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Development of Current COVID-19 Vaccines, A Review

Shaofeng Xu

Biochemical engineering department, UCL

zcbesxu@ucl.ac.uk

Abstract. The virus known as severe acute respiratory coronavirus 2 is extremely pathogenic. and has already give rise to worldwide contagious pandemic. SARS-CoV-2 new variations, particularly the Omicron strain, are a major global concern. To reduce the spread of virus, considerable efforts have been made towards the development of effective vaccines and drugs against SRAS-CoV-2. The current available vaccines include inactivated vaccines (Sinopharm and Sinovac), protein-based vaccines (Novavax), DNA vaccines, RNA vaccines (Moderna and Pfizer), viral vector vaccines (Oxford-AstraZeneca). These various vaccinations act in different ways to improve human immunity with their own strengths and drawbacks but both of them could work very effectively to prevent infection. In this review, recently significant progress in the development of COVID-19 vaccination, including vaccine type, efficacy and safety issues, and variant protection are summarized.

Keywords: Sars-Cov-2, BNT162b2 (Pfizer), ChAdOx1 nCov-19 (AstraZeneca) and mRNA-1273 (Moderna)

1. Introduction

COVID-19 is a worldwide pandemic threatening people's life all over the world. This is because it has already resulted in millions of infections and deaths over 18 months since the onset of pandemic [5]. From the last update at April 2022 from world health organization, confirmed cases and deaths have been achieved 492,189,439 and 61,594,74 [6] while vaccine dose administrated is still being encouraged to boost public immunity. To make matter worse, the current pathogens are still undergoing mutation leading to increased transmissibility. 5 variants of concern have been reported, known as Alpha, Beta, Gamma, Delta and Omicron. At the same time, many countries have experienced huge number of positive case and death such as America, india and Brazil.

COVID-19 is a novel positive-strand RNA coronavirus (SARS-Cov-2), which is a member of the Coronaviridae family. [1] [2]. The genome is a single-stranded positive-sense RNA about 29.9kb and this genome is packaged by an envelope, associated with 3 structural proteins (spike, envelope and membrane proteins) [3]. Overall, this virus contains 16 non-structural(nsp1-16) and 4 structural proteins (spike, envelope, membrane, and nucleocapsid proteins) [44]. The spike protein S that binds to receptor ACE2 will mediate invasion then inducing antibodies to spike proteins helps block the invasion. Thus, the vaccine's goal is to produce neutralising antibodies to viral spike proteins. This could block infection by preventing uptake through the human ACE2 receptor.

Nowadays, massive attempts have been made to develop safe and effective vaccines that could reduce the spread of virus. By 2022 January, 10 types of vaccines are already approved by world health organization such as Pfizer(mRNA), Moderna(mRNA) and Sinopharm (attenuated), Johnson &

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Johnson (viral vector vaccine), Novavax (protein subunit vaccine) and hundreds of them are going through preclinical trials [6] [7]. Although current vaccine could not put an end to the pandemic spread completely, it could protect human from death and hospitalization to a large extent.

This article will then discuss and compare different subtypes of vaccines approved by WHO, including how do they work, their advantages/disadvantages, their safety issues, adverse effects and efficacy in clinical trials through the recorded data from volunteers. At the end of article, the vaccine efficacy against COVID-19 variant will be discussed as well.

2. Vaccine type

2.1. Whole virus vaccines

The immune response is triggered by a weakened (attenuated) or inactivated form of coronavirus in whole virus vaccinations. They will be treated by heat, chemicals, or radiation ahead of injection so weakened vaccine will replicate within cells but not infect them. On the other hand, inactivated vaccines can not replicate within cells and infect them but can still trigger immune response.

Attenuated and inactivated vaccines are well-established technology, easy to manufacture, unit cost cheap, easy to transport and administrate. In addition, without the use of adjuvants, attenuated can also target and generate significant cellular immunity, which is required for protection [9]. However, using a live-attenuated vaccine may enhance the risk of recombination between the vaccine strain and the wild-type virus, leading to the creation of new viral types [11] and inactivated vaccine are relatively poor at cell mediated response so it might require repeated doses and or/ booster doses. Also, the production and formulation of vaccine are labor-intensive and have strict quality control so large-scale production will be slowed down.

2.2. Protein-based vaccine

One type of protein-based vaccine is Protein-subunit vaccine which consists of viral antigenic fragments (eg: viral spike protein) produced by recombinant protein techniques [13]. They are manufactured easily, have relatively less side effects and well-tolerated than whole virus vaccines. But they are less immunogenic so might require an adjuvant to improve it [14]. 33 SARS-Cov-2 protein subunit candidates vaccines are in clinical development with one of them shown to have capability of inducing high titers of neutralizing antibodies [25].

Another protein-based vaccine will employee non-infectious virus shells in the similar structure as coronavirus to trigger immune response; refered as virus-like particles for they lack the key genetic material [26]. Nowadays, 5 virus-like particle vaccines are already in clinical trial stage [6] [7] [27].

2.3. DNA vaccine

This novel type uses the nucleic acid as genetic instruction for SARS-CoV-2 protein to generate an immune response. It operates through injection of genetically engineered plasmid containing antigen-encoding DNA sequence [7]. This is because plasmids provide a simple way to transfer genes between cells because they can duplicate the main chromosomal DNA on their own [11]. Antigens will then be expressed on the surface of host cells, which can be detected by immune system and trigger immune response.

2.4. RNA vaccine

RNA vaccines work by injecting mRNA, which is subsequently taken up by antigen presentation cells (APCs) and other target cells, causing them to express appropriately folded and glycosylated antigenic proteins in the cytosol, as shown in figure 1 [18]. Next, the cellular immune response against encoded proteins will be triggered. Besides, for self-amplifying RNA vaccines (saRNA), they include a replicon based on alphaviruses non-structural proteins, capable of self-amplifying in host cells [19]. Therefore, It will produce more protein and have a higher immunogenicity than traditional mRNA vaccines [20].

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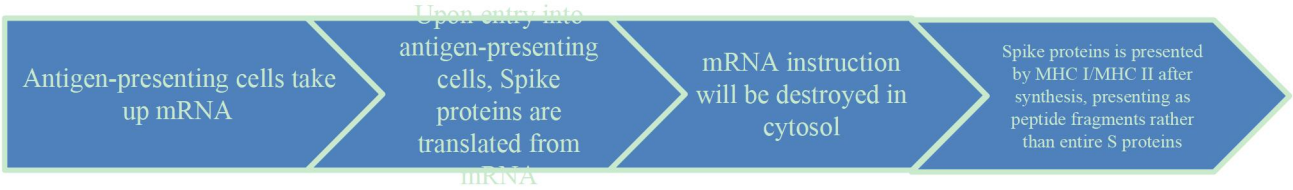


Figure 1. Working process of mRNA vaccine. mRNA will bind to ribosome in cytoplasm and translate to produce properly folded and glycosylated proteins in cytosol before being destroyed in cytosol.

On the one hand, it takes advantages of fast development, promising clinical trial results and scalable manufacturing through cell-free production. On the other hand, this vaccine is extremely difficult to be stored, because it is susceptible to hydrolysis, it must be kept frozen at -80 to 20 degrees to ensure stability in a long term [21]. Therefore, its thermostability need to be improved.

2.5. Viral vector vaccine

The viral vector uses a genetic code of making specific antigens in host cells. It acts as a delivery system, invading cells and inserting code into host cells for SARS-CoV-2 antigens, as shown in figure 2 [18]. The code contains the full length SARS-CoV-2 protein, which could trigger an antibody response to virus infections by blocking virus invasion in type 2 alverlar cells of the lungs, lowering infection morbidity and severity [30]. Because the virus used as vectors had been chemically weakened, human body could develop strong immunity without developing disease. The commonly used vectors are adenovirus, measles virus and vaccinia virus. Adenoviruses can be classed as both replicating and non-replicating vectors, although they have characteristics of both [29].

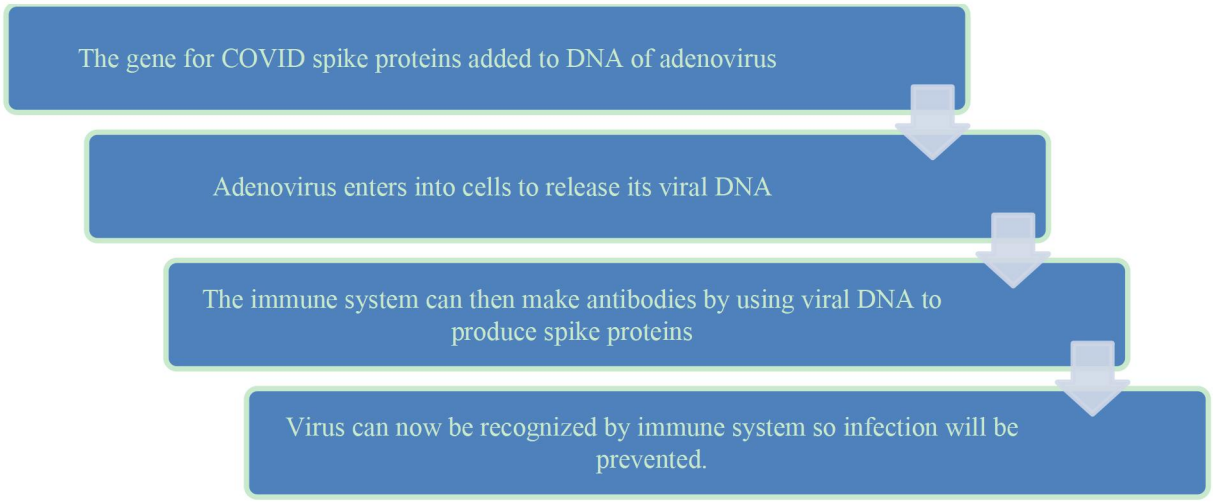


Figure 2. Working mechanism of viral vector vaccine and how does it boost immunity. It works differently than RNA and DNA vaccine and is extremely useful in avoiding mild to severe Symptoms of COVID-19.

One drawback for this type of vaccine is that the vaccine's effectiveness will likely be diminished if people have previously been exposed to the viral vector and established an immune reaction against it. However, what makes Janssen viral vector vaccine advantageous over other candidates is that it is only administered in one dose, which will reduce the manufacturing cost [28].

One example of viral vector vaccine is Oxford vaccine produced from a weakened variant of a common cold virus called an adenovirus from chimps that has been engineered to contain coronavirus genetic material [4]. The genes of spike proteins on surface of coronavirus will be put into harmless adenovirus to make a vaccine. Next, this viral particle enters cells, starting to produce spike protein and leading to the production of antibodies which activate T-cells to destroy cells with spike proteins.

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3. Efficacy and safety issues

3.1. Whole virus vaccines (Sinopharm)

An Clinical trials including 40832 participants who have at least received one dose of 2-dose inactivated vaccines from either SARS-CoV-2 WIV04 (5 μg/dose) or HB02 (4 μg/dose) strains or an aluminum hydroxide-only control, with a primary end point [12]. Meanwhile, the primary key efficacy and objective was the efficacy of avoiding positive PCR test and the secondary outcome is severe cases of COVID-19 and/or mortality. Both of these 2 outcomes were detected or measured at least 14 days after injection of the second dosage among participants who had no virologic evidence of infection randomly.

These participants have mean age of 36.1 years, 84.4% are men and 94.6% has received one dose. At the same time, 26 volunteers were found to have positive symptom in WIV04 group per 1000 person-years, 21 in HBO2 and 95 in alum-only group [12] from table 1. Thus, efficacy for these two Sinopharm vaccines was 72.8 percent in the WIV04 group and 78.1 percent in the HB02 group when compared to an aluminium hydroxide-only control, which are average value taken from a wide range of age group for total sample. As a result, their efficacy against symptomatic COVID-19 has been proven when compared to an aluminium hydroxide-only control.

None severe cases has been spotted in vaccine group, which demonstrate 100% protection against death. After 7 days of injection, 41.7 percent to 46.5 percent of participants in these three groups experienced adverse reactions, with only a few major side effects. (less than 0.5% in these 3 groups) [12].

Table 1. The protection rate of Sinopharm vaccine against pathogen among three group of vaccine recipients.

	Number of volunteers infected per 1000	**Efficacy (%)**
WIV04	26	72.8
HB02	21	78.1
Aluminum hydroxide-only group	95	

3.2. Protein-subunit vaccine (Novavax)

The safety and effectiveness of coronavirus 2 infection in adults without severe acute respiratory syndrome were investigated. In clinical testing, the Novavax vaccine was found to be safe and associated with a strong immune response in healthy people, with the purpose of determining immunisation efficacy against PCR positive results at least 7 days after the second dose [15].

On the total tested sample of 29.949 volunteers from December 27, 2020 to February 18, 2021, 19,714 of them received vaccine and 9868 got placebo. Three months after injection, 14 positive cases were reported within vaccine recipients and 63 among placebo recipients, which confirm the findings about 90.4% vaccine efficacy. Moreover, only ten moderate and 4 severe cases has been found, proving almost 100% vaccine efficacy against moderate-to-severe COVID-19 symptom. In turn, adult participants received two doses of this vaccine, which provided 89.7% protection against SARS-CoV-2 infection and good effectiveness, with no hospitalization or death reported among volunteers in the vaccination group.

In terms of safety, tenderness and injection-site soreness were the most common side effects. but the median duration will be no longer than 2 days. Also, other common side effects are headache, fatigue and malaise after 2 dose and have the duration of 1 day or less and any severe fever among both vaccine and placebo recipients was less than 1%.

3.3. Viral vector vaccine (Johnson & Johnson vaccine)

It is shown that 90% people will be generated antibodies after one dose of it, greater than 2 doses of vaccine. A single dose of the vaccine could effectively prevent moderate to severe COVID-19 in 66%,

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and prevent hospitalization and death in 100%, according to data examined by the US Food and Drug Administration to authorize the vaccine's marketing [17]. This is because after 14 days of vaccination, 468 total confirmed cases were found in the trial group with total 43783 participants, which was divided into two age groups: 18-59 years and 60 and older in a 1:1 ratio. Overall, there were 464 mild to moderately severe cases, with 116 cases in the vaccine group against 348 from the placebo group. Also, very little severe side effects and allergic reactions limited to fever, headache and myalgia had been developed towards volunteers with 9% fever among volunteers [22].

3.4. RNA vaccine (Moderna and Pfizer)

In the controlled trials of Pfizer, a total of 43548 participants were chosen, with one group receiving the vaccination and the other a placebo in a 1:1 ratio. 180 COVID-19 cases were identified, 8 from the vaccinated population and 172 from the placebo group [23]. Thus, 95% effectiveness at preventing viral infection could be shown [24]. Ten severe cases were found among 170 cases, with the placebo group accounting for nine of the ten severe cases [23].

The Moderna vaccine (mRNA-1273) trial enrolled 30,420 volunteers and half of then receive the vaccination and the rest receive a placebo [24]. In the placebo group of 15,210 participants, 185 people were infected with COVID-19 virus, whereas 11 people were infected in the vaccine group, indicating that the vaccine is 94.1 percent effective.

If adverse effects need to be taken into account, 27% vaccinated group and 12% for placebo group has experienced side effects. Shoulder injury, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia were among the major adverse events observed. Oro-facial and oculofacial side effects were reported in moderna and Pfizer vaccine group. Facial, labial, and glossal edoema, as well as acute, transitory, unilateral peripheral facial paralysis, were among the rare (1:1000) side effects identified..

3.5. Viral vector vaccine-Oxford-AstraZeneca (AZD1222)

In a 2:1 ratio, 32,451 participants were randomly assigned to receive either AZD1222 or placebo. In those 65 and older, overall vaccine efficacy was 74 percent, with projected vaccine efficacy at 83.5 percent (Ann R et al, 2021). There were no severe COVID-19 cases among 17,662 participants in the vaccine injection group in the completely immunised analysis subgroup, which prove 100% protection against death and hospitalization. It's also extremely safe, with very few major and medically attended side effects occurring. However, Thrombosis with Thrombocytopenia Syndrome (TTS) is a new form of adverse event, which involves significant blood clotting episodes and low platelet counts, although this is extremely rare after injection [27]. More rigorous studies need to be performed to fully assess significance of these events.

4. Variant protection

After discussing the efficacy against unmutated version of pathogens, the efficacy against mutated version of Sars-Cov-2 need be taken into account as well. A variant is a slightly altered or mutated version of virus, with omicron being one. It is strikingly different from some other COVID variants because of huge changes it has undergone. To be more specific, the new variety features 32 spike protein alterations and ten receptor binding domain mutations that help it enter cells. The evidence indicates that omicron infection tends to be milder because fewer people getting infected need hospital treatment compared to other variants [31].

It is widely known that both the original SARS-CoV-2 strains and the alpha variant of the virus induce clinical illness can be prevented by vaccine effectively, which appeared in early 2021[34] [35] [36]. Although two doses of immunizations could effectively prevent serious diseases and death, when it comes to delta and omicron variants, vaccine efficacy against infection and mild sickness has been reduced [37] [38] [39]. This shows 2 doses of COVID vaccine may not be enough so boosters are required to improve protection from both mild and severe illness [32] [33] [40] [41] [42].

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A test-negative case-control paradigm (B.1.617.2) is used to determine vaccine efficacy against symptomatic sickness due to omicron and delta. After receiving two doses of BNT162b2, ChAdOx1 nCov-19 (AstraZeneca), and mRNA-1273 (Moderna) for primary immunisation and a booster dose of BNT162b2, ChAdOx1 nCov-19, and mRNA-1273 for additional immunisation [43], the effectiveness could then be calculated.

886.774 persons were diagnosed with the omicron variant, 204154 people were infected with the delta variant, and 1572621 people tested negative between November 27, 2021 and January 12, 2022. Vaccine effectiveness was better among delta versions than omicron variants at all time points studied, including after the primary and booster doses. For instance, at 25 weeks or more, vaccination efficacy after two BNT162b2 doses was 65.5 percent. Vaccine efficacy after booster dose improved to 62.4 percent in chAdOx1 nCov-19 primary course patients at 2 to 4 weeks, then dropped to 39.6 percent at 10 weeks or later. Vaccine effectiveness in BNT162b2 primary course patients increased to 67.2 percent 2 to 4 weeks after booster injection then fall to 45.7 percent at 10 weeks or later [43]. The most effective combination is BNT162b2 primary dose + mRNA-1273, which lead to highest vaccine effectiveness of 73.9% at 2 to 4 weeks as shown in table 2, although it will fell to 64.4% after fifth week.

Overall, this study demonstrates that primary immunization of 2 doses vaccine could not provide sufficient protection against symptomatic disease from omicron. However, after any first course, the BNT162b2 or mRNA-1273 booster significantly increases protection, but the protection will fade with time.

Table 2. Vaccine effectiveness for combination of different primary doses (in vertical column) to different booster doses (in horizontal row). The effectiveness is represented in %. Also, the combination between BNT162b2 (primary injection) and mRNA-1273 (booster shot) could develop strongest immunity against omicron.

Primary/booster dose	BNT162b2	ChAdOx1 nCov-19	mRNA-1273
BNT162b2	67.2%	/	73.9%
ChAdOx1 nCov-19	62.4%	/	70.1%
mRNA-1273	/	/	/

5. Conclusion

Above vaccines are both working quite effectively towards pandemic with own characteristics. On the one hand, the whole-virus and protein-based vaccines are relatively safe on people but less effective in combating mutated pathogens. mRNA vaccines, on the other hand, are relatively novel techniques to more effectively generate immune response to mutated viruses but has some storage issues. Also, mRNA vaccine has relatively higher efficacy against COVID-19 but inactivated vaccines have less severe side effects compared to other vaccine candidates. Last, to better protect public from mutated pathogens, booster shot is necessary to enhance their immune response. Based on these findings, development of fast and successful COVID-19 vaccines need to be achieved and encouraged worldwide to combat pandemic.

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