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A comprehensive comparison between COVID-19 vaccines: a review

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Abstract

COVID-19 started in December 2019 in Wuhan and spread worldwide. The cause of COVID-19 is the newly discovered coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Until now, this pandemic is affecting almost every country in the world and over 100 million cases were confirmed. It is expected that vaccination could be a beneficial way to control and protect against COVID-19. This review aimed to compare 4 platforms of COVID-19 vaccines and used recently developed vaccines candidates as examples to illustrate. Safety, efficacy, scaling, cost, and adaptation to the mutated virus were included. Theoretical and clinical vaccine research results were used and we attempted to conclude the advantage and disadvantage of each candidate platform. Countries should choose an appropriate vaccine for their people and satisfy the demand for vaccines.

Introduction

In late 2019, several cases of pneumonia of unknown cause was discovered in Wuhan, China, and was reported to the World Health Organisation (WHO). In February 2020 the virus was named SARS-CoV-2, and the pandemic is named COVID-19. (Simon, Nilianjan, Jyotismita 2020) Afterwards, a pandemic from the coronavirus has stormed the world. This disease has spread worldwide, leading to go an ongoing pandemic(Zimmer, Carl 2021). To date, there are over 100 million infections and over 2.5 million deaths. And the virus has been mutated into about 30 strains of which there are more infectious and lethal ones. Prevention and treatment of COVID-19 have been a challenging situation to all human beings. Against the pandemic, humans have developed multiple methods, one of the most helpful one is the vaccination.

Vaccination allows people to acquire immunity against the virus and provides long-term protection. Herd immunity could be achieved when large population have received vaccines (Why is vaccination so important, 2021). Vaccine development of this pandemic is facing many concerns. Means of manufacturing and transport must be adjusted for different countries and population (Wang et al., 2020) and special individuals may have requirements. The mutation of virus is a great challenge towards vaccine design and the scale production needs to be improved to fulfil the demand of vaccine worldwide in short time. There are 12 (Craven, 2021) authorized vaccines in total, of which 8 (www.who.int, 2020) have been EOI (Expression of Interest)

accepted before March, including Pfizer and BioNTech's BNT162b2, Moderna's mRNA-1273, Sinovac's Coronavac etc. Starting from the very beginning of the pandemic, governmental research laboratories, universities and pharmaceutical companies have shown great interest in developing a safe and efficient vaccine. Ranging from conventional platforms like inactivated and subunit vaccines, to novel platforms like mRNA vaccines, candidates from various platforms have joined the vaccine race. Each route has its own advantages and disadvantages. This paper aims to discuss and compare the routes of vaccine development, in order to provide reference for the needed individuals and organizations.

Survey methodology

COVID-19 vaccines are mostly still in research processes and not much information were open published. In this review, multiple databases were used for background theoretical analysis. Information published by company websites, news media and organisations were used to compare the practical characteristic of each type of vaccines.

mRNA vaccines

Synthesis of viral mRNA encoding crucial domains of SARS-CoV-2 and enclosure with lipid nanoparticles is the basic principle of mRNA vaccine. Decoding of genome of SARS-CoV-2 strains enables researchers to identify the key position of the virus, and mRNA of this part could be manufactured in vitro. The mRNA is then stabilized with adjuvants and enveloped with lipid nanoparticles to promote cellular uptake and protect constructs from degradation.

There are two main types of mRNA vaccines, non-replicating (NRM) and self-amplifying (SAM) ones. Despite the difference in the presence of a replicase component, their general working principle remains the same. Once injected, lipid coverage may help with mRNA entering to the cell by lipophilicity. The mRNA constructs will then be translated by free ribosomes to produce polypeptides. The peptide, with immunogenicity, is secreted by exocytosis or presented on cell surface after post-translational modification. The immunogenicity of the peptides may trigger the immune response, and immune memory is thus formed. On infection, the immune system may recognize the part of peptide on shell of the virus, and then the virus would be attacked.

Theoretically, there are several advantages of developing a mRNA vaccine. First, its design and production are rapid (Funk, Laferrière and Ardakani, 2020), which would be particularly suitable for the current situation given the severity of the pandemic. Second, unlike inactivated vaccines, the development of a mRNA vaccine do not require the handling of infectious materials, which would make the production safer (Funk, Laferrière and Ardakani, 2020). Third, they are able to induce a strong and quick antiviral response, both humoral and cell-mediated (Funk, Laferrière

and Ardakani, 2020). Lastly, the scaling up for a worldwide production would be feasible (Funk, Laferrière and Ardakani, 2020).

However, development of mRNA vaccines are relatively immature compared to other conventional ways of developing vaccines as there were no approved mRNA vaccines before COVID-19. It also possible that inflammatory reactions may be induced (Funk, Laferrière and Ardakani, 2020). Besides, most formulations require a cold chain for storage in order to sustain the vaccines' longevity and stability, which could be quite inconvenient for developing countries or regions. Moreover, boosting would likely be necessary to achieve long-lasting immunity (Funk, Laferrière and Ardakani, 2020), which again, may cause some inconvenience in the developing world.

Multiple developers have selected this route for development of their vaccines. The leading players are Pfizer and Moderna. Their BNT162b2 and mRNA-1273 have both been approved for a rollout (Craven, 2021) on a nationwide/regionwide level in dozens of countries or regions (Table 1). Other competitors include CureVac, Arcturus Therapeutics, University of Washington etc. (Table 1)

For Pfizer's BNT162b2, over 43,000 (Polack et al., 2020) participants were recruited around the world for its Phase III trial and showed that this candidate was 95% (Polack et al., 2020) effective, which was supported by Phase I results. Pfizer's vaccine has been approved for emergency use or a nationwide rollout in over 30 (Craven, 2021) countries or regions. Typical side effects include short-term, mild to moderate pain at the site of injection, fatigue and headache. A probability of higher than 83% (Polack et al., 2020) that at least one adverse event is detected. In general, the incidence of serious adverse events was similar in experimental and control groups, 0.6% and 0.5% respectively (www.cdc.gov, 2020). European Medicines Agency (EMA)'s safety committee found no link between post-vaccination deaths and the vaccine (Ana Catarina PINHO, 2021), even in elderly and immunocompromised people.

As for Moderna's mRNA-1273, in a Phase III trial with over 30,000 participants, efficacy of 94.1% (Baden et al., 2020) was demonstrated. The safety profile for Phase III also met expectations described in U.S. Food and Drug Administration (FDA)'s guidance (Vaccines and Related Biological Products Advisory Committee Meeting, 2020). Common adverse events include pain at the injection site, fatigue, headache, etc. which had a median duration of 2 to 3 days (Baden et al., 2020). The incidence of serious adverse events was both 0.6% (Baden et al., 2020) in the vaccine and the placebo groups, which showed no statistically significant difference in terms of occurrence of serious adverse events due to the vaccine. There is not enough evidence showing that there is a causal relationship between the serious adverse events (SAE) and the vaccine (Vaccines and Related Biological Products Advisory Committee Meeting, 2020). Candidates from CureVac, Pfizer (a variant of the above Pfizer candidate), Arcturus

Therapeutics, Univerisity of Washington, Providence Therapeutics and Chulalongkorn University are currently under development as well, with pre-clinical and clinical trials taking place.

Inactivated vaccines

An inactivated vaccine is synthesised by inactivating or killing a pathogen, in hopes of decreasing its infectivity without compromising its immunogenicity (Callaway, 2020). The vaccine is administered in vivo with adjuvants (Callaway, 2020). Starting with a strain, the viruses are exposed to either chemical or physical agents, such as formaldehyde or heat, to eliminate their infectivity by destroying viral RNA or DNA and in turn deprive their ability to replicate. However, the immunogenic elements are remained relatively unaltered, which enables the immunogenicity to be retained. The inactivated vaccine is administered to incite an immune response by presenting the viral antigens to the immune cells and form immune memory. If the same or similar species of antigen is recognised on the second time, the immune system would be able to respond and induce an attack on the viruses rapidly.

Theoretically, the advantages of developing inactivated vaccines are that their manufacturing is relatively mature and their formulation is rather simple. However, the inactivated viruses do not enter cells in vivo. Hence, the stimulated immune response contains only humoral but no cellular immunity. Additionally, the inactivated vaccines are made of live viruses cultivated in cells. Thus, high-level biosafety facilities are much needed. For the same reason, it may be costly and difficult for scaling up. (Funk, Laferrière and Ardakani, 2020)

Several developers have selected this route for their own vaccines. The leading players are SinoVac and Sinopharm, which are state-owned entities of China, and thus they enjoy abundant labour and material. Their candidates, CoronaVac(Sinovac) and BBIBP-CoV (Sinopharm) has been approved for emergency use in several countries and regions (Table 1). Other competitors include Bharat Biotech, Valneva; National Institute for Health Research (NIHR), Shenzhen Kangtai Biological Products, etc. (www.raps.org, 2021)

For Sinovac's CoronaVac, multiple international Phase 3 trials were carried out in Brazil, Turkey and Indonesia. A trial that involved 9000 patients from the healthcare industry was also launched. The efficacy shown in the Brazil trial was originally 78%, but after including patients with mild infections, the efficacy became 50.4% (Sinovac: Brazil results show Chinese vaccine 50.4% effective, 2021). The vaccine showed 91.25% (Kucukgocmen, 2020) effectiveness in the Turkey trial. Frequently observed side effects include injection site pain, fever, fatigue etc. Up until 4/3/2021, no serious adverse events were reported (Craven, 2021).

Phase 3 trials of Beijing Institute of Biological Products's BBIBP-CorV are underway in Morocco, Peru and the United Arab Emirates (UAE). Data from Phase 1/2 trials published

demonstrated that the vaccine candidate was able to incite “strong neutralizing antibody response” (Xia et al., 2020). The adverse reaction rate is relatively low (Xia et al., 2020). Phase 2 and Phase 3 results of BBIBP-CorV are still under evaluation. The health ministry of the UAE announced that the vaccine efficacy was 86% (Cyranski, 2020) based on interim Phase 3 trials results and there were no serious safety concerns. Candidates from Bharat Biotech, Valneva, Chinese Academy of Medical Sciences and Shenzhen Kangtai Biological Products are also under development, with pre-clinical and clinical trials underway.

Adenovirus vaccines

An adenovirus vaccine is a recombinant vaccine composed of adenovirus as vector and target gene as antigen. Modification of adenovirus, like deletion of E3 domain, increases the efficacy of using as vector. (Lasaro and Ertl, 2009) The identified viral gene could be coding a specific protein according to the targeted viral characteristic and can be recombined with adenovirus by genetic engineering. Upon administration, adenovirus enter human cells, and get its genome expressed. Target gene is expressed in the same way. Expressed targets are secreted via exocytosis or presented on cell surface and stimulate immune response.

Adenovirus vaccine stimulates both humoral and cellular immunity and thus the effect is strong and long-lasting. Adenovirus, as a vector, has a rather large genome compared to other vectors like lentivirus, adeno-associated virus and influenza virus. As a result longer target genes could be loaded. Unlike influenza virus, adenovirus itself seldom cause any disease in healthy adults. However, the pre-existing immunity of certain adenovirus vectors can affect its efficacy. Additionally, adenovirus vaccine may not work in immunosuppressed or immunodeficient people, and severe adverse effects may occur.

Major developers of adenovirus vaccine are CanSinoBio-Beijing Institute of Biotechnology, The Gamaleya Research Institute of Epidemiology and Microbiology, Oxford-AstraZeneca, and Johnson & Johnson. All four vaccines have reached or completed phase 3 trial, and have shown efficacy and safety. The Oxford-AstraZeneca and the Gamaleya ones both have been approved for use (Table 1) (AZD1222 and Sputnik V)(www.raps.org, 2021) .

Cansino has chosen human Ad5 virus as vector and thus named their candidate Ad5-nCoV, and the targeted COVID-19 viral gene encodes RBD of spike protein. The Phase 1 and phase 2 experiment both showed significant increase of RBD-specific antibody in all dose group (Zhang et al., 2021). Phase 3 clinical trials started in September 2020. So far, the Phase 3 trial has recruited 40500 in total and it's still underway (www.raps.org, 2021). No severe adverse event was reported in the trial in Brazil according to the REUTERS (Roxanne Liu, 2021). No key information has been published about phase 3. Pain on infection site, fever, and fatigue are

common adverse effect, but mostly experienced at mild or moderate level. However, it is also found that around half of the participants had high pre-existing anti Ad5 immunity in Phase 2, and will lead to lower antibody response. (Zhang et al., 2021)

Johnson & Johnson has used adenovirus serotype 26 (Ad26) as vector and full-length spike protein of SARS-CoV-2 as target antigen to develop their vaccine JNJ-78436735. The result of Phase 1/2a study showed 90% of participants developed S-binding and neutralising antibody 29 days post-vaccination, which was described as a strong humoral response. (Sadoff et al., 2021) Two randomised Phase 3 clinical tests are running with total up to 90,000 participants started from September and November 2020 respectively. One of the test was two-dosed to evaluate the benefit of the second dose (www.raps.org, 2021). According to the announcement published by the company, the efficacy of JNJ-78436735 is 85% (Johnson & Johnson COVID-19 Vaccine Authorized by U.S. FDA For Emergency Use | Johnson & Johnson, 2021).

For Oxford-AstraZeneca's AZD1222, they applied simian adenovirus vector ChAdOx1 to avoid pre-existing immunity, which does not infect human generally. The AZD1222 consists of vectors with the structural spike protein of SARS-CoV-2. The published Phase 3 clinical trial was done in Brazil, South Africa and the UK. The result showed an overall efficacy of 70.4% across all groups but the efficacy of the group receiving half dose followed by a standard dose was higher than the group receiving two standard dose (90% and 62.1% respectively). Three cases of suspected unexpected serious adverse event was reported and the study was suspended once due to this reason (Voysey et al., 2021; www.raps.org, 2021).

The Gamaleya Research Institute of Epidemiology and Microbiology developed a heterologous COVID-19 vaccine by using two types recombinant adenovirus vector (rAd5 and rAd26). The phase 1 / 2 study was done to access the efficacy and safety of the combination of the two types in two formation (frozen and lyophilised) (Logunov et al., 2020). Their Phase 3 clinical trial was done in Russia, Belarus and the United Arab Emirates with about 40,000 participants (The Sputnik V vaccine's efficacy is confirmed at 91.4% based on data analysis of the final control point of clinical trials, 2021). The Phase 3 trial data in Russia was published on 2nd of February. It was announced that according to the 21977 adult participants in Russia, the vaccine efficacy was 91.6 % and most adverse events reported was mild, including injection site reaction, flu-like symptoms. Total 68 participants reported serious adverse events and 4 deaths occurred but was all considered having no association with the vaccine. Recently, a few countries have approved and purchase the vaccine for use (Logunov et al., 2021).

Subunit vaccines

A subunit vaccine is a vaccine, like inactivated vaccines, made from a non-live component (usually proteins or peptides) of the pathogen and the components involved can be any

molecule.(MODULE 2 – Subunit vaccines - WHO Vaccine Safety Basics, 2021) Thus, recombinant subunit vaccine can be also called recombinant protein vaccine (Recombinant Subunit Vaccines | Sartorius, 2021).

The main component of the subunit vaccine is called the target protein. It is usually the most characteristic and most immunogenic part of the pathogen. Usually, spike protein or its RBD is selected to be the target for SARS-CoV-2. The subunit vaccine is developed by finding out the corresponding gene of target protein by genome-wide sequencing of the viral strain. The target is then expressed in a recombinant system, and then made into formulation with adjuvants. After administration of the vaccine, the immune system would recognize the target protein as external antigen, and APCs would present the target to other immune cells. As a result, immune memory is formed.

The development of subunit vaccine tends to be simple and fast once the genome of pathogen is sequenced and analyzed. And the subunit does not have ant infectivity, so the safety to patients with immunosuppression and immunodeficiency efficiency could be guaranteed. Synthesis of the target could be achieved in bioreactors so high scalability is an advantage that could not be ignored in wide application. Among all vaccines, the subunit one enjoys the balance between development and speed, which means that it is the best developed among fast ones, and fastest among best developed ones.

However, the subunit represents only a small proportion of the whole pathogen. Even if it's the most recognizable and characteristic one, the immunogenicity pales when facing the whole antigen. Same to the inactivated one, the subunit vaccine could stimulate only humoral but not cellular immunity due to lack of infectivity. Another weakness of recombinant subunit vaccines is that the potential denaturation of antigens can occur, because this risk can cause the proteins to combine with different antibodies rather than the specific antigens which is the target protein (Benedette Cuffari 2021).

To the end of March, none of the recombinant subunit vaccines is in distribution.And currently there are 24 of them in development. The protein subunit progress-leading ones are adjuvanted recombinant protein vaccine developed by Zhifei, NVX-CoV2373 recombinant glycoprotein developed by Novavax and RBD developed by West China Hospital Sichuan University and two of them are at clinical phase 3 the last one is at phase 2b.

ZF2001, the recombinant subunit vaccine developed by Chongqing Zhifei Biological Products Co., Ltd and the Institute Microbiology at the Chinese Academy of Sciences, was the first one in China and second one in the world that enters the clinical trials. ZF2001 reached phase 3 at November 6 2020 which planned injection into 29000 healthy volunteers aged over 18 across China ,Uzbekistan, Indonesia, Pakistan and Ecuador, and some domestic phase 3 clinic trials

have already been conducted in Xiangtan, China. Up to February 4 2021 there is no more information about efficacy or safety has been reported (Reuters Staff 2020).

Novavax is an American vaccine development company which focus on developing the protein vaccine called NVX-CoV2373 which is based on modified spike protein with Matrix-M1 as adjuvant. To date, it has two different times for different places to enter the phase 3 at September 23 2020 in UK with 15000 healthy volunteers aged over 18 and November 2020 in USA and Mexico with 30000 healthy volunteers aged over 18. The result of UK phase 3 is 89.3% efficacy. The efficacy by strain was calculated to be 95.6% against the original COVID-19 strain and 85.6% against the UK variant strain. Also the interim analysis showed that severe, serious and medically attended adverse events occurred at low levels so that the percentage of adverse reactions happening is low. There is no information for USA and Mexico phase 3 result because to date, Prevent-19 has randomized over 16000 volunteers that is not enough for testing and predicted to complete the plan before February 15 2021 (Novavax 2021).

The recombinant subunit vaccine of West China Hospital Sichuan University that uses baculovirus production expressed in Sf9 cells as the subunit protein and insect cells as the recombinant system to develop high-quality recombinant vaccine has entered phase 2b with two research group that are adults group (aged 18-59 years) and elder adults group (aged 60-85 years), and each group includes 2000 volunteers. The estimated completion date for primary outcome measure would be May 15 2021 so there is no further information released (Cao, 2020; Clinicaltrials.gov. 2021).

TABLE 1:

Primary Developers	Vaccine Name	Vaccine type	Countries/ Regions that Approved /Authorized
Sinovac	CoronaVac	Inactivated vaccine	Albania, Armenia, Azerbaijan, Bangladesh, Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Cambodia, China, Chile, Colombia, Dominican Republic, Ecuador, Egypt, Georgia, Hong Kong, , Philippines, Singapore, Thailand, WHO etc.
Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	WIBP-CorV	Inactivated vaccine	China
Beijing Institute of Biological Products;China National Pharmaceutical Group (Sinopharm)	BBIBP-CorV	Inactivated vaccine	Afghanistan, Algeria, Angola, Argentina, Bahrain, Bangladesh, Belarus, Bolivia, Brazil, Brunei, China, Congo, Dominican Republic, Egypt, Ethiopia, , Guyana, Hungary,

			Indonesia, Iraq, Jordan, Kazakhstan, Laos, Macau, Maldives, Morocco, Mozambique, Namibia, Nepal, Peru, Philippines, Senegal, Serbia, Seychelles, Sierra Leone, , Turkmenistan, UAE, Venezuela, Vietnam, WHO etc.
Bharat Biotech, ICMR Ocugen	Covaxin	Inactivated vaccine	Botswana, Guatemala, Guyana, India, Iran, Mauritius, Mexico, Myanmar, Nepal, Paraguay, Philippines, Venezuela, Zimbabwe
Valneva; National Institute for Health Research (NIHR)	VLA2001	Inactivated vaccine	/
Chinese Academy of Medical Sciences, Institute of Medical Biology	N/A	Inactivated vaccine	/
Shenzhen Kangtai Biological products	N/A	Inactivated vaccine	/
CansinoBio-Beijing Institute of Biotechnology	Convidicea (PakVac, Ad5-nCoV)	Adenovirus vaccine	Argentina, Chile, China, Ecuador, Hungary, Malaysia, Mexico, Moldova, Pakistan
Johnson & Johnson	Ad26.COV2.S	Adenovirus vaccine	Andorra, Bahrain, Bangladesh, Botswana, Brazil, Canada, Chile, Colombia, Denmark, European Union, Faroe Islands, Greenland, Iceland, India, Kuwait, Liechtenstein, Malaysia, Maldives, Mexico, Moldova, Nigeria, Norway, Philippines, Saint Vincent and the Grenadines, South Africa, South Korea, Switzerland, Thailand, Tunisia, United Kingdom, US, WHO, Zambia
Oxford-AstraZeneca	Vaxzevria / Covishield (AZD1222)	Adenovirus vaccine	Afghanistan, Albania, Algeria, Andorra, Angola, Argentina, Armenia, Australia, Bahamas, Bahrain, Bangladesh, Barbados, Bhutan, Bolivia, Botswana, Brazil, Brunei, Cabo Verde, Cambodia, Canada, Cambodia, Caribbean, Chile, Colombia, Congo, Costa Rica, Djibouti, Dominican Republic, South Korea, South Sudan, Sri

			Lanka, Sudan, Suriname, Taiwan, Tajikistan, Thailand, Timor Leste, Tonga, Togo, Tuvalu, Uganda, Ukraine, UK, Uzbekistan, Vietnam, WHO (Oxford; SII/SK), Yemen, Zambia etc.
The Gamaleya Research Institute, Acellena Contract Drug Research and Development	SputnikV	Adenovirus vaccine	Albania, Algeria, Angola, Antigua and Barbuda, Argentina, Armenia, Azerbaijan, Bahrain, Bangladesh, Belarus, Bolivia, Brazil, Congo, Djibouti, Ecuador, Egypt, Gabon, Ghana, Guatemala, Guinea, Guyana, Honduras, Hungary, India, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Laos, Lebanon, Maldives, Mali, Mexico, Moldova, Mongolia, Montenegro, Morocco etc.
Pfizer BioNTech; Fosun Pharma	Comirnaty (BNT162b2)	mRNA-based vaccine	Albania, Andorra, Argentina, Aruba, Australia, Bahrain, Bangladesh, Bosnia and Herzegovina, Brazil, Brunei, Canada, Caribbean, Chile, Colombia, Costa Rica, Ecuador, European Union, Faroe Islands, Greenland, Hong Kong, Iceland, India, Iraq, Israel, Japan, Jordan, Kuwait, Lebanon, Liechtenstein, WHO etc.
Moderna, BARDA, NIAID	Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based vaccine	Andorra, Brazil, Botswana, Canada, European Union, Faroe Islands, Greenland, Guatemala, Honduras, Iceland, Singapore, South Korea, Switzerland, Taiwan, Thailand, United Kingdom, United States, Vietnam, WHO etc.
CureVac	CVnCoV	mRNA-based vaccine	/
Providence Therapeutics; Candian government	PTX-COVID-19-B	mRNA-based vaccine	/

Chulalongkorn University's Center of Excellence in Vaccine Research and Development	N/A	mRNA-based vaccine	/
Aruturus Therapeutics and Duke-NUS Medical School	ARCT-021(LUNAR-COV19)	Self-replicating RNA vaccine	/
University of Washington; National Institutes of Health Rocky Mountain Laboratories; HDT Bio Corp Gennova Biopharmaceuticals	LNP-nCoVsaRNA	Self-amplifying RNA vaccine	/
Chongqing Zhifei Biological Products Co Ltd and the Institute Microbiology at the Chinese Academy of Sciences	ZF2001	Subunit vaccine	China, Uzbekistan
Novavax	NVX-CoV2373 Recombinant glycoprotein	Subunit vaccine	/
West China Hospital Sichuan University	RBD	Subunit vaccine	/

Discussion

Safety

The safety of vaccines varies among routes. All vaccines share some side effects, mild or severe, could occur. Most commonly observed adverse effects are redness and pain at injection site, fever and dizziness. The severe ones include lymphadenopathy and arrhythmia. Developers have taken measurements for compensation, but they could not be completely avoided. Rate, severity and prognosis is largely determined by route of the vaccines.

The adenovirus vaccine contains live virus. Thus, it could be helpless or even threatening to patients with immunosuppression or immunodeficiency, although developers have taken measures to weaken the virus's virulence. The other ones, in contrast, does not contain any infective components so that the unexpected infection could be avoided. However, other adverse effects may occur. The most common side effects are fever and injection site pain. Some severe but rare events are lymphadenopathy and arrhythmia(Polack et al., 2020) . In practice, 7966 of 12296 participants in the clinical phase 3 trial of Gamaleya's vaccine in Russia reported mild adverse events, including flu-like symptoms, injection site reaction and headache. The severe

adverse event was surveyed in 21826 volunteers taking at least one dose, and only 2 reported cases were vaccine-related (Logunov et al., 2021). Phase 3 trial of AZD1222 enrolled 11636 participants, and 168 patients reported serious adverse event, but only three was related to the vaccine, including one case of haemolytic anaemia (Voysey et al., 2021).

Inactivated vaccine has a relatively higher level of safety because they used killed pathogen and they could not convert into a more threatening phenotype. According to phase 1/ 2 trial of BBIBP-CorV, 29% of recipients had adverse events like fever, but are mild (Xia et al., 2021). For vaccine designed by Wuhan Institute of Biological Product and Sinopharm, 15% of participant reported adverse events within 7 days post-vaccination and the adverse events are all self-limited(Xia et al., 2020). The phase 1/2 result of inactivated vaccine developed by West China Second University Hospital did not have severe adverse events. Slight pain and redness are the common adverse symptoms reported (Pu et al., 2020).

Subunit vaccine is developed by genomes of pathogen which is harmless and enjoys a simple and fast way to produce more heterologous proteins. Because it does not have ant infectivity so that it is theoretically safe for patients. Interim analysis of 15000 volunteers received 2 doses of Novavax's subunit vaccine in clinical phase 3 showed that level of adverse events occurrence is low (Novavax 2021)_x0005_ (no information about exact rate, type or severity of the adverse effects is released).

mRNA vaccines are relative safer as its manufacturing process does not require toxic chemicals or cell cultures which could be contaminated by external viruses (Pardi et al., 2018). Thus, this gives mRNA vacciens an edge of dodging mutual risks from other vaccine platforms like viral vectors, inactivated and subunit vaccines (Pardi et al., 2018). Moreover, short production time presents less opportunities to introduce contaminants like microorganisms (Pardi et al., 2018). Furthermore, thoretically, infection and genomic integration into the host cell DNA would not be a concern for mRNA vaccines (Pardi et al., 2018). However, a potential concern is that mRNA vaccines might elicit potent type I interferon responses (Pepini et al., 2017), which is associated with inflammation and autoimmunity (Theofilopoulos et al., 2005). Also, it has been demonstrated by previous studies that external RNA increases the permeability of packed endothelial cells and may cause oedema (Fischer et al., 2007), blood coagulation and pathological thrombus formation (Kannemeier et al., 2007). The incidences of severe adverse events of Pfizer's and Moderna's vaccines are both less than 1% (Baden et al., 2020) (Polack et al., 2020), and provided that there found no statistically significant difference of severe adverse event incidence between the placebo and experimental groups (Baden et al., 2020) (Polack et al., 2020), this shows that mRNA vaccines are theoretically and clinically safe.

Efficacy

All vaccines are effective and efficient in theory, but the human body is a complicated system, all theories remain to be proven by real-world obseravation. The mRNA and adenovirus may enter human cells for production of antigen, thus they stimulate both humoral and cellular

immunity, which is superior to the other two. But efficacy of adenovirus vaccine might be affected by pre-existing immunity against adenovirus. And the immunity developed by subunit vaccine could be easily escaped by mutated virus. As the body of human is a huge and complicated system, all theories remain to be proven by real-world observation.

Inactivated viruses have no replicability in vivo, and it has lower immunogenicity. Adjuvants are used to compensate for this weakness (Ulmer, Valley and Rappuoli, 2006). The efficacy of the COVID-19 inactivated vaccine varies compared with other types. The BBIBP-CorV was announced to have 86% of efficacy, but the measured efficacy of CoronaVac produced by Sinovac has a significant difference between its phase 3 trials. (50.4% in Brazil and 83.5% in Turkey)(www.raps.org, 2021). For the adenovirus vaccine, adenovirus's replicating ability is eliminated, so a higher dosage of viral particle is needed for appropriate immunogenicity. According to phase 3 trials of the two adenovirus vaccines approved up to 4th February, the highest efficacy using an applicable dosage was 90% and 91.6%, respectively (AZD1222 and Sputnik V).

The efficacy of mRNA vaccines are very satisfactory, with 95% (Polack et al., 2020) for Pfizer's BNT162b2 and 94.1% (Baden et al., 2020) for Moderna's mRNA-1273 according to the results from their respective phase III trials. Comparing to other platforms, mRNA vaccines are generally of the highest efficacy. However, two doses are required for complete vaccination for both Moderna and Pfizer candidates in order to boost the efficacy to its fullest. Among all developers of subunit vaccines, only Novavax has released their results of phase 3 in UK. The efficacy for NVX-CoV2373 is 89.3% which is not higher than mRNA or adenovirus, but better than the inactivated ones. (Novavax 2021)_x0005_

Scaling

As massive injections of vaccine is needed in a pandemic, economical mass production is a vital character of a vaccine. Being able to be manufactured in large scale and low cost makes a vaccine competitive in global market.

A difficulty in producing inactivated virus vaccine is the need of high-level biosafety facilities. Enjoying the well-prepared manufacturer and supplier, the two Chinese inactivated virus vaccine are able to be manufactured at the speed of 100 million doses per year (Majumder, 2021). However, not all inactivated vaccine could take this advantage.

Development of advanced cell culture technologies and chromatography techniques largely improved the large scale production of adenovirus vaccine (Kallel and Kamen, 2015). However, there is still a demand adenovirus production and therefore the productivity of adenovirus vaccine is relatively lower than mRNA and subunit vaccine. J&J manufactures the vaccine through Janssen Pharmaceutical Companies and can manufacture 1 billion doses through 2021.

Oxford-AstraZeneca has 4 manufacturers to produce their vaccine and the scale were all above 100 million doses per year (Majumder, 2021).

mRNA vaccines are relatively easier to scale-up. This is because mRNA vaccines can be synthesised in vitro without working with live viruses. The production of the vaccine was simple and quick because it was cell-free, only an aqueous phase enzymatic reaction was involved (Stanton, 2020). Productions for other platforms like inactivated vaccines, which involve cells, require bioreactors that provide massive space for cell growth (Stanton, 2020). The large space is essential as to lower competition for resources among cells within the same bioreactor. Meanwhile, enzymatic reactions work the most efficient when substrates and enzymes are dense (Stanton, 2020). Thus, mRNA vaccines require less space to produce. Also, enzymatic reactions are much more rapid than cell culture, which also explains why mRNA vaccine scaling up is comparatively easier.

Subunit vaccine is easy for mass production and there are many subunit vaccine has used in worldwide such as the hepatitis B and the cervical cancer vaccines.(What are protein subunit vaccines and how could they be used against COVID-19) For Novavax, they add the gene of coronavirus spike protein into insects cells grown in laboratory dish and these proteins would be easily separate and purify into a subunit vaccine (Novavax 2021_x0005_).

Cost

Cost of the production of a vaccine depends on many factors like the equipments and consumables. Cultivation in cell strains and high-level biosafety facilities usually make a vaccine expensive. Developers of inactivated vaccines, like Sinopharm, has not yet revealed the cost of vaccines. However, it could be guesstimated by comparing with other inactivated vaccines like flu vaccines. An review of WHO Regional office of Europe showed the average price of influenza vaccine was \$ 4.55 per dose with maximum \$14.29 in the 11 reported procurement in 2013 (Review of vaccine price data: submitted by WHO European Region Member States, 2021).Thus, it could be speculated that the cost of inactivated virus vaccine would probably be around or below \$14.29 per dose. The Chairman of Sinopharm Group suggested that the price of two shot of their vaccine would not be higher than 1000 CNY ($\approx$ 160 USD) (Majumder, 2021). Adenovirus vaccine appeared to have lower price. According to the companies, the price of AZD1222 is around \$4 per dose while the price of Johnson & Johnson only cost \$10 per dose and a single dose would be enough. The price of Sputnik V was confirmed to be less than \$10 per dose(Covid: What do we know about China's coronavirus vaccines?, 2021) . For mRNA vaccines, Moderna's mRNA-1273, which has two doses, was priced at approximately USD 32 to USD 37 per dose. Pfizer's BNT162b2, which also has two doses, was priced at USD 19.50 per dose. Compared to other platforms, mRNA vaccines are moderately priced. Although subunit vaccine is simple to develop, there is no this kind of vaccine ready for distribution. So there are

no references to deduce the price for a dose of subunit vaccine. Recombinant expression systems are required, with less demanding than the facility for inactivated or adenovirus vaccine development to develop a subunit vaccine. So the price may cheaper than other vaccines. Due to differences in many factors, the expenses of each vaccine is not comparable. For example, one country might be rich in biosafety equipment, and another one good at mRNA manufacturing. As a result, inactivated vaccine would be a better choice for the former country, while the latter one tends to choose mRNA vaccine.

Adaptability to mutations

In the COVID-19 pandemic, several variants of SARS-CoV-2 was discovered worldwide. To the end of February, 2021, about 30 major variants have been identified globally, such as N501Y discovered firstly in UK. Mutation may be threatening in prevention and treatment of COVID-19, including effectiveness of vaccines. Mutations on spike protein altered the transmission ability and became one of the major issues affecting vaccine development. SARS-CoV-2 is a species that mutates rapidly. Generally, it takes flu virus 5-7 years to escape from immune recognition, while now some SARS-CoV-2 variants have shown the same symptom in only 1 year. There are a series of domains that mutate especially quickly that have been identified. RBD of the spike protein is one of them. Many cases have been found, which primarily affects the vaccines that target the RBD region and result in a limited immune response.

Inactivated vaccine mostly inactivates the whole virus and designed as antigen; hence the influence of mutation could be relatively low. The Indian company Bharat Biotech experimented on their vaccine, Covaxin, using the UK variant and three other strains of hCoV-19/India/2020770. The result showed similar neutralising activity to that of the original hCoV-19/India/2020770 strain(Sapkal et al., 2021) . For adenovirus vaccines, mutations could decrease some vaccine's efficacy targeting the gene sequence coding for the RBD. However, for the adenovirus vaccine, which chose the whole spike protein gene sequence, like Ad26.COV2. S, are expected to function normally.

The subunit vaccine might be the most affected one. Most of the developers have chosen the spike protein, or its RBD, as designed antigen. However, these are the domains that mutates very fast. As a result, subunit vaccine may lose when facing mutated variants. mRNA vaccines are affected at a moderate extent. Both Moderna's mRNA-1273 (Miller, 2020) and Pfizer's BNT162b2 (www.pfizer.com, 2020) encode for the full-length spike protein, which means that mRNA vaccines are more adaptive to mutations compared to candidates that only targets the RBD, as spike protein is more resistant to mutation than RBD in general. However, mRNA vaccines would be less adaptive to mutations compared to candidates that use the whole virus as

mutations may induce greater effects on spike protein compared to the whole virus.

Transport and storage

mRNA vaccine has the highest requirements for storage and transportation. Since the mRNA is rather unstable, it has to be frozen all the time in the transport chain, between factory and patient, to prevent degradation. Pfizer suggests their products to be kept in between -60 and -80°C (Pfizer.com, 2021), while Moderna declares temperature for storage to be between -15 and -25°C (<https://www.modernatx.com/>, n.d.).

Inactivated vaccine requires a storage temperature of 2-8 °C since they are easily damaged in extreme temperature. Take the vaccine of Sinovac as an example, the company suggested a storage temperature of 2-8 °C (Here come the Chinese COVID-19 vaccines, 2021). Adenovirus vaccine has a similar storage requirement as inactivated vaccine. The component in vaccine used in viral vector vaccine is unstable above 8 °C. Recently, the use of freeze-drying formulation was found to increase the storage time as it inhibits the denaturation of active components(Chen et al., 2020). In COVID-19 vaccine development, the AZD1222 has a shelf life of around 6 months under 2 to 8 °C in regular fridge (ACIP Storage and Handling Guidelines for Immunization | CDC, 2021). The vaccine of Gamaleya requires a similar storage condition but vaccine must be in dry form (Covid: What do we know about China's coronavirus vaccines?, 2021). Storage temperature is highly restricted for adjuvant in subunit vaccine (Vangroenweghe, 2017). Similar to the inactivated vaccine, most subunit vaccines require storage temperature above 0 °C at around 2-8 °C. Vaccines from Novavax also required refrigeration at 2-8 °C(Covid vaccine development: The shots available and the doses administered, 2021).

Conclusions

In this paper, we have discussed, and compared aspects of vaccine routes, including the principle and manufacturing, safety and efficacy, scaling and cost, etc. What we have found out is that the inactivated vaccine might be less efficient, while it could be the safest one, and the need of biosafety equipment makes it expensive and less scalable. Meanwhile, mRNA vaccines have been demonstrated to be effective and safe, and mRNA's synthesis tends to be simple. However, they require stringent storage and transportation conditions. Subunit vaccines are applicable to people who have weak immune systems and safe to use, they can be produced in the fermentation tank with mass production, but they have the worst resistance to mutation. Adenovirus vaccine has an efficacy between mRNA vaccine and subunit vaccine but is harder to scale up. It is preferable for developing countries because the storage and transport condition is more likely to be achieved. In summary, each route has its advantages and disadvantages.

Authorities need to apply the route that fits the reality best. For a developed country, the mRNA vaccine might be a good choice for its high efficacy. While for the developing countries, where there are no enough freezers for transport and storage of vaccine, subunit vaccine outstands for high safety and low price. COVID-19 is an unfortunate tragedy to the whole population. For the sake of the safety and wellbeing of all humans, we urge pharmaceutical companies, universities, governments and everyone, to put down our differences and battle our common enemy. With concerted effort, we shall prevail.

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