Developing Universal Cure and Other Tools based on Coronavirus Disease 2019 (COVID-19): A Literature Review

Leshi Zhou

Shanghai High School International Division, Shanghai, 200051, China

Abstract. The start of the outbreak of COVID-19 poses a challenge to every citizen in the world, regardless of our different occupations. Today, people have grown more familiar to not only to the methods of prevention for COVID-19, but also the biochemistry of the disease, thanks to the intense research done about COVID-19. The understanding of COVID-19 also facilitates in producing cures for both COVID-19 and other contagious diseases that can possibly lead to an outbreak. The knowledge accumulated from past research and newly discovered research methods plays a significant role in the success of the global knowledge of COVID-19. New understandings gained from investigating COVID-19 will improve our understanding to coronaviruses in general, and aid in future studies in the field of virology and other related fields. Examples of techniques that aided COVID-19 study are viral neutralization, lipid nanoparticle technology, polymerase chain reaction, observational and molecular research. In addition, the outbreak has increased awareness of global health. Currently, there are still many unanswered questions of COVID-19, such as questions related to long covid, the origin of SARS-CoV-2, and the surprising number of mutations of Omicron, which will be answered by further and future studies. Molecular studies include collecting samples of viruses found in the environment and analyzing their viral sequence. Internet research is also an important part of studying a certain disease or virus. Through using specific examples to explain how people different groups of people view COVID-19 and the production process of pandemic facilities, the literature review highlights the importance of utilizing technology, conducting scientific research, and staying alerted for the unexpected, as we can greatly improve global health and prevent future pandemics.

Keywords: COVID-19; Scientific Research; SARS-CoV-2; Vaccine Development; Virology.

1. Background

Starting from December the 31st in 2019, the first COVID-19 case was spotted in a seafood market in Wuhan, China. The case sparks intense discussion and vigorous research, as people have never seen the disease before. The disease is named COVID-19 for the year of its discovery. Different from prior pandemics, including SARS-CoV-1 and MERS-CoV, COVID-19 is particularly contagious, as it is passed directly from person to person. The virus that caused the disease is named SARS-CoV-2, and it belongs to the family of coronaviruses named for their spike-shaped protein. The virus primarily attacks the lungs, creating symptoms ranging from cough to shortness of breath. At the beginning of the epidemic, many citizens suffer from COVID-19 both physically and mentally due to a lack of knowledge about the virus, as the virus is new and mysterious. In consequence, researchers are seeking for a cure, which is the vaccine; it is an efficient way to slow the spread of the disease and protect individuals against it. In 2020, the vaccine is produced successfully in an efficient manner [5], saving many lives. The research methods of COVID-19 played a significant role in this success. Therefore, the process of discovery to the cause of COVID-19 and its cure is important.

Methods on researching COVID-19 and building its technology involves a comprehensive understanding of many concepts, and the ability to apply them. During the process of studying the virus, scientists commonly use the light and electron microscopy, allowing scientists to see the virus at a macromolecular level, and their chemical responses. The most common procedure of studying a virus is first to understand the structure of the virus, and each part of the virus' role, which can be done by examining pictures of the virus. Second, scientists will detect an immune response to the virus, which means examining the relationship between antigen and antibodies. Some ways to perform this includes virus neutralization, hemagglutination inhibition, and enzyme linked immunosorbent assay. In particular, virus neutralization is implemented in the production of the aforementioned mRNA-1273. This test involves putting the target virus into a sample. If the sample has antibodies, then the virus will not replicate. Similarly, it will start reproducing if there are no antibodies. Other than studying the virus itself, scientists will attempt to track the origin of the virus, which involves examining the samples collected from the place where the virus is discovered, and researching about the location. The samples will be compared with many other samples to draw a conclusion.

Other than conducting experimental and observational investigations, internet research is also a media to receive information about COVID-19. The pandemic becomes a significant topic today, as it influences people of every country and age group. In consequence, given the popular media of the internet, many information is being passed through the internet, but simultaneously, the need for checking the genuinely of the sources increases. For instance, many official organizations will choose to publish their findings on the internet in the form of a written report. COVID-19 becomes a trending topic to discuss on the internet between netizens, and there are numerous sources about COVID-19 on the internet. While some people are curious about the biochemistry of coronavirus, it is also important to consider how did the authors of the internet sources find their information; in other words, we should consider the process of retrieval of information about COVID-19, which can include questions such as “how did he or she know that coronavirus triggered the lung disease?” For instance, the World Health Organization (WHO) is a reliable source for information related to global health, and publishes information about COVID-19 by doing research on a neutral perspective. WHO gathers its information by looking through scholarly scientific articles [1]. To keep the information updated and ensure its truth, the WHO collaborates with other organizations, in which intense teamwork is implemented. Specifically, BIREME, which is a specialized center of the WHO [2], builds the database for the content of the WHO, guaranteeing its credibility and the accuracy of the content.

2. Discussion

2.1 Different Peoples’ Reactions of the COVID-19 Outbreak

People’s initial response towards the outbreak of COVID-19 in overall is fearful. For instance, the data is frightful— shortly after the first COVID-19 case is discovered, there are 2,830,000 million cases confirmed around the globe [8]. The speed at which the number of cases increases is out of people’s expectations, causing many to feel frightened. Also, to prevent the spread of COVID-19, strict regulations of isolation are implemented. Consequently, people are forced to stay at home and separated from each other, and many fear that they will lose their job due to the coronavirus outbreak [8], especially impacting people who do service industries. According to a survey conducted by Dr Urvish K. Patel, who is part of dept. of neurology and a medical advisor at emedihealth.com, the majority of people find information about coronavirus from news outlets [8], indicating the importance of the pandemic as a global issue. Few decide to ask their friends and family for information related to COVID-19, indicating how COVID-19 is a new event for everyone. In the survey, there is also a question about whether citizens think antibiotics can kill the coronavirus. Seventy four percent of the surveyed responded no as the answer, implying that most people viewed COVID-19 as a completely new global threat that needs absolutely different methods from prior pandemics to relieve, which serves as a reasonable cause for the great amount of stress generated at the beginning of the outbreak.

2.2 How Scientists Study the Source of the Virus

In May of 2020, the World Health Organization (WHO) decides to call upon a group of scientists to conduct research about COVID-19 from its roots, which means starting from its origin. The study plans to research on the zoonotic source of SARS-CoV-2, how it got into the human population, and intermediate hosts in the pandemic. After conducting the study, scientists will get a better knowledge of COVID-19 and prevent future outbreaks. Before the study starts, WHO first needs to decide on which people will participate in the study. To ensure the efficiency of the study, the people are expected to be multidisciplinary experts. After recruiting the experts, they held online meetings to have an overview on the content they are studying, establishing a detailed plan and setting clear objectives [13]. Like a group project, they divided labor, with smaller groups researching different areas. The whole research is divided into phases, and each phase will be dedicated to research specific areas of COVID-19. In overall, it is based on observations; from observations scientists propose a hypothesis.

Then the study is made put into action. The first phase primarily focuses on epidemiology, animals and the environment, and molecular epidemiology and bioinformatics. First, scientists track the emergence of the disease— whether it emerged in October or November of 2019. They closely inspect morbidity caused by respiratory disease in October and November, collect samples from hospitals, and look at reports of purchases for medicine. They review data on number of deaths caused by any disease and the reported cases in Wuhan and the rest of the Hubei Province. After the National Notifiable Disease Reporting System (NNDRS) in China performs clinical review on the data, the researchers evaluate the data. They discover that although ninety two out of 76,253 cases are compatible with SARS-CoV-2 infection, none of them are caused by the virus, indicating that the virus did not emerge before December of 2020, which is the time that wider transmission start. Next, the experts research on the origin of SARS-CoV-2. It is widely believed that the outbreak starts from Huanan market, but through molecular analysis, they discover that early cases in December of 2020 are not associated with the market. In addition, the researchers examine viruses from animals, as they may be the possible source of COVID-19. The study shows that coronaviruses highly related to SARS-CoV-2 are present in bats and pangolins, suggesting that they are possible candidates for the origin of COVID-19, but no direct evidence of the presence of the virus is found in animals. Other than observational research, the scientists also read published studies. adding another possibility to the way COVID-19 is introduced. [8]

In the next phase, the researchers will trace the origin of SARS-CoV-2 biologically, which includes its ancestor. They start with the market; they perform serological tests on animals and cold-chain products. The result is that they find detect high amounts of antibodies of the virus in them, suggesting the emergence of SARS-CoV-2 from animals, adding another possibility of through which pathway did COVID-19 emerge in human population. Then, they examine animals directly. Specifically, they analyze the viral sequence and antibodies related to SARS-CoV-2 in the Rhinolophus bats. Many of them contain traces of the virus, increasing the possibility of a zoonotic source.

Finally, the researchers come up with four hypotheses, which are direct zoonotic transmission to humans, introduction through intermediate host, introduction through food chin, and laboratory incident. Introduction through intermediate host become the likeliest way of transmission of SARS-CoV-2, which means that both animals and humans play a role in the outbreak of COVID-19. Another host has to be identified in order to answer the question of the source of SARS-CoV-2. Today, the origin of SARS-CoV-2 still remains a mystery, and scientists can only come up with likely theories that are subject to further investigations.

2.3 The Principle of COVID-19 Test

The COVID-19 test makes use of a technique called polymerase chain reaction (PCR) to detect the presence of SARS-CoV-2. PCR involves the use of primers, which are short sequences; primers will replicate a specific DNA sequence. For the case of testing SARS-CoV-2 [20], the test uses a modified version of PCR called quantitative polymerase chain reaction (qPCR). First, healthcare workers will collect throat and nasal swabs from people. The SARS-CoV-2 virus uses RNA as a genetic material, the genetic material in the individual will first be converted from a single strand to a double strand, creating DNA; the two strands of DNA are separated again. Then, primers will attach to each strand; the primers are specified in duplicating only the genetic sequence of the viral DNA of SARS-CoV-2. If more copies of viral DNA are further created, fluorescent dyes will attach to the DNA to signal successful replication, confirming that the individual is positive of the virus. If the primers fail to duplicate the sample from the individual, no copies will be produced, as the SARS-CoV-2 primers do not match the individual's genetic material. The aforementioned method is highly accurate, as PCR can identify specific pathogens or bacteria. However, to conduct PCR testing, a copy of the DNA from SARS-CoV-2 is needed. Also, PCR requires more analysis, which means that the individual needs to wait a longer time to know his or her result.

To meet up with the high demand for testing COVID-19, a quicker antigen testing is developed. Unlike former COVID-19 tests that require intense analysis, the rapid antigen test instead detects spike proteins in the nasal swab, and it does not require expertly knowledge. First, the individual will mix the nasal swab with a liquid. If the virus is present in the swab, then it will bind to the gold-conjugated antibody. The antibody-gold conjugate is a y-shaped protein produced by the immune system that specifically detects the presence of SARS-CoV-2; it can also be defined as an antibody of SARS-CoV-2. When it combines with the antigen, which is SARS-CoV-2, an immunocomplex is formed. Then the individual will drip the mixture into the test device. Through capillary action, the formed liquid first travels to the test line, which indicates the presence of the immunocomplex with a visible red line [22]. If the individual is free of SARS-CoV-2, no line will appear. In the test zone, there are another set of antibodies that only binds to the target virus. if SARS-CoV-2 is detected, then the antibodies will bind to the formed immunocomplex in the sample, and gold nanoparticles allow the bind to appear visibly in a red line, as gold have the ability to make molecules visible. Then, the liquid will continue traveling to the control line; a visible red line must appear in order for the test to be valid, regardless of whether the individual is infected with SARS-CoV-2. The control zone contains antibodies that bind to unbound mobile antibodies, indicating that the test is performed properly. The rapid antigen test is convenient because it shows the results quick and people can find out whether they are infected with COVID-19 instantly at anywhere, as the tools for rapid antigen testing are easy to carry. However, the cost for this convenience is that rapid antigen testing is not accurate as PCR. Therefore, this kind of testing is more suitable for urgent circumstances.

2.4 Production of Vaccine

Seeing the rapid spread of COVID-19, research laboratories are studying the virus to create a vaccine. Although social distancing, constant sterilization, and wearing masks can greatly hinder the spread of COVID-19, vaccines are needed, because they prevent both COVID-19 and other diseases caused by coronaviruses. Currently, three types of COVID-19 vaccines are available in the United States: the protein subunit vaccine, viral vector vaccine, and the mRNA vaccine. The protein subunit vaccine, with the biotechnology company Novavax as the representative, injects proteins that cause COVID-19 and adjuvant into our body. The adjuvant is an ingredient that teaches our body on building protection against COVID-19. When we receive the injection, the body will recognize that the proteins are a stranger to the body. Then, the adjuvant will instruct the body to build corresponding antigens, therefore building protection. The adjuvant will also activate some immune cells. Therefore, the possibility of severe symptoms is greatly reduced, as the body learns to fight the disease. Moreover, the viral vector vaccine injects a harmless virus, which is also the vector virus, into our body. The vector virus will use the cells in our body to produce a protein that is found on the surface of SARS-CoV-2. Then, our cells will break down the vector protein and the immune system will create antibodies that can fight the created protein off. In this process, the body builds the mechanisms that can fight the actual virus that caused COVID-19. Finally, the mRNA vaccine works in a similar way to the viral vector vaccine. The mRNA vaccine injects a piece of messenger RNA, and will instruct the cells to make a piece of spike protein. Once the spike protein is created, our bodies will build antibodies and other immune cells to fight the protein. However, the mRNA vaccine is a relatively new type of vaccine. The mRNA vaccine is based on the thought that the virus can be created in our body, instead of having to inject a copy of the virus into our body. Although it has similar working mechanisms with the viral vector vaccine, the mRNA vaccine has greater flexibility because it injects a genetic code into the body, instead of a modified version of the virus. Hence, people are showing a greater interest in producing the mRNA vaccine.

For instance, on December eighteenth in 2020, the medical research center US National Institutes of Health and Moderna the release the mRNA-1273. The vaccine aims to prevent COVID-19 and create antibodies for those who are not infected. Even if an individual is infected, with the vaccine, he or she will not have severe symptoms. The vaccine is a research result of the collaboration of many organizations, highlighting the importance of teamwork and efficient collaboration. The speed of the release of the vaccine is surprisingly quick, as the first COVID-19 case is spotted in December 31 in 2019.

The production of mRNA-1273 uses the prototype pathogen preparedness approach, which involves selecting a representative virus among a certain viral family that is going to serve as a prototype [5]; then as the researchers study the virus, they will generalize information about it, allowing the research results to be applicable to the viruses in a viral family and ensuring the applicability of the produced vaccine. In the case of mRNA-1273, the prototype is MERS-CoV, which will be studied extensively to ensure the quality of the vaccine. During the research process, the team sets three goals for their research, which are fast, reliable, and universal [5]. A vaccine has to fulfill these three qualities to be released.

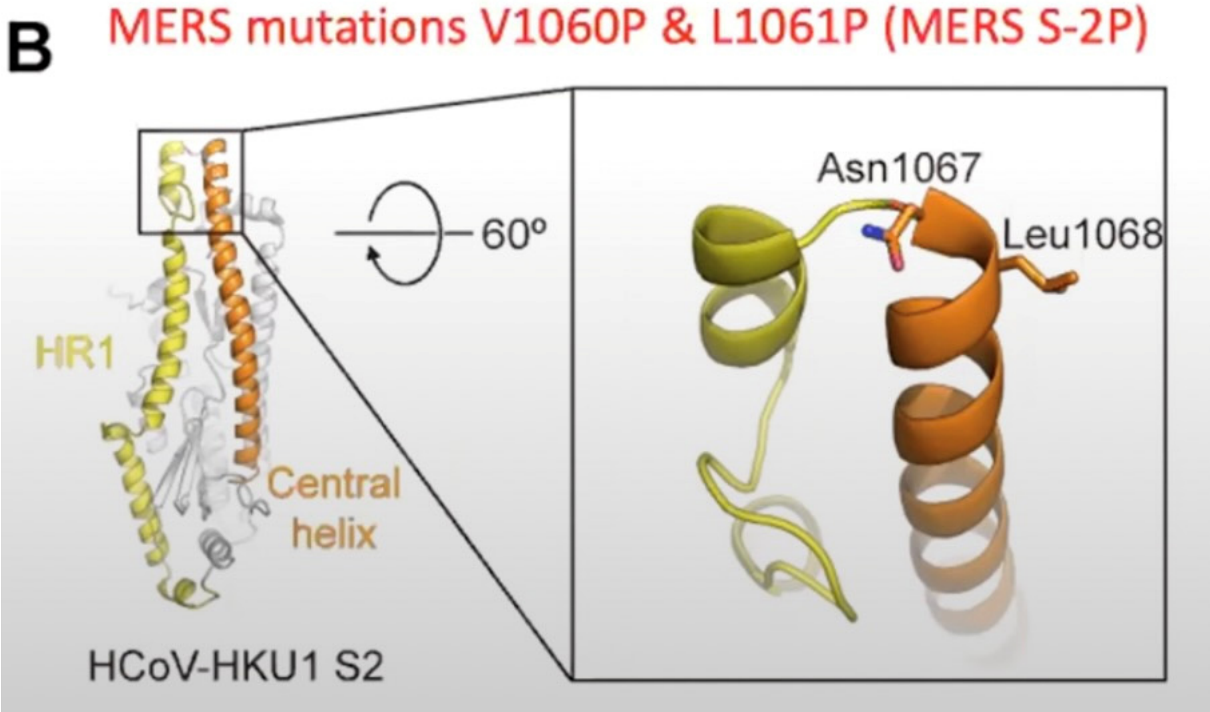

Figure 1. The picture shows the structure of the HKU1 spike proteins. Researchers identify two proline substitutions at the top of the heptad repeat 1 and central helix. The two proline substitutions together are named 2P; 2P can stabilize MERS-CoV, which is significant to vaccine development. 2P is going to use as a mutation to stabilize the spike protein, making the spike protein an effective antibody for the vaccine. [3]

Before producing the mRNA-1273, scientists have to study the different viruses within the family of coronavirus. Scientists need to have comprehensive knowledge on coronavirus before making a vaccine. Thus, the knowledge from previous studies aids in producing the vaccine. First and foremost, scientists have to thoroughly understand the structure of spike proteins. To study the structure of the spike protein, researchers use the cryo-electron microscopy. This kind of microscopy is a variation of transmission electron microscopy (TEM). It involves examine a specimen under cryogenic temperatures, which is usually under 113 kelvins. The low temperature keeps the specimen at a frozen state, allowing scientists to capture high-resolution images. The images clearly show the interior and exterior structure of the protein, allowing scientists to learn the structure of the protein. Then, scientists will study the use of each part of a virus. The study shows that the coronavirus uses its spike proteins on its surface to enter into our body and stick to our ACE2 receptor. Therefore, the spike protein serves as the bridge between our body and the virus. Hence, the spike protein and the viral sequence of SARS-CoV-2 should serve as the target for creating the vaccine, as it will be the primary antibody needed to resist SARS-CoV-2. First, researchers need to stabilize the spike protein in its pre-fusion conformation. Stabilizing the spike protein in its pre-fusion conformation will make them better immunogens [6]. This step uses the stabilized spike protein technology, according to the National Institute of Allergy and Infectious Diseases [6], and the principle that beta coronavirus spike proteins improve their immunogenicity in the prefusion state.

Then, researchers can set a clear goal of designing a pre-fusion stabilized spike antigen for the vaccine using the 2P. The antigen is the basis of an ideal vaccine development. First, 2P will neutralize MERS-CoV. The neutralized version of MERS-CoV is called MERS-CoV S(2P), and it acts as the antibody in the vaccine.

Then, the researchers need to find a way to deliver the spike protein in the form of a vaccine during a pandemic, which has to be fast and reliable. Moderna helps in the combining all the components of vaccine— the MERS-CoV S(2P) and the mechanism to deliver it into the body. Moderna places 2P for spike proteins into a mRNA sequence. The mechanism to deliver the neutralized spike protein into our body is called nanoparticle technology. The lipid nanoparticle encodes the mRNA sequence of MERS-CoV S(2P) and delivers the immunogen into the muscle, telling the muscle to make its own spike proteins, thus creating resistance. The lipid nanoparticle consists of polyethylene glycol lipid mixed with MERS-CoV S(2P) in an acetate buffer. The mixture is neutralized by Tris-Cl pH 7.5. The whole vaccine creation process is regulated by current good manufacturing practice (cGMP), which is a set of regulations established by US Food & Drug Administration (FDA). Then, mice and non-human primates are the first candidates to use mRNA-1273. The vaccination in mice confirms the immunogenicity of the vaccine, as they show neutralizing antibody responses. In detail, there is no signal of respiratory disease in animal candidates [12]. Then the vaccine can be put in trial through three clinical phases.

The science of the produced vaccine is that it is a mRNA vaccine [24]. Unlike the traditional vaccine, which injects a weakened version of the virus, the mRNA vaccine injects a messenger RNA to instruct and order the cells in the body to build a spike protein. The built protein will not create harmful effects for the body, as the immune system will not recognize the built spike protein and other incoming proteins akin to the spike protein as invaders. Therefore, the body makes an antibody itself.

2.5 How Scientists Confirm Their Study Results

mRNA-1273 is put into test, with about thirty thousand Americans receiving a total two doses of the vaccine for each individual. The candidates are carefully selected; to be a candidate, he or she has a provide a blood sample and a nasopharyngeal swab [7]. Specifically, the candidates will receive one dose of the vaccine for every twenty-eight days. At the end of each phase, participants are required to record any symptoms in a diary and use a thermometer to measure their temperature. Participants will be grouped into three groups; each group receives different amounts of mRNA-1273 for each dose. After the three phases end, researchers in Moderna write and analyze the observed results in the form of a report. In the three phases, healthcare workers conclude that the vaccine produces positive responses in the candidates, denoting the success of mRNA-1273 and signaling to researchers that they can continue developing mRNA-1273. The whole trial is led by Moderna, who is also the main sponsor for the production of mRNA-1273. The trial allows researchers to know whether two doses of the vaccine will protect the individual from infection, whether the vaccine can reduce symptoms when infected, and whether one does will be enough.

After the candidates receive the vaccination, researchers will inspect the t-cell responses against the injected spike protein using a technique called intracellular cytokine-staining assay [9]; this evaluation is performed by NIAID Vaccine Research Center. The intracellular cytokine-staining assay can determine the production and accumulation of cytokines after cell stimulation. Immune responses generate cytokines, so evaluating the number of cytokines can determine the effectiveness of the immune response produced by the vaccine. This technique performs immunophenotype, which is by using cell surface markers to detect an antigen specific response.

2.6 What are Scientists Currently Researching About COVID-19

During the two years that have passed since the pandemic, researchers are conducting intensive investigation on COVID-19 and ways to prevent future outbreaks. In consequence, many answers have been known about COVID-19, including its composition and ways to prevent it. However, there are still unsolved questions waiting for scientists to answer about the disease, which is also what they are currently researching about COVID-19.

One of the unknown phenomenons of COVID-19 is about the omicron variant [14]. It is a variant of the coronavirus, and is more dangerous and mysterious than SARS-CoV-2. The omicron can have evolved from a certain coronavirus that increases its fitness, as it binds more effectively to human cells. For instance, the omicron has more than fifty mutations, and about thirty-two of them can change the amino acid in the spike protein [19]. The mutations aid in high transmission of the variant; the extraordinary number of mutations is unlike any prior virus, which is also the reason that it is extensively studied. In addition, many of the mutations on the omicron are rare, and the omicron has three sublineages, presented as BA.1, BA.2, and BA., with BA.1 and BA.2 already spreading to the human population. When the omicron first emerged in Botswana, researchers at Botswana Harvard H.I.V. Reference Laboratory collect samples from individuals who are positive with SARS-CoV-2. They discover that some samples share fifty mutations in a combination that is never seen before, signaling the presence of a new virus, which is named omicron. Later, more cases of Omicron are discovered, indicating its high rate of transmission. Scientists conclude that the Omicron's high number of mutations allows it to get pass several antibodies, posing a potential threat to those who receive antibodies for SARS-CoV-2 through vaccination. However, immune cell responses and booster shots can still protect people from Omicron, as they allow the body to create more types of antibodies. Currently, scientists are still trying to find the origin of omicron; its appearance, like SARS-CoV-2 is also sudden. A widely believed theory is that the mutations build up in a person who has an extremely weakened immune system; an alternative theory is it continually mutates in order to avoid detection by antibodies.

2.7 Impacts of COVID-19 on Scientific Research

The outbreak of COVID-19 highlights the importance of scientific research, especially in virology and immunology. Specifically, scientists are realizing the importance of strong understanding of protein structures, monoclonal antibodies, and human immune response. In order to produce a vaccine for COVID-19, researchers are putting intense investigation on discovering the antibody, as it is the primary component to produce an immunity. This mechanism will also be used in future studies about viruses. Moreover, some technologies have received more attention after the outbreak, such as purification of samples, modern crystallization, and robotic technology.

The outbreak significantly raises attention for pediatric research, as the disease apparently varies between adults and children [13]. Conducting pediatric research allows scientists to stop the spread of the disease among children. Other than the disease that the outbreak causes, researchers also examine the mental health problems caused by the pandemic; the pandemic prevents children from going to school and talk to classmates physically, which can create mental health problems.

Most importantly, the pandemic triggers a sense of urgency, as its occurrence is sudden. Seeing the spread of the COVID-19, research and healthcare facilities become the top priorities of public funding; people are paying more attention towards public health. In consequence, scientists have learned to prepare for unexpected events in prevention to another outbreak of a virus. The act of preparing for the unknown or unexpected is called strategic preparedness. By adopting strategic preparedness, scientists can detect earlier presence of virus, and stop the presence quickly so that there will not be another breakout. For example, currently the henipavirus is being studied, which are fruit bat-borne viruses; its fatality rate is at forty percent to seventy five percent. It appears on WHO's list of potentially dangerous pathogens; the list contains viruses that have high fatalities. To study the virus, scientists look at samples of the virus obtained from an immune patient's blood cells and data from crystal structure studies. Similar to studying SARS-CoV-2, they examine the surface proteins upon the henipavirus that allows it to bind to the body.

References

[1] World Health Organization. (2020). Global research on coronavirus disease (COVID-2019). Www.who.int. https:// www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov.

[2] BIREME - PAHO/WHO | Pan American Health Organization. (n.d.). Www.paho.org. Retrieved November 1, 2022, from https://www.paho.org/en/bireme.

[3] Dr Kizzmekia Corbett: SARS-CoV-2 mRNA vaccine development enabled by prototype pathogen preparedness. (n.d.). Www.youtube.com. Retrieved November 1, 2022, from https:// www. youtube. com/watch?v=881eS5UAlA8.

[4] Peruse NIAID's New Pandemic Preparedness Plan | NIH: National Institute of Allergy and Infectious Diseases. (n.d.). Www.niaid.nih.gov. Retrieved November 1, 2022, from https:// www. niaid. nih. gov/ grants-contracts/peruse-pandemic-preparedness-plan#: ~: text= Prototype% 20pathogens% 20are% 20 representative% 20viruses%20from%20viral%20groups.

[5] Corbett, K. S., Edwards, D. K., Leist, S. R., Abiona, O. M., Boyoglu-Barnum, S., Gillespie, R. A., Himansu, S., Schäfer, A., Ziwawo, C. T., DiPiazza, A. T., Dinnon, K. H., Elbashir, S. M., Shaw, C. A., Woods, A., Fritch, E. J., Martinez, D. R., Bock, K. W., Minai, M., Nagata, B. M., & Hutchinson, G. B. (2020). SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature, 586. https:// doi.org/10.1038/s41586-020-2622-0.

[6] Basic and Preclinical Coronavirus Research | NIH: National Institute of Allergy and Infectious Diseases. (n.d.). Www.niaid.nih.gov. Retrieved November 1, 2022, from https://www.niaid.nih.gov/diseases-conditions/basic-preclinical-coronavirus-research #: ~: text = Stabilizing% 20coronavirus% E2% 80% 99% 20spike%20proteins%20makes%20them%20potent%20and.

[7] Jul 29, & 2020. (2020, July 29). Moderna's mRNA-1273 Vaccine Put to Biggest Test - Physician's Weekly. https:// www.physiciansweekly.com/modernas-mrna-1273-vaccine-put-to-biggest-test.

[8] Patwa, P. (2020, April 25). How Are People Thinking, Responding and Reacting to Covid-19? Entrepreneur. https://www.entrepreneur.com/article/349819.

[9] Jackson, L. A., Anderson, E. J., Rouphael, N. G., Roberts, P. C., Makhene, M., Coler, R. N., McCullough, M. P., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A., Flach, B., Doria-Rose, N. A., Corbett, K. S., Morabito, K. M., O'Dell, S., Schmidt, S. D., Swanson, P. A., & Padilla, M. (2020). An mRNA Vaccine against SARS-CoV-2-- Preliminary Report. New England Journal of Medicine, 383(20). https://doi.org/10.1056/nejmoa2022483.

[10] Final-joint-report origins-studies-6-April-201 - WHO-convened Global Study of Origins of SARS-CoV-2: - StuDocu. (n.d.). Www.studocu.com. Retrieved November 1, 2022, from https://www.studocu.com/es-ar/document/universidad-de-buenos-aires/epidemiologia/final-joint-report-origins-studies-6-april-201/ 17348597.

[11] Miller, J. (2020). mRNA-1273 Clinical Development Program. https:// www.cdc. gov/ vaccines/ acip/ meetings/ downloads/slides-2020-08/COVID-02-Miller-508.pdf.

[12] Weiner, D. L., Balasubramaniam, V., Shah, S. I., & Javier, J. R. (2020). COVID-19 impact on research, lessons learned from COVID-19 research, implications for pediatric research. Pediatric Research, 88(2), 148–150. https://doi.org/10.1038/s41390-020-1006-3.

[13] COVID-19's "Unknown Unknowns" Are What Should Worry Us. (2022, March). American Council on Science and Health. https://www.acsh.org/news/2022/02/28/covid-19%E2%80% 99s-%E2% 80% 98 unknown-unknowns%E2%80%99-are-what-should-worry-us-16157.

[14] COVID-19: What is the Omicron variant? (2021, November 30). United Nations Western Europe. https:// unric. org/ en/covid-19-what-is-the-omicron-variant/.

[15] National Human Genome Research Institute. (2022, January 18). Understanding COVID-19 PCR Testing. Genome.gov. https://www. genome. gov/about-genomics/fact-sheets/Understanding-COVID-19-PCR-Testing.

[16] #ChemVsCOVID: How lateral flow tests for COVID-19 work. (2021, November 6). Compound Interest. https:// www.compoundchem.com/2021/11/06/lateral-flow-tests/.

[17] www.ncbi.nlm.nih.gov/books/NBK572322/bin/fdacovideuas_151215.pdf.

[18] “DNA” vs. “RNA” vs. “mRNA”: The Differences Are Vital. (2021, January 8). Dictionary.com. https:// www. dictionary.com/e/dna-vs-rna-vs-mrna-the-differences-are-vital/.

[19] Zimmer, C. (2021, November 26). New Virus Variant Stokes Concern but Vaccines Still Likely to Work. The New York Times. https://www.nytimes.com/2021/11/26/health/omicron-variant-vaccines. html#: ~: text= Omicron%20first%20came%20to%20light%20in%20Botswana%2C%20where.

[20] Chapter 5 -Lesson 4 Virology Techniques. (n.d.-b). https://agrilife. org/ vetmed/ files/ 2012/ 10/LS _5_ 4_sample_lesson.pdf.

[21] Benefits and Reasons for Molecular PCR Testing. (n.d.). Www.orlandomedicalnews.com. Retrieved November 1, 2022, from https://www.orlandomedicalnews.com/article/2869/benefits-and-reasons-for-molecular-pcr-testing#:~: text= Key% 20 benefits% 20to% 20 Molecular% 20PCR% 20testing% 3A% 201%2024-hour.

[22] Coronavirus Disease 2019 (COVID-19). (2020, February 11). Centers for Disease Control and Prevention; CDC. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/how-they-work.html.

[23] Komaroff, A. (2020, December 10). Why are mRNA vaccines so exciting? Harvard Health Blog. https://www.health.harvard.edu/blog/why-are-mrna-vaccines-so-exciting-2020121021599.

[24] Study: mRNA COVID-19 Vaccines Perform Better Than Viral Vector Vaccines. (n.d.). Pharmacy Times. https:// www.pharmacytimes.com/view/study-mrna-covid-19-vaccines-perform-better-than-viral-vector-vaccines.