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VACCINATION FOR CORONAVIRUS DISEASE 2019: OPPORTUNITY, HOPE AND CHALLENGES

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Abstract

COVID-19 continues to become a global threat. The development of COVID-19 vaccine has a potential to induce long-lasting cellular and humoral immunity and ending this pandemic. Currently, there are 213 vaccines in development, with 66 in clinical trials and 9 in phase III. In one hand the vaccines are developed using novel vaccine platforms including DNA and mRNA based, antigen-presenting cell, viral vector, protein or peptide-based, inactivated virus, and live attenuated virus platform. Each of these platforms has its own strength and weakness; however, they generally enable the vaccine to be developed safely, more quickly, and easier to upscale. In the other hand, the demand for COVID-19 vaccine has led to the development of vaccine being fast-tracked. Concerns are being raised for the efficacy, safety, equitability, and acceptance of these vaccines. Many are worried about the possibility of antibody-dependent enhancement that may worsen the recipient's condition. Vaccine design therefore should take into account previous experience with vaccine-associated disease enhancement. Researchers should adhere to stringent standards of safety and efficacy when conducting vaccine's clinical trials. Accelerated trials should also adhere to the Declaration of Helsinki for the ethics of medical research. Global partnership for vaccine development and equitable distribution is also needed to prevent resurgences of cases. Finally, there is a need to combat misinformation and distrust of COVID-19 vaccine in the eye of the general public.

Keywords: *SARS-CoV-2, COVID-19, vaccine, safety, efficacy.*

Introduction

Since its discovery in late 2019, SARS-CoV-2 infection has spread into the whole world. Until the writing of this review, there have been over 42 million cases, with more than and over 1.1 million deaths attributed to COVID-19 [*WHO, 2020a*]. So far, the five countries with most cases of COVID-19 are The United States of America, India, Brazil, Russian Federation, and Argentina. Meanwhile, Indonesia sits at the 17th place with around 380 thousand total cases with more than 13 thousand deaths [*WHO, 2020c*].

This unprecedented disaster has driven many countries to look for cure by repurposing older antiviral and parasiticidal drugs. Currently, there aren't any drugs yet proven to be effective against COVID-19. Drugs such as hydroxychloroquine and lopinavir/ritonavir have been shown to be ineffective. The antiviral drug remdesivir that was championed to beat the disease remained controversial due to the recent result of the interim report of Solidarity trial by WHO [*Pan H et al., 2020; WHO, 2020b*].

As more and more of these drugs failed to show benefit, researchers turn to vaccines as a potential solution for this pandemic [*Pan H et al., 2020; Poland G et al., 2020; Siemieniuk R et al., 2020*]. While potentially beneficial in preventing infection and inducing immunity in the population, there are many safety and ethical issues that need to be addressed when developing a vaccine. This is especially true as the urgent nature of this pandemic has driven many companies into a race for vaccine development. In this review, we would like to discuss important issues in COVID-19 vaccine development, their opportunities, hope, and challenges.

Phases of Clinical Trials for Vaccine Manufacturing

The phases of vaccine development and medicine development in general can be divided into preclinical, clinical, and post-licensure studies. The preclinical phase of vaccine development consists of exploring vaccine candidate and testing it on animals or in vitro tissue or cell culture. Exploration of vaccine candidate requires extensive studies about pathogen biol-

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ogy. In this stage researchers look for potential antigen molecules, the genetic diversity of said molecules, and the demographic of infection. Multiple ways of pathogen evasion from the immune system and the mutation rate for each potential antigen are studied and taken into account to produce an effective vaccine candidate [*Preiss S et al., 2016; Stern P, 2020*]. The vaccine candidates are then tested unto animals or cell culture to study the safety, their ability to provoke an immune response i.e. their immunogenicity, and their efficacy in inducing protection [*Preiss S et al., 2016; The College of Physicians of Philadelphia, 2020*].

The clinical phase studies the safety and efficacy of the vaccine candidate in the human population. This usually consists of 3 phases. Phase I study usually involves fewer number of healthy people (<100) focuses on safety [*Preiss S et al., 2016; Stern P, 2020*]. Phase II study focuses on finding the dose, dosing frequency and establishing proof of immunogenicity. This phase usually involves hundreds of people, which include people that shared characteristics with the target population for the vaccine. Phase III is a large scale randomized controlled trial focusing on whether the vaccination dose and schedule have the desired clinical effect or not. At all phases, the safety profile and the adverse effect of the vaccine must be documented. After phase III, the vaccine can be submitted for licensure.

Currently, there are 213 vaccines for SARS-CoV-2 in development, 66 of which are undergoing clinical trial, and 9 of which are in phase III [*Milken Institute, 2020*]. The whole process of vaccine development until licensure generally takes around 10 to 30 years to complete [*Preiss S et al., 2016; The College of Physicians of Philadelphia, 2020*]. However, during pandemic situation such as now, economic and political conditions are pressuring the development of COVID-19 vaccine as fast as possible. This has resulted in fast-tracking of vaccine development, such as carrying out clinical trials without established preclinical phase, or combination of phase I and II concurrently [*Jamrozik E, Selgelid M, 2020*]. This has raised concern for the safety of the clinical trial participants.

This might also yield vaccines with marginal efficacy [*Krause P et al., 2020*]. To be able to yield herd immunity COVID-19 vaccine must be at least 50% protective to those who take it, and should be given to more than 70% of the population. A vaccine with 10-20% protection will produce a false sense of security that will cause more infection [*Jamrozik E, Selgelid M, 2020; Milken Institute, 2020*].

There are some issues that researchers need to keep in mind to ensure an effective and safe vaccine. First is the establishment of a clear correlate for protection and not just immunogenicity [*Krause P et al., 2020*]. It is clear that for some pathogens, e.g. Hepatitis C, serological conversion or the presence of circulating antibodies after administration of vaccine doesn't always correlate with clinical protection [*Mauss S et al., 2014*]. The same must be ascertained for COVID-19.

Clinical endpoint also needs to be defined. If the clinical endpoint is set to be protection from asymptomatic infection, the clinical trials might result in underestimating the value of the vaccine, that is a vaccine that gives some protection might be falsely assumed as not effective [*Le T et al., 2020*]. However, if the clinical endpoint is set to prevent very severe disease, the value of the vaccine might be overestimated, that is a vaccine that doesn't prevent enough transmission might be falsely assumed as effective because it reduces incidence of critical COVID-19 [*Le T et al., 2020*].

There are also problems in selecting the sample for the clinical trials. COVID-19 pandemic has affected almost all country in the world and trials using only samples from certain country might not apply to other countries where racial diversity, poverty, and malnutrition rate differ [*Jeyanathan M et al., 2020; Krause P et al., 2020; Stern P, 2020*]. This is because the vaccine's efficacy is also influenced by the age, gender, ethnicity, and comorbidities of the recipients. Infants and elderly people, for example, are known to have a less robust immune reaction while showing more adverse effects [*Ciabattini A et al., 2018; Pichichero M, 2014*]. The children populations are particularly important to take note of. While it is true that children are less prone to get COVID-19 or to transmit it, this population still play some role in spreading infection [*Kelvin A, Halperin S, 2020; Li X et al., 2020*]. Few phase III trials include children as their participants, thus the effectivity and safety of the vaccines on these populations are less known [*Hodgson S et al., 2020; Hwang T et al., 2020*].

There are also some ethical issues especially in challenge trials where healthy people are purposefully infected with SARS-CoV-2. While such trials could potentially further accelerate vaccine development, health risk for participants and community should be considered [*Binik A, 2020; Evers D et al., 2015; Jamrozik E, Selgelid M, 2020*]. Researchers and health organizations should pay atten-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

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tion that the clinical trials do not violate the Declaration of Helsinki despite the urgent context of vaccine development [*WMA, 2018*].

VACCINE PLATFORMS FOR COVID-19

Vaccine platform is the vehicle used to deliver the pathogen's factors or properties which are expected to induce immune reaction from the host. In order to produce an effective vaccine more quickly and cheaply, the many COVID-19 vaccines now in development utilize vaccine platforms previously not available. These platforms have their own advantages and disadvantages; some are more efficacious or safe than others. The advantages and disadvantages of the vaccine platforms are summarized in table 1. More comprehensive list of COVID-19 vaccine in development can be found in the Milken Institute vaccine tracker [*Milken Institute, 2020*].

ATTENUATED VIRUS AND INACTIVATED VIRUS

Virus based vaccine consists of live virus or inactivated virus which is injected to the body of the host. Attenuation can be introduced by introducing mutations in key virulence factors, while inactivation of virus can be introduced by radiation, heating, or by chemical sterilization [*Kaur S, Gupta V, 2020; van Riel D, de Wit E, 2020*]. One disadvantage of this method for COVID-19 is the requirement of SARS CoV-2 grown under Biosafety level 3(BSL3) (27-29). Regardless, three vaccines based on inactivated virus are going through clinical trials. One of these vaccines is the Sinovac vaccine which Indonesia is currently one of the locations for phase III testing [*Zhang Y et al., 2020*].

Protein-Based Vaccine

Protein-based vaccine consists of purified proteins obtained from the virus, cells infected with the virus, recombinant cells that express viral protein. This type of vaccine usually requires more adjuvant in order to be sufficiently immunogenic. New technologies such as the Baculovirus Expression Vector System, has given this platform new life. Currently, this platform is the most used in COVID-19 vaccine development [*Kaur S, Gupta V, 2020; Pandey S et al., 2020; van Riel D, de Wit E, 2020*]. Target molecules include receptor binding domain of S, E, M and N proteins of SARS-CoV-2 [*Adalja A et al., 2019; Kaur S, Gupta V, 2020; Pandey S et al., 2020; van Riel D, de Wit E, 2020*].

VIRUS VECTOR-BASED VACCINE

This type of platform uses a recombinant virus such which contain genes for the desired antigen. This vaccine platform was previously used for MERS-CoV and Ebola vaccine [*Kaur S, Gupta V, 2020; van Riel D, de Wit E, 2020*]. The virus used as vector can be non-replicative or replicative. Non-replicative vector only delivers its genome and lets the cell synthesize the desired antigen in order to induce an immune reaction. Replicative vector uses attenuated but infectious virus. It does what a non-replicative vector does and then replicate and infect another cell, thus resulting in more cells producing the desired antigen. This comes with a risk of developing mild infection and cellular abnormality due to insertion of the vector recombinant DNA to the gene [*Søborg C et al., 2009; Pandey S et al., 2020; Zhu F et al., 2020*].

DNA AND RNA BASED VACCINE

Nucleic acid based technology is widely used technology for COVID-19 vaccine, due to the relatively short time needed to develop [*Kaur S, Gupta V, 2020*]. The platform is also very safe to produce because it doesn't need handling of infectious material [*Kaur S, Gupta V, 2020; Pandey S et al., 2020*]. DNA or mRNA of the desired antigen is inserted into host cell and the gene expression machinery of the host cell is expected to express the antigen, inducing an immune response. mRNA based vaccine is preferred over the DNA based because mRNA doesn't need crossing the nuclear membrane and thus faster in expression [*van Riel D, de Wit E, 2020*].

ANTIGEN PRESENTING CELL BASED VACCINE

This platform utilizes antigen presenting cells (APC), usually dendritic cells designed in vitro to present the desired antigen. The APCs are expected to induce cellular and humoral immunity in the host. This platform is not popular for COVID-19 due to the time needed to develop and multiple doses needed to induce effective immunity [*van Riel D, de Wit E, 2020*].

RACE FOR VACCINE AVAILABILITY

While multinational large companies are racing to produce a safe and effective vaccine, there is a concern that there wouldn't be enough vaccine produced for everybody. Developing countries fear that once vaccines are produced, they wouldn't have access to them. It is estimated that 67% of the total population (in Indonesia it translate to around 160 million people) need to be immune for herd immunity to develop. Therefore up scaling of vaccine production and equity of access for COVID-19 vaccine is very important to prevent resurgences of cases [*Le T et al., 2020; Roush K, 2020*].

One solution to this problem is a global partnership. In April 2020, WHO has launched Access to COVID-19 Tools (ACT) Accelerator, a global coalition that involves various philanthropist, scientist, research companies and health organization around the world. This coalition strives to not just accelerate vaccine's development but also upscale its production and ensure equitable access to COVID-19 tests, treatments, and vaccines [*Hsu Y et al., 2020*].

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Table 1

Advantages and Disadvantages of Vaccine Platforms (26,28)

Type of vaccine platform	Advantages	Disadvantages	Vaccine/Developer Example	Phase
Live attenuated virus	- High immunogenicity. - Usually doesn't require multiple doses	- Requires high biosafety level to produce - Risk of developing an infection, spontaneous recombination and mutation, reverting to more infectious state - Cannot be used for infants, pregnant, or immunocompromised people - Requires cold chain	- Indian Immunological Ltd (11) - CDX-005/ Codagenix, Serum Institute of India (11)	- Preclinical - Preclinical
Inactivated virus	- Less risk of developing infection nor spontaneous mutation - Has already been tested for previous viruses such as SARS CoV	- Requires high biosafety level to produce - Requires booster to maintain immunogenicity	- Sinovac/Institutio Butantan/Biofarma (30) - Wuhan Institute of Biology/Sinopharm (33)	- Phase III (NCT04582344, 669/UN6.KEP/ EC/2020) - Phase III TR2000034780, NCT04560881)
Protein-based	- Rapid development due to new technology such as Baculovirus expression vector - Less adverse effect - Safe to produce	- Lower immunogenicity - Uncertain long-lasting protection	- Novavax, Emergent Biosolutions, Praha Vaccines (34)	- Phase III (EudraCT 2020-004123-16, NCT04583995)
Replicative viral vector	- Has a good history of use for MERS CoV - Safe to produce - The vector can act as adjuvant thus inducing good immune response	- The host might already have immunity against the vector, rendering it less effective for such population - Possible to induce antibodies to the viral vector and diminish the efficacy of the booster vaccine - Possible carcinogenesis due to vector DNA incorporation into host	- Institut Pasteur, Themis, University of Pittsburgh CVR, Merck Sharp & Dohme	- Phase I/II (NCT04497298, NCT04498247)
Non-replicating viral vector	- Safe to produce - Less adverse effect than replicative viral vector - The vector can act as adjuvant thus inducing good immune response	- No previous vaccine has been approved using this method - Less immunogenicity than replicative viral vector - The host might already have immunity against the vector, rendering it less effective for such population	- CanSino Biologics, Beijing Institute of Biology (32) - Gamaleya Research Institute (35) - AZD 1222 (formerly ChAdOx1)/ Oxford University, AstraZeneca	- Phase III (NCT04566770, NCT04568811) - Phase III (NCT04564716, NCT04587219) - Phase III 06922165132)
DNA based	- Temperature stable - Simple, quick, and safe to produce - Cost-effective	- Some risk of recombination causing abnormality - Lower immunogenicity - Requires additional carrier or device to insert into cell	- INO-4800/Inovio Pharmaceuticals (36)	- Phase I/II (NCT04336410, NCT04447781)
mRNA based	- Simpler than DNA based vaccine to produce - Safe to produce - Cost effective	- Less stable than DNA based vaccine - Requires efficient carrier to insert into cell - Low immunogenicity	- mRNA1273/Moderna, National Institute of Health (37) - BNT162b2/BioNTec, Pfizer, Fosun Pharma (38)	- Phase III (NCT04470427) - Phase III (NCT04537949)
APC based	- Potential to induce cellular and humoral immune response	- Longer develop time - Requires cold chain - Requires more complicated administration to the host.	- aAPC Vaccine/ Shenzhen Genoimmune	- Phase I (NCT04299724)

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The "Solidarity Trial" held by WHO also helps to gather participants for clinical trials from around the world, especially from where the burden of this pandemic is large. While the primary purpose is to lower sampling bias, this also pushes for collaboration of lower-income countries paving the way for more equitable access for vaccines. The Solidarity Trial also facilitates the testing of multiple vaccines by using a pooled/common control, thus making the process more efficient [*Krause P et al., 2020*].

PASSIVE IMMUNIZATION/ADOPTIVE IMMUNITY

Passive or adoptive immunity can be achieved by using the sera of patients who recovered from COVID-19 (convalescent plasma therapy). Because it is believed to contain polyclonal antibodies directed to several natural epitopes of SARS-CoV-2, this approach had been tried in the management of COVID-19 patients as an empirical therapy [*WHO, 2014*]. It's consideration was based on the experiences in the past with SARS, MERS, H1N1-pandemic, measles, etc. [*Cheng Y et al., 2005; Hung I et al., 2011; Ko J et al., 2018*]. The efficacy of the convalescent plasma (CP) therapy is depended on its ability to antibody-neutralization of the virus, to opsonize the circulating virus in the blood, to accelerate the infected cells clearance, and to block the new infection.

The evaluation of several studies concerning the potential of CP as a therapeutic tool has been conducted [*Ahn J et al., 2020; Duan K et al., 2020; Shen C et al., 2020; Zhang B et al., 2020*]. Patients who involved in these studies usually were in critically ill condition, had many co-morbidities such as hypertension, cardiovascular disease, obesity, chronic kidney disease, or cerebrovascular diseases; they were all needed ICU admission for mechanical ventilation, or extracorporeal membrane oxygenation, or high-flow nasal canulla oxygenation. It has been shown that its administration for the critically ill patients led to the improvement of the clinical condition of almost all patients with reduced death rates. Patients in the treatment arm exhibited a significant difference in the clinical parameters (body temperature normalization, pulmonary lesions and ARDS resolution, weaning off the mechanical ventilation, etc.), laboratory parameters (levels of CRP, procalcitonin, IL-6) [*Ahn J et al., 2020; Duan K et al., 2020; Zhang B et al., 2020*]. There were also patients who experienced viral seroconversion after 7-37 days of CP therapy [*Shen C et al., 2020*]. The only problem for these studies is the lack of controlled or randomization of the study subjects, that impede the researchers to come to a conclusive statement. Further evalution in clinical trials is needed and is currently ongoing [*Yan X, 2020*].

THE EXPECTED IMMUNE RESPONSE TOWARD THE VACCINES

As a major antigen, the S protein of SARS-CoV-2 is a potential target for the vaccine. The protein is located on the outer side of the virus and vital for the ability of viral infection. Previous studies using both SARS-CoV and SARS-CoV-2 also showed that antibodies against receptor-binding domain of S protein have strong neutralizing capacity [*Jeyanathan M et al., 2020*]. Except for the D614G mutation, which now has become the most prevalent genotype, there seems to be low variation in the S protein [*Duan L et al., 2020; Jeyanathan M et al., 2020*]. It is no surprise that most vaccines in development use this molecule as their target.

In order to understand the expected immune response towards COVID-19 vaccination, some fundamental concept of natural infection with the virus must be appreciated. Firstly, SARS-CoV-2 infects cell through the interaction of the receptor-binding domain of the spike (S) protein with the angiotensinogen converting enzyme-2 (ACE2). Assistance from serine protease such as TMPRSS2 is needed [*Duan L et al., 2020; Jeyanathan M et al., 2020*]. Secondly, it seems that SARS-CoV-2 suppresses the innate immunity by a yet unknown mechanism. This can be seen from the low level of plasmacytoid dendritic cells, type 1 interferons, and the delay of activation of adaptive immunity by APCs in severe COVID-19 patients [*Duan L et al., 2020*]. This suppression might also explain why elderly immunosenescent patients who have a weaker immune system have a more severe disease course [*Duan L et al., 2020; Jeyanathan M et al., 2020; Poland G et al., 2020*]. The less robust innate antiviral response will cause a higher viral load which will overwhelm the adaptive immune system and provoke excessive secretions of cytokines in the later course of the disease.

Thirdly, SARS-CoV-2 also seems to inhibit the adaptive immunity, especially the Th1 response. This inhibition can be seen from the low level of CD8+ lymphocyte more prevalently seen in severe cases of COVID-19 [*Jeyanathan M et al., 2020; Poland G et al., 2020*]. The roles of Th2 and antibody-mediated immunity remain to be understood (Figure 1), as patients with mild or asymptomatic disease usually have lower antibody titer than those with severe disease [*Jeyanathan M et al., 2020; Poland G et al., 2020*]. However, this might also be attributed to higher viral load in severe diseases which induce a more pronounced Th2 response. However, it is still generally accepted that high neutralizing antibodies titer confers protection to the patients [*Jeyanathan M et al., 2020*].

Vaccines against COVID-19, therefore, are expected to induce both innate and adaptive immune sys-

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tem in the host. Ideally, vaccines are expected to prime the innate immune system, inducing the so-called "trained immunity" by which immune response against future pathogen invasion is upregulated [*Netea M et al., 2020; Zhou R et al., 2020*]. Vaccines are also anticipated to provoke adaptive immunity, generating sufficient neutralizing antibodies that prevent interaction between the S protein and the ACE2 protein. More importantly, vaccines should ideally induce adaptive cellular immunity and generate enough CD8+ T lymphocytes, which will destroy infected cells [*Jeyanathan M et al., 2020; Poland G et al., 2020*]. All of these will result in reduction of the viral load and prevention of dysregulated cytokine secretions.

Opportunities and Challenges

Overall, vaccines have a potential to end this pandemic. In the best-case scenario, an effective vaccine will stimulate long-lasting cellular and humoral immune response just by one injection. The generation of memory T cells will ensure CD8+ T cells that can kill virus-infected cells [*Kaur S, Gupta V, 2020; Pandey S et al., 2020; van Riel D, de Wit E, 2020*]. The generation of memory B cells will ensure antibody with sufficient titers to neutralize and opsonize circulating virus [*Kaur S, Gupta V, 2020; Pandey S et al., 2020; Roush K, 2020; van Riel D, de Wit E, 2020*].

However, on the other side, there are also risk that the vaccine might not work effectively against the

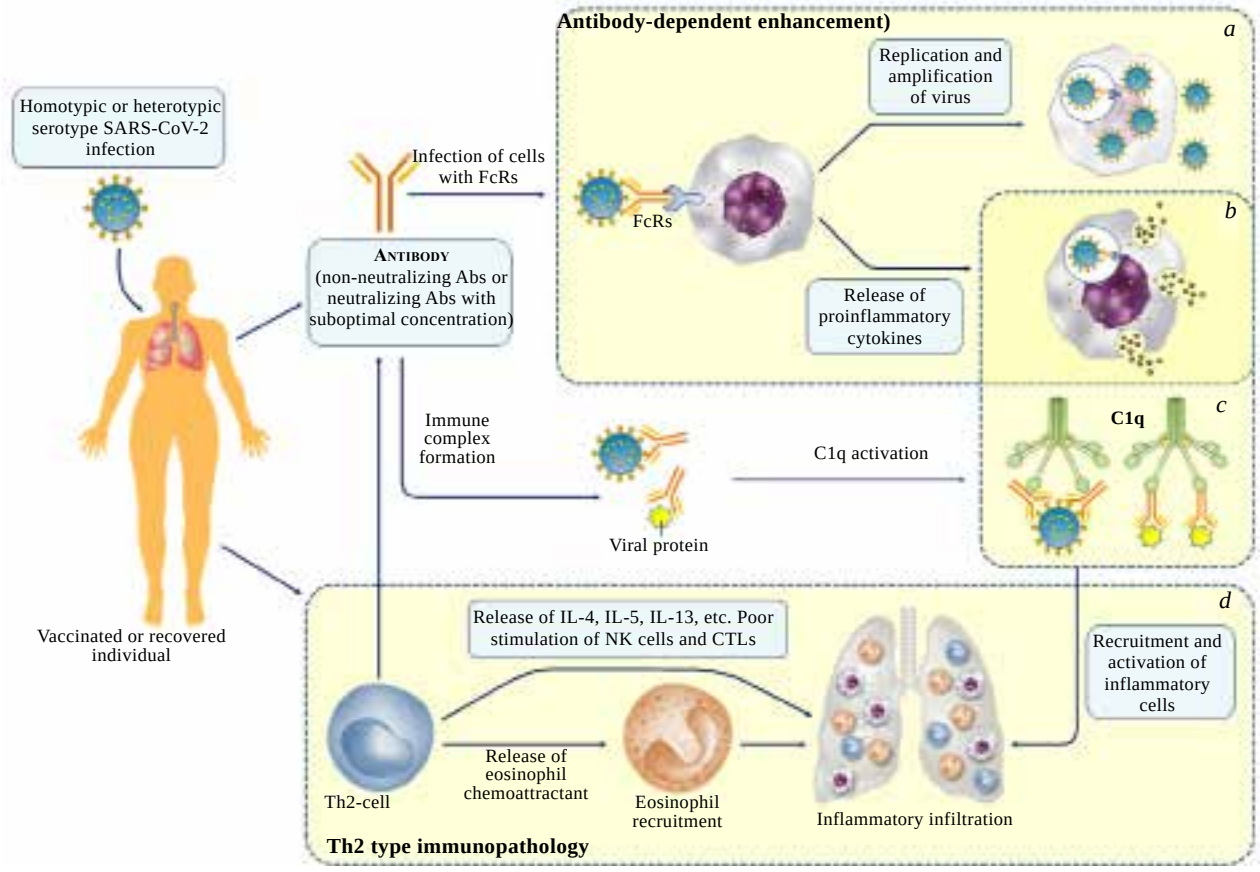

Figure 1. *Vaccine-associated disease enhancement*

Homologous SARS-CoV-2 infection will be blocked by neutralizing antibodies (Abs) resulted either from previous natural infection or vaccination. Heterotypic serotype virus infection might cause non-neutralization by the preexisting Abs. Vaccine-associated disease enhancement may occur through two different mechanisms, i.e. induction of non-neutralizing Abs or suboptimal concentration of neutralizing Abs, or Th2-biased immune response and immunopathology. Virus-antibody complexes bind to Fc receptor on the surface of immune cells such as monocyte-macrophage and dendritic cells. This will enhance virus uptake and viral load termed "antibody-dependent enhancement" (ADE) **(a)**. The virus may evade the killing process and replicate within the cells and disseminate, or may induce the release of proinflammatory cytokines **(b)**. Antigen-antibody complexes can also activate the complement pathway which further increase the inflammatory responses **(c)**. Th2-biased immune response will induce the secretion of type 2 cytokines (IL4, IL-5, IL-13) as well as eosinophil chemoattractant, resulting in eosinophil infiltration and proinflammatory cytokine production in the lung. Moreover, the Th2 type immune response can lead to poor stimulation of Natural killer cells and $CD8^+$ cytotoxic T lymphocytes (CTLs). Both events will result in unchecked viral replication and hyperinflammatory condition which eventually lead to acute lung injury or acute respiratory distress syndome **(d)**. This figure was redrawn and modified from Su S.and co-authors [*Su S, Du L, Jiang S. , 2020*].

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virus. SARS-CoV-2 is an RNA virus which has a higher propensity for mutation. Mutation in targeted antigen will render a vaccine less effective. COVID-19 vaccines also use new platforms, some of which have undocumented safety profile [*Le T et al., 2020*].

The possibility of antibody-dependent enhancement (ADE) must also be considered. In ADE the presence of non-neutralizing antibodies or antibodies at sub-neutralizing levels paradoxically will worsen the progression of the disease. The presence of antibodies against a virus will facilitate virus entry into macrophages through the FcγRII (Figure). Stable antibody-virus interaction will end up in virus destruction. However, in the case of weak binding from non-neutralizing antibodies, the virus can escape and replicate. These will result in higher viral titer and the release of more immune mediators such as IL-6 and IL-10 [*Khandia R et al., 2018; Zaichuk T et al., 2020*]. This phenomenon has been observed in multiple viruses such as Dengue virus, Zika Virus, SARS-CoV-1 and MERS-CoV [*Khandia R et al., 2018; Lee W et al., 2020*]. There are concerns that the new COVID-19 vaccines might induce ADE and cause a more severe disease such as the case with Dengvaxia in the Philipines recently [*Bhopal S, Nielsen M, 2020*]. However, it should be noted that (fortunately) there has not been any report of ADE in the result of all phase I/II vaccine clinical trials, in trials using non-human primate, nor in clinical trials using convalescent plasma therapy [*Lee W et al., 2020; Wen J et al., 2020*]. There are much more to understand about the role of ADE in causing severe COVID-19. Currently, there haven't been any clinical feature nor biomarker that is useful to distinguish severe infection from ADE. Further research in this matter is surely needed [*Arvin A et al., 2020; Lee W et al., 2020*].

Although ADE seems to play a lesser role in causing severe COVID-19, previous experiences with vaccine-associated disease enhancement such as RSV, SARS CoV, and Dengue vaccines could still teach us valuable lessons (Figure) [*Bhopal S, Nielsen M, 2020; Su S et al., 2020*]. The vaccine should be able to induce high titer of neutralizing antibody since subpar concentration of antibody might induce ADE such with the case of Dengue and SARS CoV vaccine [*Bhopal S, Nielsen M, 2020; Su S et al., 2020*]. Th2-biased response should be avoided as it is more associated with severe disease both in RSV and COVID-19. This can be done by avoiding adjuvants that are associated with Th2 activation such as alum and instead using Th1-biased adjuvants [*Bhopal S, Nielsen M, 2020; Su S et al., 2020*].

Finally, the acceptance of the general public is also a concern. The general population is scared about the safety of the vaccine in this hastened state of development. One study in Israel reported that only 75% of the general population is willing to be vaccinated for COVID-19. At the same time, only 78% of doctors and 61% of nurses are willing to be vaccinated [*Dror A et al., 2020*]. The people's trust and confidence in researchers and health professionals play an important role in reducing this vaccine hesitancy. Health professionals and researchers should maintain good communication and assure the people that the highest safety and efficacy standards are being used in this accelerated vaccine development [*Bhopal S, Nielsen M, 2020; Dror A et al., 2020*]. For this reason, the Coalition for Epidemic Preparedness Innovations and other organizations had held a scientific working meeting on March 2020 to discuss about the designs of the vaccine that will reduce the safety concerns and recommend the desired animal models and assessment of the immunologic response in phases of clinical trials to determine the dimension of the risk [*Lambert P et al., 2020*].

As COVID-19 continues to be a global threat, a safe and effective vaccine can be one of the greatest weapons to finally end this pandemic. However, many uncertainties about the efficacy, safety, equitability, and public acceptance of the vaccine remain. With the development of many vaccines entering phase III, we hope that these uncertainties be answered with satisfactory result.

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