020. Authorities imposed lockdown in the area to curb the further spread. A total of 107 people were tested randomly and 54 people were found infected. The state reported 791 cases in single-day spike, total cases have become 11,066 with 54.48% active and under

treatment, 44.92% recovered already, and mortality rate in the state is 0.6 percent, the lowest in India. Stage three is community transmission when contact tracing by identifying the infected person who has travel history from the area where infection existed is not possible. In this situation the entire community becomes vulnerable. In community transmission large (half or more than half) population is found infected in randomly conducted testing. Comparing the situation in India, in brief, the Kerala state has the lowest number of infected people while neighboring states Karnataka and Tamil Nadu have three times more cases which are the matter of worry. The reasons of a large number of COVID-19 cases in these two states must be worked out and steps must be taken to reduce and eliminate the virus. In another state West Bengal of India, community spread has occurred [41]. Community transmission can be stopped by improving diagnostic facilities, hospitalization of patients, and doctors' availability for services. In a community spread or transmission, infected people move around as healthy individuals. In community transmission, the scientific justification can not be ascertained about the route of infection. Once the community transmission has started the lockdown is not beneficial anymore. The RT-PCR's negativity is not enough to declare a person virus free, the person's RNA test may be positive next time after a few days depending on the viral load in the person develops in this period. A complete viral clearance of an infected person is needed before discharging the individual so that the person has no transmission potential. Till a proper and efficient vaccine invented there is a need to look for the drug to control the pandemic and save lives and stop the outbreak.

2.8. Super Spreader

The concept of SARS-Cov-2 "super spreader" and the terms related to it need to be defined for understanding and controlling the disease. A software engineer working in the town of Gurugram in India where 8000 corona cases existed [42] came to his village to get married where 369 guests participated in the wedding on May 12, 2020. After two days of marriage, the bridegroom died of fever. Listening to this there was a panic among the guests, who attended the marriage, and local administration. When tested, 79 guests were found coronavirus positive. When their contact tracing and testing were conducted, 24 more people were coronavirus positive. It is a typical case of "super spreader". A normal COVID-19 patient infects 2 - 3 persons. When individuals or groups infect a large numbers of people they are "super spreaders" by Epidemiologists' definition [43]. The term "R0" (R-naught) defines the number of a person infects. When $R_0 = 2.5$, then an individual infects on average 2.5 persons. In other words, the reproductive number is 2 or 3. The other term used to define the COVID-19 spread is the "Pareto Principle" also known as "80 - 20 (80/20) Rule" used in other happenings. It says 80% of incidents happen from 20% causes. When defines COVID-19, then 80% of infections coming from 20% carriers. There are two opposite possibilities, one when a large number of infected individuals transmit the dis-

ease to few people or no one, second is more alarming in which few or just one infected individual becomes the reason for bulk infection. Maintaining physical distancing or social distancing (two meters minimum), using three layers N95 mask covering both nose and mouth, washing hands with hand soap, and sanitization of places will diminish the chances of a person becoming a super spreader. Treatment, contact tracing, quarantine, and isolation are other important ways to stop super spreading. Super spreaders have contributed much to spreading COVID-19 globally since the pandemic began. Stopping a person or group becoming super spreader will help to control the outbreak along with applying the other methods. Quarantining or isolation or self-isolation of individual, group or a locality will stop the outbreak. Infecting up to 500 people by a super spreader was noticed. It happened [43] in a fish processing plant in Ghana in May 2020.

Author Contribution

All authors contributed equally

Statement of Human and Animal Rights

No animal and human rights issues exist in this research. No animal or human experiments were conducted in this research.

Authors' Qualification

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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