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The Perspective of Covid-19 Vaccines: What Needs to Be Known and Its Expected Effect on the Human Population?

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Abstract

Background: The COVID-19 pandemic is a devastating blow to the entire world community and changes the order of human life. **Purpose:** All efforts and strategies are being carried out to contain and reduce the spread of the SARS-CoV-2 virus by tightening the health protocol and using vaccines for the public. Currently, several vaccines are available and have passed phase 3 clinical trials, such as vector vaccines (Gamaleya Sputnik V Russia, University of Oxford/AstraZeneca, CanSino, and Janssen Pharmaceutical Companies), mRNA-based vaccines (Moderna/BioNTech/Fosun Pharma/Pfizer), inactivated vaccines (Sinovac and Sinopharm from China, Covaxin from Bharat Biotech India) and adjuvanted recombinant protein nanoparticles (Novavax from the USA), which are expected to be able to suppress the spread of the virus and produce a minimum of 70% herd immunity in a population. This study uses a narrative review from reputable publications and is closely related to the topic. **Result:** Each vaccine's efficacy varies from the lowest, namely, the Sinovac vaccine (CoronaVac) 50%, to the highest the Novavax vaccine (NVX-Cov2373) 96% effectivity value. However, further rigorous research is still being carried out to develop an effective and efficient vaccine. Health workers are the last bastion to handle COVID-19 patients. **Conclusion:** The primary purpose of the present immunization is to prevent and minimize the spread of COVID-19. At this time, the availability of a variety of vaccines is expected to provide strategic answers to the pandemic scenario that has afflicted countries all over the world.

Keywords

Vaccine Development and Manufacturing, COVID-19, SARS-COV-2,

Vaccine

1. Introduction

The vaccine strategy is an appealing and effective medical approach for controlling the coronavirus type 2 that causes a severe acute respiratory syndrome, stopping its spread, and protecting patients who are at high risk of infection [1]. The vaccination process has taken place in all countries, including Indonesia and Malaysia. Vaccination is anticipated to provide herd immunity to a minimum of 70% or 80% of the population [2].

The evaluation of patients positive for SARS-CoV-2 revealed that the antibody binder and leading bidders targeted receptor-binding domain subunit S1 (Spike 1) [3]. One of the main challenges when making vaccines is how effectively the vaccine can generate an immune response in the human body instead of the vaccine's safety. Characteristic responses such as immunity include the formation of neutralizing antibodies, the construction of T cell responses, and the prevention of disease following immunization (response induced by the vaccine causes an increase in the severity of illness) [4]. Innate immunity, which serves as our immune system's initial line of defense, is critical in defeating SARS-CoV-2 [5].

Medically and biologically, the genetic variety of viruses that result from mutations is very important because it has a big impact on how infectious diseases are prevented and how they can be treated, as well as how vaccines are used [6]. At present, the dominant circulating variant in spike protein mutations of the virus from Britain (B.1.1.7, deletion 69 - 70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, and there are mutations in other genomic regions as well), South Africa (B.1.351) and Brazil (P.1) [7] are facilitating rapid viral spread [8] [9] that may interfere with the effectivity of the vaccine program.

COVID-19 Vaccine Development

Vaccines have prevented measles, polio, hepatitis B, and many others as preventive infectious diseases in recent decades. People who get vaccines have a much lower risk of getting sick because they teach the immune system how to look for and fight pathogens like viruses or bacteria [10]. Vaccine development has several clinical stages before being used in humans.

The steps were preclinical studies, clinical trials (Phases I, II, III), marketing surveillance, and human challenge studies. The vaccine is tested in animals for efficacy and shows safety in the preclinical step. In a clinical trial, the vaccine was tested on a small healthy group (Phase I) and then a large group (Phase II) to thousands for efficacy and safety (Phase III) [11]. Ongoing studies after the vaccine are approved and licensed; Phase IV is used to monitor adverse events and study the vaccine's long-term effect on the population. In the last phase,

studies are given, followed by pathogen administration which the vaccine is designed to protect. Such trials are uncommon in people, as they present considerable ethical challenges [12].

Most research on the COVID-19 vaccine shows that there are more differences in vaccine development. Normal vaccine development for each step-in sequence but fast-track vaccine development for COVID-19 were performed in parallel [13]. This affects several things, such as the financial risk for the industry to product effectiveness and efficacy (**Table 1**).

There are many different COVID-19 vaccines in development using other technologies. New manufacturing platforms, structure-based antigen design, computational biology, protein engineering, and gene synthesis have provided tools to make vaccines with speed and precision. Antiviral vaccines were classified into two broad categories. Gene-based vaccines deliver gene sequences that encode protein antigens produced by host cells [10]. These include live virus vaccines, recombinant vaccine vectors, or nucleic acid vaccines. Protein-based vaccines include whole-inactivated viruses, individual viral proteins or subdomains, or viral proteins assembled as particles, all of which are manufactured in vitro. Recombinant vaccine vectors and nucleic acid vaccines are best suited for speed because they can be more easily adapted to platform manufacturing technologies in which upstream supply chains and downstream processes are the same for each product. Precision is achieved by knowing the atomic structure of the vaccine antigen and that the targeted epitopes are preserved in the vaccine [16].

Table 1. Advantages and disadvantages of vaccine development methods [14] [15].

Vaccine	Advantages	Disadvantages
Viral vector	Highly an innate immune response, induction of T cell immune responses, and cell B. Widely used for MESR-COV.	Induction of anti-vector immunity: cell-based manufacturing. It is integrating into the host genome and induces cancer.
DNA vaccine	Not contagious; shortly stimulation of the innate immune response; free cell and egg; stable, fast, and scalable production; clicking the induction of T cell immune response and B.	Potential for integration into the human genome; low immunogenicity in induces anti-immunoglobulins synthesis.
RNA vaccine	Degradation is natural in the body, not contagious, does not integrate into the human genome, is a noncell egg virus, fast, and scalable production; shortly stimulation of the innate immune response; clicking the induction of T cell immune responses and cell B.	Potential for instability reactogenicity reported.

The method of COVID-19 manufacturing is not yet known, which one will be effective and safe. Data from the global COVID-19 R & D landscape include 115 vaccine candidates, of which 78 are confirmed as active and 37 are unconfirmed, and of the 78 confirmed, active projects, 73 are currently at exploratory or preclinical stages [17]. The WHO data show that as of 26 December 2020, there were 56 COVID-19 vaccine candidates in the clinical evaluation, of which 13 were in Phase III and 166 candidates in the preclinical evaluation. Of the 13 in phase III, four submitted data to regulatory authorities for emergency authority use.

In Indonesia, the Minister of Research and Technology has prepared a 'Merah-Putih' vaccine derived from the domestically made S subunit vaccine. In its construction, the government involved *BioFarma*, the Eijkman Institute, the Indonesian Institute of Sciences (LIPI), and four major universities. the production journey is still in the preclinical stage; to reach stage III, it will be carried out in 2022 [18] as SARS-CoV-2 is like the highly pathogenic SARS-CoV and MERS-CoV, experiences in the development of vaccines against other beta coronaviruses may facilitate COVID-19 vaccine development [19]. There are many types of COVID-19 vaccines in action using different technologies. Different types being tested include recombinant protein subunit vaccines, nucleic acid vaccines, viral vector vaccines, inactivated viruses, and live attenuated vaccines [20].

A live attenuated vaccine is a conventional method that has a long story of successful application in smallpox and polio. Live attenuated live more like natural infections with a wide range of natural viral antigen production over a long period and are often more immunogenic than nonreplicating vaccines. One live vaccine that improves the immune system and decreases SARS-CoV-2 is the Baccile Calmette-Guerin (BCG) [16] [21] [22]. During the early development of SARS-CoV vaccines, inactivated virus vaccines were once a leading strategy. Studies using UV and formaldehyde-inactivated SARS-CoV can induce neutralizing antibody response, and phase I clinical trial using β-propiolactone inactivated SARS-CoV-2 vaccine demonstrated that it is safe, well-tolerated, and can elicit SARS-CoV-2 specific neutralizing antibodies [23]. The inactivated vaccine for Sinovac also showed safety and effectiveness in producing IgG and reducing virus titters and pathological changes in the lungs without observable antibody-dependent enhancement of infection [22].

Nucleic acid vaccines are genetic vaccines consisting only of DNA or RNA, which are taken up and translated into protein by host cells and elicit immune responses. Because they contain nonviral coats, naked nucleic acids are not generally subject to pre-existing immunity, which can hamper the clinical efficacy of recombinant virus vaccines [24]. mRNA is a minimal and transient information carrier. It does not interact with the host genome, is safe, and can be manufactured rapidly. Any protein can be encoded and expressed by mRNA, which offers maximum flexibility concerning, the development of vaccines for infectious diseases and cancer and protein replacement therapies [25]. Vaccine products from this method include Moderna, BioNTech/Pfizer, Curevac, Arc-

turus, Academy of Military Sciences of China, Chulalongkorn University, and AstraZeneca/Shenzhen Kangtai, which have entered clinical trials [22].

Protein subunit vaccines comprise purified immunogenic proteins or peptides derived from viruses. In contrast with traditional vaccines, subunit vaccines have fewer side effects and higher safety at the injection site [26]. However, whether immunological memory will be formed correctly is not guaranteed. Therefore, adjuvants and vaccine delivery systems are needed to enhance immune response candidates that constitute minimal structural components of SARS-CoV-2 that can prime protective immune responses in the host when administered with molecular adjuvants for enhanced immunogenicity. For example, contemporary SARS-CoV-2 subunit vaccine candidates are formulations of full-length S protein or S1/S2 subunits with adjuvants. The front runner among developers is Novavax, which initiated a Phase I/II trial on 25 May 2020 [27]. Additionally, Sanofi Pasteur/GSK, Vaccine, Johnson & Johnson, and the University of Pittsburgh announced that they expected to begin.

Viral vector vaccines effectively introduce genes encoding viral antigens into host cells. The infected cells produce and release immunogenic antigens within a certain period after vaccination [28]. Subunit vaccines and protein-induced immune responses are usually short-lived, and consequently, multiple injections are typically required to induce and maintain a systemic immune response [22]. Several viral vectors for CoV vaccines have been developed, such as adenovirus (AdV), modified vaccinia virus Ankara (MVA), measles virus (MV), Venezuelan equine cephalitis virus (VEE), vesicular stomatitis virus (VSV), Newcastle disease virus (NDV), rabies virus (RV), RSV, and others [29]. Through November 3, 2020, 18 replicating viral vector vaccines and 26 nonreplicating viral vector vaccines were under development for COVID-19. The former is designed mainly for measles virus, VSV, influenza virus, avian paramyxovirus, and NDV. The latter is based mainly on human adenovirus types 5 or 6, chimpanzee adenovirus, parainfluenza virus 5 (PIV5), influenza virus, AAV, and MVA [30].

2. Discussion

The vaccination movement on the global population can have a positive effect on overcoming the damaging effects of the COVID-19 pandemic; even with minimal protection against infection, vaccination can have a significant influence on preventing COVID-19 outbreaks [31]. There is an enormous direct development of vaccine candidates to prevent COVID-19 transmission, consisting of 84 trials that are still in clinical evaluation (15 of them have been in phase 3 and 5 vaccines in phase 4 clinical trials) and 184 in preclinical analysis with different routes of administration, doses, and schedules (**Table 2**).

Some vaccines that are currently and have passed phase 3 clinical trials are vector vaccines (Gamaleya National Research Centre for Epidemiology and Microbiology, University of Oxford/AstraZeneca, CanSino Biological Inc/Beijing Institute of Biotechnology, and Janssen Pharmaceutical Companies), mRNA-based

Table 2. Number of doses, intervals, and route of administration of vaccine candidates.

Doses and Interval	Vaccine in Development
One dose;	**13**
Day o	13
Two doses;	**51**
Day o + 14	6
Day o + 21	19
Day o + 28	26
Three doses;	**1**
Day o + 28 + 56	1
Administration	
Oral	**2**
Injection;	**69**
SC/Sub-Cutaneous	3
ID/Intra-Dermal	3
IM/Intra-Muscular	63

vaccines (Moderna/National Institute of Allergy and Infectious Diseases and BioNTech/Fosun Pharma/Pfizer), inactivated vaccines (Sinovac, Wuhan Institute of Biological Products/Sinopharm, Beijing Institute of Biological Products/Sinopharm, and Bharat Biotech) and adjuvanted recombinant protein nanoparticles (Novavax) [1] [32] [33] [34].

Each type of vaccine has a different level of efficacy. This can be caused by several factors, including viral mutations, the dynamics of immune cells responsible for developing immunity when exposed to the SARS-CoV-2 virus, or viral-derived antigens such as vaccines [35]. There's a good chance that the severity of this disease is determined by a complex interaction between the host, virus, and environment, which results in varying clinical outcomes [36] [37]. Although in one study, viral vector-based COVID-19 vaccines lower local side events than mRNA-based [38].

2.1. mRNA Vaccine

In clinical trials, mRNA-based vaccines were more than 90% effective against SARS-CoV-2, such as Moderna/BioNTech/Fosun Pharma/Pfizer. Although the vaccine may have side effects, this vaccine has high effectiveness, despite the local and systemic reactogenicity to the mRNA vaccine. The advantages of mRNA vaccines are the speed of vaccine production (only a few weeks) and the ability to generate a T_H2 and T_H1 response [39]. T_H1 cells are required for the host's defense against intracellular infections. In contrast, T helper 2 (T_H2) cells organize beneficial to type 2 immune responses, such as those against helminths and tis-

sue repair, contributing to chronic inflammatory disorders [40]. T_H2 and T_H1 should be balanced; If a patient's T_H1 immune response is incorrectly organized, an increased immune response leads to a cytokine storm that triggers T_H2 cells, with a poor prognosis [41].

2.2. Virus Vector Vaccines

Currently, approximately 25 research groups are working on a viral vector vaccine. Viruses such as rubeola or animal viruses are genetically designed to produce coronavirus proteins within the body. There are two types: people who will still replicate in cells and people who cannot because a key gene has been deactivated [42]. The use of adenovirus vaccines has been used in the USA and Europe, and two vaccines have shown promising initial results, namely, the Serotype 26 adenovirus vector vaccine (Ad26.CoV2. S; Johnson & Johnson) and the ChAdOx of the Chimpanzee adenovirus vector vaccine (AstraZeneca) (Creech *et al.*, 2021). Both vaccines have efficacy in preventing hospitalization and death of patients with COVID-19, but they are still not maximal in preventing diseases caused by the new variant SARS-CoV-2 [39]. The Sputnik V vaccine (Gam-COVID-Vac) uses a combination of rAd type 26 (rAd26) and rAd type 5 (rAd5) vaccine vectors, rAd26-S, and rAd5-S given separately intramuscularly at 21-day intervals. Gam-COVID-Vac has 91.6% efficacy in preventing COVID-19 infection [32].

2.3. The Vaccine-Inactivated

Inactivated or killed vaccines made from cultured and then chemically inactivated viruses are one path to vaccine production, which can produce native antigenic epitopes (binding to T cell and B cell antibodies) expressed in a stable and conformational manner [43]. One approach used in the production of vaccines from the killed virus is using beta-propiolactone, especially for the vaccines developed by Wuhan Institute of Biological Products/Sinopharm, Beijing Institute of Biological Products/Sinopharm, and Sinovac/Instituto Butantan/BioPharma [22]. Sinopharm and Sinovac are two companies working on this form of the vaccine, which has been tested in a phase 3 trial and received international approval for use as a COVID-19 vaccine [39].

Bharat Biotech (BBV152/Covaxin) from the Indian vaccine industry has succeeded in making a vaccine derived from the intact virion of the SARS-CoV-2 virus that has been killed (inactivated virus). Based on phase 3 clinical trials, the Covaxin vaccine showed high clinical efficacy (81%) against COVID-19, as well as high immunogenicity against some of the variants [44]. The presence of the additive/adjuvant *Algel-IMDG* can increase the immune response of T cells to COVID-19, which leads to long-term protection [30].

2.4. Subunit Vaccine Proteins

As a recombinant protein subunit, Protein S is another approach to vaccine development. This method may protect immunized animals *in vitro*, but it can

Table 3. Types of vaccines circulating in various countries.

Vaccine	Mechanism	Efficacy	Dose	Storage	Country of Origin
Moderna (mRNA-1273)	mRNA Vaccine Encapsulated. The mRNA encoding against the protein spike is protected in lipid nanoparticles (soap bubbles). Once absorbed, cells express spike protein resulting in immune response (immunogenicity).	94% (original strain)	0.5 ml divided into two doses, each dose for 28 days.	−20˚C = 6 months 2˚C - 8˚C = 30 days	USA [1]
BioNTech/Pfizer (BNT162b2)	mRNA Vaccine Encapsulated. The mRNA encoding the protein spike is protected in lipid nanoparticles (such as soap bubbles). Once absorbed, cells express spike protein resulting in immune response (immunogenicity).	95% (original strain)	0.3 ml divided into two doses, each dose for 21 days.	−70˚C = 6 months 2˚C - 8˚C = 5 days	USA and Germany [33]
Oxford/ AstraZeneca (ChAdOx1/ AZD1222 [Covishield])	Virus Vector Vaccines. The dsDNA encodes against the spike protein that is protected in the virus. Infected cells express the spike protein resulting in immune response (immunogenicity).	82% (original strain), 10% (South African variant B1351)	Two doses, intermittent each dose 12 weeks.	2˚C - 8˚C = 6 months	English + Swedish [34]
Johnson & Johnson (JNJ 78436735/ Ad26.COV2. S)	Virus Vector Vaccines The dsDNA encoding against the spike protein is protected in the virus. Infected cells express the spike protein resulting in immune response (immunogenicity).	72% (USA strain), 57% (South African variant B1351)	One dose.	2˚C - 8˚C = 3 months −20˚C = 2 years	USA [48] [49]
Gamaleya (Sputnik V/ Gam-Covid-Vac)	Virus Vector Vaccines The dsDNA encoding against the spike protein is protected in the virus. Infected cells express the spike protein resulting in immune response (immunogenicity).	91.6% (original strain)	0.5 ml in 2 doses, each dose for 21 days.	2˚C - 8˚C = 6 months, −20˚C = 2 years	Russia [32]
Novavax (NVX-Cov2373)	Vaccine particles that resemble viruses The nanoparticles are covered by a synthetic material called Spike protein. Have additional ingredients called adjuvants to increase immune reactions (immunogenicity).	96% (original strain), 86% (B117 UK variant), 55% (B1351 South African variant)	Two doses, break each amount 21 days.	2˚C - 8˚C = 6 months −20˚C = 2 years	USA [46]
Sinopharm (BBIBP-CorV)	Vaccine inactivated, SARS-COV-2 is chemically inactive (with a chemical called beta-propiolactone), so it cannot replicate, but all the protein remains intact.	79% (original strain)	Two doses, break each amount 21 days.	2˚C - 8˚C	China [50]

Continued

Sinovac (CoronaVac)	Vaccine is inactivated, SARS-COV-2 is chemically inactive (with a chemical called beta-propiolactone), so it cannot replicate, but all the protein remains intact.	50% (original strain)	Two doses break each dose for 14 days.	2˚C - 8˚C	Indonesia [51]
Bharat Biotech (BBV152/ Covaxin)	The vaccine is inactivated, SARS-COV-2 is chemically inactive (with a chemical called beta-propiolactone), so it cannot replicate, but all protein remains intact.	81% (original strain)	Two doses break each dose for 28 days.	2˚C - 8˚C	India [44]

produce a polarized immune response [45]. An example of vaccines that use this method is Novavax, using adjuvant Matrix-M-based saponin, which has 89.3% efficacy in patients with COVID-19 through phase 3 clinical trials in the UK [46]. SCB-2019 Vaccine was promising and successful against the severity of COVID-19 including the delta variant in the phase 2/3 trial [47]. More than 60% of vaccine development currently uses the protein subunit approach (**Table 3**) [39].

2.5. Impact of Vaccination on the Human Population

COVID-19 outbreaks have resulted in many worldwide illnesses and mortality, as well as jeopardizing people's and community's economic and social well-being. Despite the high death events, SARS-CoV-2 infection remains a threat to most of society [52]. Vaccination is still an important preventative strategy for lowering disease burden and preventing new outbreaks. Thus, the development and deployment of vaccine supplies is a top priority for communities around the world today. Eight vaccinations against COVID-19 had been authorized globally as of March 31, 2021, which namely include ChAdOx1 (AZS1222) [AstraZeneca/ Oxford, UK]; COVAXIN [Bharat Biotech, India]; BNT162b2 [Pfizer-BioNTech, USA]; mRNA-1273 [Moderna, USA]; ADENO 26 CoV2.S [Johnson &Johnson, USA]; and Sputnik V [Moscow, Russia] [53]
https://drive.google.com/open?id=10z8XeicgTHxvz7AINAB_82q2KSHLxMsl.
People should think about vaccines which have safe and available, the possibility of using two different types of vaccines or boosters, and the types of vaccines that can keep people from getting new infections and multiple kinds of vaccines.

3. Conclusions

Various vaccinations have been developed around the world to help combat the COVID-19 pandemic. Because of discrepancies in how the vaccines were developed, particularly in terms of efficacy and side effects, vaccination hesitancy and pharmacovigilance may become distinguishing aspects of the COVID-19 pandemic's next stage as supply meets demand. This page will explain some of your questions about vaccines, like where they are made, how many doses they con-

tain, and how they are stored.

The vaccine effort is projected to establish herd immunity in at least 70% of the population, allowing them to quickly recover from the pandemic and resume their usual lives. The presence of viral mutations is one of the elements that can alter vaccine effectiveness, so more research into the efficacy of viral genetic mutations is still needed.

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Author Contributions

ST and AKHH conceptualized and drafted this article. ST, W, and SASS reviewed and edited the paper. All authors contributed and approved the final report.

Conflicts of Interest

There is no conflict of interest in this study.

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