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Opportunities and Challenges of Covid-19 Vaccine Production, A review

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Abstract
Background*: The emergence of a new virus that is still in the same big family as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV) viruses, namely Coronavirus Disease 19, has a major impact on the world. Transmission between humans is very fast through the splash of sputum or saliva of sufferers of COVID-19 when coughing or sneezing, which results in high cases of infections that lead to severe respiratory disease and death. So that countries around the world are competing to develop safe and potential vaccines.*
Materials and methods*: The method used in compiling this literature review is literature study using primary sources or new literature in the form of official books and the latest international journals and continuously with the title of the article.*
Results*: The results obtained from this article indicate that the development of vaccine production has great potential but that there are challenges for each process in its development.*
Conclusion*: The potential in vaccine development is very large so that it is estimated that within 12-18 months the vaccine production process can be marketed because it is assisted by advanced technology and previous studies of the development of the Sars and Mers viruses. Challenges in the development of religious vaccines start from the selection of antigens, platforms, the accuracy of the test animals used, the completeness of laboratory facilities, HCT, delivery routes, storage stability, mucosal immunity, preventive immunopathology, vaccine efficacy, potential duration and vaccine safety. Vaccines and the right solution are expected to produce a potential vaccine.*
Keywords*: Opportunities, challenges , production, COVID-19, vaccine.*

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I. Introduction

Coronavirus (CoV) is a large family of viruses that cause illnesses ranging from the common cold to more severe illnesses such as *Middle East Respiratory Syndrome* (MERS-CoV) and *Severe Acute Respiratory Syndrome* (SARS-CoV). The novel coronavirus (nCoV) is a new strain that has not been previously identified in humans. The novel coronavirus (nCoV) was discovered in late December 2019 in the Wuhan area, China[1].

This viral infection causes various pathological conditions ranging from mild, moderate to severe. It was found in cases induced by the corona virus (CoV) which causes mild upper respiratory tract infections and colds, but in more severe cases it will cause acute respiratory syndrome to death. The spread of the virus is also fast due to the easy transmission process through *droplets* arising from coughing, sneezing or breathing. Later these *droplets* will penetrate the human body through the mouth or nose [2]. Quoted from other sources that transmission can also be through urine and feces [3].

Coronavirus is classified as a RNA virus that has the ability to cross-react with hosts through genetic shift or genetic reassortment, which means that the virus mutates rapidly and becomes recombinant in the new form of the corona virus. Coronavirus is similar to avian influenza virus or also known as avian influenza virus (AIV) and also has the same antigenic drift (genetic shift). So that it has the possibility of producing the new virus strains that are not recognized by antibodies, causing a global pandemic [3].

Based on the infected cases from nCov, there have been 54 million cases from around the world with high mortality rates, so that starting from November 15, 2020, data on death cases had reached 1,320,913 cases [4]. The high number of infected cases and deaths due to the nCov pandemic has made all countries are competing to find a vaccine. To develop a vaccine requires a complex process with a long time, where the vaccine development period is usually 12-15 years. Unlike the case with conventional medicine which focuses more on the treatment of a disease with symptoms that appear while vaccines are used in people who have not shown symptoms of the disease and to prevent the disease.

The vaccine development method, although it is said to be very effective in fighting infectious diseases like measles, polio, etc. Although vaccines have great potential in overcoming a pandemic that occurs, there are many obstacles that confront them so that it must be designed as well as possible so that the vaccine production process runs smoothly. These obstacles can vary, starting from challenges during formulation to the vaccine testing stage itself, so this article appears to explain the potential and challenges that exist in the development of vaccine production that is currently taking place around the world.

II. Materials and Methods

This review article is compiled based on a literature study using official book sources and international journals with the requirements of being published in the last 10 years. Other supporting data that is also listed in this review article comes from online media with a search method using continuous important words in key points in the article title: the potential and challenges of Covid-19 vaccine production.

III. Results and Discussion

Potential microorganisms such as mold / yeast can be used in the production of ethanol, which is an environmentally friendly process and has economic value. A wide variety of substrates and treatment conditions are used in the ethanol production process.

In addition to the high vaccine prospects, there are several challenges that arise in the vaccine development process, which are as follows in Table 1:

Table 1. Challenges during vaccine production

NO	CHALLENGES	REFERENCES
1.	The test animals used must be suitable and safe	5
2.	Inadequate and limited laboratory facilities	6
3.	The selection of appropriate antigens	7
4.	The accuracy of the platform used	7
5.	The phase 3 of HCT test that againsts ethical values	8
6.	The importance of determining the route of administration	9
7.	Maintaining vaccine thermostability in distribution	9
8.	Achieving mucosal immunity in vaccines	7
9.	Prevention of immunopathology	6
10.	Recurrent outbreaks due to spills from Sars and Mers	5
11.	Ensuring vaccine efficacy	5
12.	The accuracy of dose and determining the potential duration of vaccine	10
13.	Ensuring vaccine safety	7

The development of the Sars-CoV-2 vaccine has enormous potential because it is very much needed, and it is estimated that the time needed for the vaccine to be marketed is around 12-18 months, this is supported by the following factors:

1. There has been previous experience with the Corona vaccine (Sars-1, Mers)
2. Advanced vaccine platform technology
3. Parallel processes (especially in clinical trials) and global efforts
4. Regular relaxation

The magnitude of the impact caused by the Covid-19 pandemic has caused countries around the world to compete in finding a vaccine. Quoted from the BBC that more than 120 vaccine candidates have been developed in the launch of the Covid-19 vaccine[11]. The development of the Covid-19 vaccine has enormous potential because it is needed quickly as a public health priority. In fact, it took years in the development of conventional vaccine manufacturing. However, with efforts being made around the world, and starting with previous research to develop a coronavirus vaccine, this could shorten the time it takes to develop a potential COVID-19 vaccine. It is estimated that it will take 12-18 months for the vaccine to be marketed, it can be seen from (Figure 1) that each stage of the Covid-19 vaccine test is carried out in a shorter period of time compared to conventional vaccines.

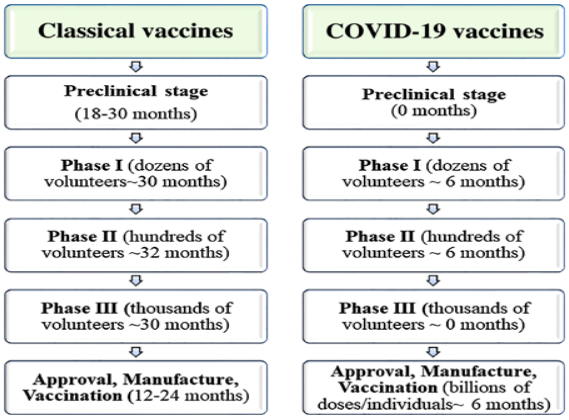

Fig. 1. Differences in the clinical trial phase of the covid-19 vaccine with conventional vaccines[11]

This can be seen from China's swift efforts. With the existing samples, complete genome sequencing of SARS-CoV-2 was successfully carried out. Posted on January 10, 2020, at virological.org by Edward C. Holmes on behalf of a consortium led by Yong-Zhen Zhang [12] and later at GenBank (GenBank: MN908947.1). The rapid sequencing and publication of data allows early initiation of vaccine development. On January 11, 2020, the United States National Institutes of Health (NIH) began developing a vaccine for COVID-19 [13]. In theory, a recombinant protein vaccine or vector-based vaccine could only be developed from the sequence information. The binding pattern of the SARS-CoV-2 protein to the ACE2 receptor was first published on the BioRxiv preprint server on 19 February 2020 [14].

Along with this, this development process has many obstacles and challenges in various aspects which are as follows:

1. Test animals must be safe

Based on previous experience with Sars and Mers CoV it were difficult to find animal species that would be affected in the same way as humans so various test animals were tried out for vaccine testing including NHP (Macaque, Green African monkey), mice, hamsters, and ferrets as well as added Animal species that are susceptible to obtaining the best model approach [15,16,17]. (Journal 5) In general, it is difficult to find a test animal model capable of having nearly the same disease pathogenesis in humans as well as similar physiology and immune response. In in vivo testing, the test animal model that is commonly used is mice because they have 85% genetic similarity with humans, and are able to reduce research costs because they are relatively cheap and there are no ethical problems [18] . However, the problem that arises in the differences between humans and mice is the ACE 2 receptor gene. Mice cannot develop respiratory syndrome, because mice have the ability to rapidly eliminate the virus in their body.

The shortcomings of mated mouse models that do not produce SARS or MERS can be replaced by the use of old SARS strains or mice, mice-adaptedMERS, and hACE2 or DPP 4 transgenic mice. [15,] In addition to other experimental animals that can be selected, such as civets , which are used as an influenza model, capable of describing the pathogenesis of SARS in humans including fever, nasal shedding, and pulmonary pathology; [15] however, their weak immune system and a lack of reagents compared to the mouse model was inhibited.

The use of pigs as experimental animal models can be another alternative because they are susceptible to MERS-CoV and SARS infection [19,20]. If susceptible to SARS-CoV-2, they could potentially be a relevant model because they have physiology, metabolism, and anatomy of respiration and immune response similar to the humans [21]. In addition to NHP which has similarities with humans, none showed clinical signs of disease and parameters in humans.

2. Limited Testing facilities such as laboratories.

As a result of Covid-19 that cannot be handled easily, there is a risk of severe disease or leading to death. The efforts made have not been able to stem and continue to put pressure on the health care system from patients. Thus this encourages the world to compete to carry out laboratory research to produce the Sars-CoV-2 vaccine. The development of experimental animal models in the Sars-CoV-2 vaccine research, encountered difficulties with the required facilities and the time required. One of these challenges lies in the need for a level 3 animal biosafety laboratory (BSL-3) which has limited availability. Jiangqing xu (2020) in his article stated that this one model non-human primate requires the large animals BSL-3 facilities [6.] It is also known that the live strain of SARS-CoV-2 cannot be isolated in all laboratories [22]. This of course will lead to limited access to experimental animal laboratory facilities and lead to intense competition in the future. According to Jiangqing Xu (2020), other alternatives such as in vitro neutralization tests are needed to increase vaccine development. Neutralizing antibody titres against RBD and the ratio of antibody response targeting RBD to all protein S are required, which would be seen as a good approach [6].

3. Antigens

The proteins that play a role in the entire structure of all corona viruses are the spike (S), the capsule or envelope glycoprotein (E) membrane protein (M) and nucleocapsid. In certain corona virus outbreaks, for example SARS, there is a part of the corona virus called receptors - the binding domains that is clearly illustrated in the S section which acts as a place for the virus to attach to the receptor (human) cell hopes called angiotensin-converting enzyme 2 (ACE2). Several other corona viruses, especially those belonging to the Betacorona virus sub group A members also have an S-formed protein called HE (hemagglutinin esterase) [23]. In the case of SARS-CoV, it was evident that only antibodies directed to protein S that could neutralize the virus and prevent infection [24]. Consequently, all the SARS-CoV-2 vaccines under development include at least a portion of the S protein. This may be limited to either the S1 or RBD domains. Non-neutralizing antibodies to protein S and other exposed proteins (E and M) are generated. Because of the supposed role of these non-neutralizing antibodies, as well as weak neutralizing antibodies, in ADE disease, the inclusion of structural (N) and / or other non-structural proteins as vaccine antigens can help create a balance. This response involves T cell-mediated and humoral immunity. This can be a highly expressed protein such as N protein or a highly conserved functional protein that has an important role in the virus life cycle. For example, the inclusion of viral enzymes such as RNA-dependent RNA polymers in vaccine design can ensure that the vaccine targets all strains of the emerging variant, because these proteins are highly conserved [24,25,26,27].

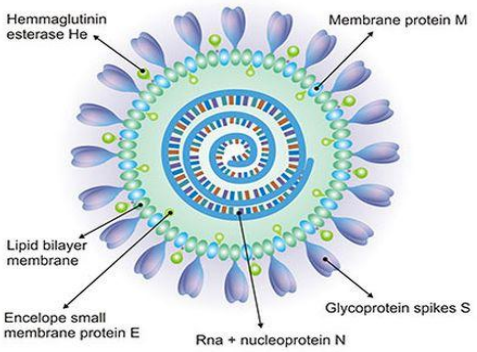

Fig. 2. Morphology of Corona virus [24,25]

4. Platforms

Multiple platforms are being developed, in which vaccine platforms are broadly divided into six categories: live attenuated viruses, recombinant viral vector vaccines which are biologically engineered to express target pathogenic antigens in vivo, attenuated or killed viruses, protein subunit vaccines, virus-like particles (VLP) and nucleic acid (DNA or mRNA) based vaccines [7].

Among the platforms that have the greatest potential for speed are platforms based on DNA and RNA, this is because these platforms do not require culture or fermentation but are based on synthesis [28]. According to

Nichole Lu, *et al.* (2020), although in its development the Sars Cov-2 vaccine with a new platform will have challenges which are:

First, the need to optimize the antigen design to obtain optimal immune response and this will continue to raise debates about the best approach.

Second, the need to monitor the appropriate experimental animal and strict safety in clinical trials to prevent the occurrence of adverse side effects from vaccines.

Third, there is a need for possibilities to improve protection, although a protective correlation can be inferred from experience with the SARS and MERS vaccines. It is important to continue to assess other matters, such as naturally acquired infections, the potential duration of immunity is unknown, single dose vaccine will provide immunity [28].

For new platform technologies, it is very important to know the viability of the vaccines being produced because most of them are not licensed, large-scale manufacturing has never been done, so the facilities capable of producing large quantities of product have not verified vaccine viability. It is important to develop vaccines using proven methods, even if they may take longer to enter clinical trials or produce large doses [28].

5. HCT

To accelerate the development of the COVID-19 vaccine, the final stage of testing has been replaced with human challenge testing (HCT). According to Jamrozik and Selgelid (2020), the Human Challenge Study (HCT) involves deliberate infection in study participants so as to accelerate vaccine development by providing rapid estimates of vaccine safety and efficacy [29]. However, the history and record of HCT is not extraordinary. According to Metzger *et al.* (2019) knowledge of infectious diseases has been acquired through human trials since the 18th and 19th centuries. A lot of totally unacceptable and unethical research has been conducted in these efforts. Like a research experimental in the year (1950–1965), at 'Willowbrook' a school for mentally handicapped children in the United States, injections were carried out to children with viral hepatitis to test for passive vaccination. Parents are not honestly informed about the risks of investigation to the children that are involved with the possibility of getting harm [30].

When viewed from an ethical perspective, it is against with that it to infect healthy person with a high-risk disease. It is known that Covid-19 has been recorded to cause a large number of severe illnesses to death around the world. Quoted from the NHS (2020) that Covid-19 hospitalized patients are around 45% not to mention those who will continue to need additional care in the long term after discharge. About 4% will need rehabilitation and 1% will need permanent nursing home care [31]. So it can be said that HCT testing will have a negative effect on the study participants, they can die or suffer permanent damage to the lungs, brain, or other organs. However, if the infection is mild or asymptomatic, the HCT test should be considered.

Based on the statement of Eyal *et al.* (2020) who explain that it allows people to be allowed to take serious risks, perhaps long-term illness or even death, but they note that risk-taking can be permitted in the current state. For example, we didn't stop firefighters from running into burning buildings and relatives were allowed to donate organs, which could result in their deaths [32]. The volunteers have the right to give their consent to take the risk or not. Chappell and Singer (2020: 2), in their writing that: it is permissible to expose some members of society (eg health workers or those who are economically vulnerable) to a certain level of ex ante risk in order to minimize the overall loss of the virus, it is permissible to expose volunteers who were fully informed of a comparable level of risk in the context of promising research on the virus [33].

If HCT is designated as a type of research, the research ethics committee (REC) should immediately evaluate it. Globally recognized standards and operational guidelines outside the legal requirements for ethical review are formulated for example in the Declaration of Helsinki, Guidelines for Good Clinical Practice files [34] and in the CIOMS guidelines (Council of International Organizations of Medical Sciences) [35].

Tambornino and Lanzerath (2020) state that there is a difference between the very high potential benefits from society and a very high potential risk for research participants / third parties so it is necessary to conduct an ethical review of COVID-19 HCT, there are 3 points that need to be considered which are [8] minimizing the risks, the appropriate approval and avoid high monetary inducements

6. Administration route

The route of administration plays an important role in the results of vaccination, where the method of administration will affect the level and quality of the immune response. Due to several vaccines cause different immune responses when administered to different mucosal pathways. There are various possibilities such as intranasal, pulmonary, oral routes that will be able to provide a much better quality than parenteral. This can be seen from the hepatitis B vaccine which can induce IgG titers when delivered to the inner lung but there are no titers when delivered intranasally, whereas in the influenza vaccine there is no difference in titers was observed between the delivery process to the lungs or to the nose [36]. Based on previous research, the development of an intranasal SARS-CoV vaccine candidate shows its eligibility as a covid-19 vaccine [37]. Vaccines that have received FDA approval are mostly given to the elderly and only cause systemic immunity. There is also no

commercial vaccine that uses the pulmonary route, so it can be concluded that oral and intranasal administration is the right choice to meet the needs of mucosal immunity. Flumist®, Fluenz®, and NasoVac® are 3 trademarks of intranasal vaccines that have been marketed.

7. Storage stability

Thermal stability is a major limitation and barrier in the distribution of vaccines worldwide. In addition, cold chain maintenance will affect 80% of vaccines financing and must be very careful in the transportation and storage which will lead to the vaccine being at a temperatures below + 2°C [38]. Niu L, *et al.* (2020) stated that the vaccines in liquid form should not be frozen because slow freezing creates tremendous pressure on the colloids. During the freezing process, water nucleation pushes the solute or particles into small volumes between the water crystals, which causes irreversible aggregation[39]. Some vaccines commonly used today require storage at + 2 and + 8 °C [40] .

Quoted based on zelogensma (2019) that some biological materials even require lower temperatures to maintain stability. In ZOLGENSMA® which is a gene therapy product based on vector-related adeno-linked virus (AAV) that requires storage conditions at a temperature of 60°C [41].

Formulation technology can increase vaccine thermostability, several parameters such as pH of the solution, ionic strength, redox potential will affect the chemical stability of the antigen and the stability of colloid suspension by changing these parameters will encourage stabilization, but of course not enough so that it requires additional stabilizers. One of them that can be used is arginine which is commonly used in formulations that contain protein, besides that arginine has the benefit of preventing aggregation. The use of an excipients is also able to stabilize the active ingredients during the manufacturing process, such as: the sugars used in the live-attenuated vaccines as a cryoprotectant to protect the lyophilization process [42].

Jieliang Wang *et al.*, (2020) stated that the lyophilized vaccines have better thermostability, because the stability of lyophilized biological products is better than biological products in liquid form. Lyophilized powder can be reconstituted before injection or used directly for inhalation or intranasal vaccination if it has good aerosol performance properties. Most vaccines are unable to tolerate slow freezing conditions especially those containing aluminum salts. The introduced TFF (Thin Film Freezing) was a solution to these problems[9]. Aso Y *et al.*, 2005 stated that In the TFF process, droplets of the vaccine suspension are dropped onto the frozen surface, and the small droplets are frozen sequentially of milliseconds (~ 10^2 K / s). The frozen pallets are then dried using a standard lyophilizer. Compared to slow freezing (for example, 1 K / min) where large ice crystals were formed, smaller ice crystals formed under conditions of rapid freezing (Fig. 2). The heat transfer direction, thickness and volume of thin films can also play a key role in reducing the forces generated during the freezing process[43]. So the TFF technology can be used to make dry powder of alum adjuvant without any aggregation or the possibility of loss of immunogenicity [44].

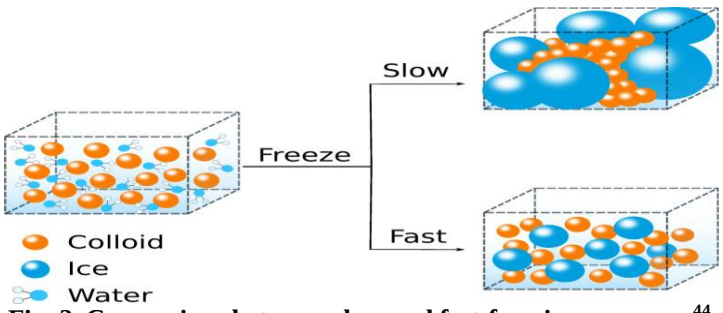

Fig. 2. Comparison between slow and fast freezing processes[44]

8. Mucosal immunity

The importance of the mucosal immune response is primarily to reduce nasal discharge, because vaccines that are currently being developed are used to prevent disease but do not necessarily reduce transmission, especially those from nasal discharge. Respiratory mucosal immunity is an important point for early clearance of severe acute respiratory syndrome coronavirus 2 (sars-Cov-2), so that immunity is trained to alveolarmacrophages and other innate cells [46,47,48,49]. Meanwhile, to achieve immunity sterilization on the mucosal surface is a big challenge, this is due to the release of virus and mucosal immunity in a short time so that a booster dose is needed. Xing *et al.* (2020) stated that the human serotype 5 adenovirus vector vaccine delivered to the respiratory mucosa induces alveolarmacrophages memory which are able to train immunity against heterologous infections [50]. But it is unclear whether pulmonary memory macrophages can be replaced by inflammatory monocytes in response to sars-Cov-2 [51]. In another study, it was stated that IN vaccines using live replication vectors or attenuated viruses could effectively induce local mucosal immunity so that the upper and lower respiratory tract is protected and reduced nasal discharge [52].

9.Immunopathology

The possibility of immunopathology is the main thing that must be considered in vaccines. The occurrence of vaccine-induced immunopathology has been proven based on studies of vaccine candidates in animal models. Apart from protecting host cells from pathogen attack, it is possible that antibodies can also mediate an increase in the pathogenesis known as enhanced antibody dependence (ADE). This phenomenon stems from the mediation of the crystallizable fragment (Fc) receptor which activates macrophages. Neutralizing antibodies block viral binding to receptors to protect host cells, non-neutralizing antibodies bind to their epitopes on the surface of the virus thereby directing the antigen-antibody complex to Fc receptor positive cells (such as macrophages) via the Fcantibody domain [53]. This activates macrophages to produce inflammatory cytokines, resulting in immune pathogenesis. Then the macrophage cells are distributed throughout the body, resulting in inflammation of various organs leading to organ failure. It is known that the interaction between T cells and macrophages is able to overcome the inflammatory response. However, the depletion of T cells allows macrophages to acquire an inflammatory response rate of [54,55,56].

Quoted from the article of Jiangqing xu (2020) it is known that specific non-receptor binding domain (RBD) antibodies are the main source for ADE; this is because it would be optimal to use RBDS as an immunogenous vaccine to reduce the potency of ADE. However, it is not yet known whether RBD alone will be sufficient to obtain neutralizing antibodies [6].

10.Spill Sars and Cov

It is possible that a similar Sars-CoV virus will emerge in the future from the animal reservoirs. So it is important to design vaccines for livestock that are used as intermediate hosts so that spills to humans can be suppressed. According to Linda J Saif (2020) a new approach is needed for to produce a vaccine capable of inducing heterologous immunity and producing broad cross-protection against CoV in each betaCoV lineage. Later we will focus on additional proteins (S2, N, etc.). The converted epitopes will result in a broader cross-reactive immunity and cross protection [5].

11. Efficacy of vaccine

The effectiveness of vaccines very needs to be validated based on the level of pre-existing immunity, in order to determine the vaccine response in various age groups in each population, especially in the elderly people with the high mortality rates [5]. The risk factor for anti-vaccine efficacy of the Sars-cOv-2 is mainly the lack of immunity. This can induce various diseases such as type II diabetes, metabolic syndrome, and cancer.

The cause of these diseases are due to weakness in the introduction of antigens, decreased quantity and function of immune cells, increased level / length and timing of changes in humoral immune components, reduced initiation of cellular responses, and impaired memory cells [57].

Other associations with immunodeficiency include age-dependent changes in humoral and immune cells; immunosenescence; malnutrition [58]; protein-energy-micronutrient deficit and telomere shortening [59]. In addition, the ineffectiveness of the vaccine in older adults [60] and children [61], especially in immunocompromised [62]. To develop an effective vaccine, it is important to understand the difference in immune response between asymptomatic, mild and severe cases and in the early and late stages of infection, and to understand why the elderly are so vulnerable to COVID-19, compared to young people who are protected better. It is estimated that 40-75% of infections may be mild or asymptomatic [63,64] and asymptomatic individuals may have significantly longer duration of viral transmission than the symptomatic counterparts [61]. Furthermore, asymptomatic and mildly ill individuals appear to develop low levels of antibody-mediated immunity, that has important implications for understanding herd immunity.

12.Potential duration

It is important to know the exact duration of the vaccine potency in various aspects such as vaccine-induced immunity that has a lifetime duration or a longer duration of immunity to naturally occurring infections. It should be noted that a single vaccine or an additional booster dose is capable of providing sufficient immunity but this can be found after further serum research studies and clinical studies in vaccinated populations [65].

13.Vaccine safety

The importance of ensuring the safety of the vaccine before it is marketed, to reduce the possibility of side effects from the vaccine itself. Vaccine safety will be determined by the platform selected, vaccine age and vaccine immunity. Matters reviewed include possible insecurity for vaccination of the respiratory mucosa against replicated live attenuated viruses or live vector vaccines [66].

The safety of vaccine was initially seen based on laboratory studies with rats or rabbits. If the test does not have a negative impact on the effect of the vaccine received, the testing process will be carried out at the next stage, that is in humans with the number of subject participants that continues to increase each stage [67]. There are 3 phases in which phase 1 with 100 healthy volunteers at this stage will see the safety of the vaccine

and the side effects that arise. In phase 2, the vaccine candidate is given to 1000 volunteers and phase 3 will experience an increase in test volunteers ranging from 1000-100,000 vaccine test participants. In each phase, the safety of the vaccine is looked at, which checks whether the vaccine is still safe after being given to the larger group, while the small group has no visible adverse effects.

The reason for the importance of the safety of this vaccine is based on existing experience. Because previously unwanted things had happened in the form of contamination with other viruses, but they didn't have a big impact. One of them was in 1955 and 1963 that the polio vaccine contained similan virus [68] (SV40) and also the rotavirus vaccine containing swine circovirus [69.70] , therefore it is important to check the purity and provide a sterile production lines. In other cases the antibodies produced from immunization induce worse disease, this is because when the antibodies come into contact with the virus, it encourages the entry of the virus into the cells and causes infection. such as influenza, dengue fever, zika, etc. However, the crona virus has yet to confirm that it will trigger the ADE mechanism [71].

IV. Conclusions

The large number of infections and deaths due to Covid-19 encourages a strong strategy in handling it, but no effective therapy has been found for Covid-19 which is already severe. The vaccine development will certainly be a solution that can be considered as a public health priority. Although there is a possibility that the pandemic will end before the vaccine is successfully marketed, vaccine development has the potential to prevent the same incident or the second wave of pandemics. So it is very important to develop promising vaccine candidates that will be stored and ready for use in the event of an outbreak or emergency situation. The development of a safe and effective vaccine against COVID-19 is the only way to save millions of human lives, and the only sure strategy out of the pandemic.

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Yasmin Azhar, et. al. " Opportunities and Challenges of Covid-19 Vaccine Production, A review." *IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*, 16(1), (2021): pp. 57-66.