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Review Of Covid-19 Vaccines

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A B S T R A C T

SAR-COV2 is still a pressing issue, 219M people were infected and more than 4.5M lost their lives. The majority of antiviral and inflammatory therapies could only provide a supportive role in treating a limited number of COVID cases. This review investigates the available vaccines in terms of their safety and efficiency in fighting the virus. Seven vaccines are similar in their side effects to other influenza vaccines and their necessity to a booster dose. Although that several technologies have been used to manufacture the vaccine, mRNA vaccines clearly show a high protection rate touched 90% specially in severe and hospitalization cases prevention. Among all available vaccines, Pfizer vaccine is an exception as it granted the full approval to be used in people age 16 and under till five years.

1. Introduction

Recently, there have been increasing experiments done over the respective vaccines to be effective against the COVID-19 [1]. All these projected vaccines have the same goal: build up strong immunity toward the virus and contribute to stopping the broad, rapid spread of the infection [2]. Such an objective could be achieved by triggering the body's reaction toward a specific antigen that exists on the virus. With SARS-CoV-2, it assists the virus to take over cells inside the body [3]. In general, most of the vaccines are activated by letting the body face the molecules of the pathogen in order to start the immune rection. However, the level of exposure different depending on the type of vaccine. Vaccines can be categorized into four types [2,3]: Whole Virus, Nucleic Acid, Viral Vector, and Protein Subunit. Some carry antigen into the body, while the others utilize the body's cells to make the viral antigen [4].

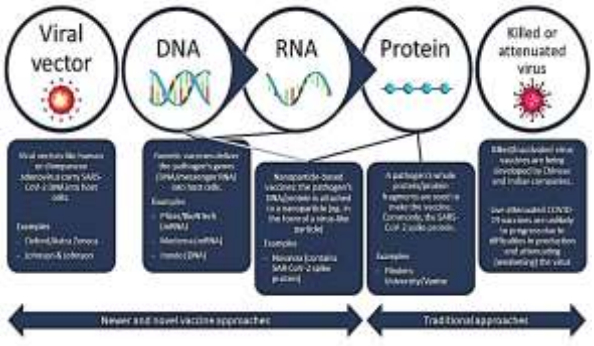

Fig (1): The new and novel vaccine approached in comparison with traditional [3].

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2. Structure Of The Spike Protein

With a size of 180–200 kDa, the S protein contains a transmembrane (TM) domain cored in the viral membrane, a short intracellular C-terminal segment, and an extracellular N-terminus [4]. S protein typically found in a metastable, contact between the virus and host cell results in a substantial realignment of (S protein) and prefusion conformation happen. Such a process allows the virus to utilize the host cell membrane. With the aid of polysaccharide molecules, the virus remains undetected and passes the host immune system [5].

The aggregate length of SARS-CoV-2 is 1273 aa. The N-terminus contain the signal peptide. Both S1 and S2subunits are in charge of membrane fusion and receptor binding [6]. S protein monomers can be seen in Coronavirus' structure, S1 and S2 subunits formed stalk region and bulbous head [7]. SARS-CoV-2 trimeric S protein's structure can be determined by using a cryo-electron microscopy utilized to unfold corresponding functions of the S Receptor Binding Domain (RBD) and its various conformations in opened and closed states [8, 9].

Basically, the CoV S protein is found in nature as an inactive state. However, S protein is activated by target cell proteases, cleaving it into S1 and S2 subunits [10] that are needed for activating the membrane fusion domain after viral entry into target cells [11]. The S protein of SARS-CoV-2 acts similarly to other coronaviruses [11,12]

3. Spike Protein Function

The S protein on the virus' surface is the major factor in the infection [13]. This trimeric class I TM glycoprotein act as a point of entry for the virus. Further, the SARS-CoV-2' S protein plays another function during viral infection by mediating receptor recognition, fusion, and cell attachment. [9,13,14,15,16,17]. The S protein that binds to the receptor is the main unit located on the surface of the viral envelope [9,17]. The S1 domain holds RBD, which binds the virus into the receptor, while the S2 domain carries the HR1 and HR2 domain[18].

4. Receptor Binding

It can be seen that recognizing the receptor ACE2 allows the SARS-CoV-2, S protein to bind to the host cell [17]. ACE2 is a homolog of ACE, which converts angiotensin I to angiotensin 1–9 [19]. ACE2 exists in the intestine, lung, and other organs such as the kidney and heart. Also, it is found on the major expressing cells, which are alveolar epithelial type II cells [20]. The formation of endosomes is promoted when the S1 subunit of the SARS-CoV S protein binds with ACE2, which triggers viral fusion activity under low pH [21].

S protein and ACE2 interaction might be used to detect intermediate hosts of SARS-CoV-2. The reason behind the selection of ACE2 is that it comes from species with a conserved primary structure like mammals and birds [22]. A comparison to measure the binding affinities between ACE2 and SARS-CoV-2 S from different mammals and animals like snakes and turtles. The result showed that the ACE2 of *Bovidae* and *Cricetidae* interacted well with SARS-CoV-2 S RBD; however, the ACE2 from turtles and snakes could not. Within the S1 subunit, specifically the RBD region, the S protein binds to ACE2, resulting in viral attachment mediation as a trimer to host cells [8]. At 14.7 nM dissociation constant (KD), COVID 19 S binds to human ACE2. It is good to note that S protein is 325.8 nM [8], which means it is more sensitive to ACE2 than is SARS-CoV S. During an investigation of COVID 19 proteins, it has been found that there is 24% difference in S between SARS-CoV-2 and SARS-CoV, while RBD is only 23%[23].

5. Viral Fusion

Viral and host cell membrane's fusion lead to viral genome's release into the host cell. The basis of fusion is the cleavage of both S1 and S2 subunits. The subunits take a noncovalent state waiting the viral fusion to happen by host proteases such as TMPRSS2, which is essential for S protein priming [11,31,32, 24]. The previous literature indicated that COVID 19 S has multiple furin cleavage sites. In other words, this raises the probability of being cleaved by furin-like proteases and eventually, infectivity is enhanced [25,26,27,28]. What happened in 1997, the avian influenza outbreak that took place in Hong Kong was a good example of the furin-like cleavage domain [29,30,31,32,33]. To sum up, the SARS-CoV-2 is more contagious than the previous SARS due to the presence of a specific furin cleavage site. The 6-HB, FP in the N-terminus, and two HR domains on S2 are all essential for viral fusion [34]. Under the action of some special ligands, the fusion protein undergoes a conformational change and then inserts into the host cell membrane [35].

6. Types Of Covid-19 Vaccine

7. Whole Virus

These types of vaccines work by using an inactive pathogen that enhances the immune response. It can be subdivided into two types. First, live attenuation uses a weakened form of the virus that can grow and replicate without causing illness [36]. Second, inactivated that contain viruses with terminated genetic material by heat, chemicals, or radiation; as a result, they become unable to infect cells and duplicate but can activate the immune system's response[37].

As far as we know from released information by vaccine's manufacturers, advanced technology is being used in both types to be approved by regulatory authorities. However, the first type is more likely to cause infection to individuals with relatively weak immunity and need special storage conditions (-90C). Such conditions add a heavy burden on third-world countries in terms of cost and time of distribution. Rarely, the vaccinated people of this type of vaccine could be prone to a more pathogenic form and triggering disease [38]. The second type of vaccine (inactivated) could be safer than live ones as it contains the disease-causing virus or parts of the virus and is suitable to individuals with compromised immunity; however, it requires cold storage [39,40,41]

8. Whole Virus Mechanism of Action

8.1. Active

This type of vaccine uses natural pathogens but in a weakened version. The body's immune system will react similarly when other pathogens invade cells, so it activates its defenses toward it, such as killer T, helper T cells, and antibody-producing B cells[40].

This reaction persists till the virus is off the system. In other words, there is enough time for memory cells to develop against the virus. As a result, it is suitable for the immune system to be exposed for the whole attenuated [41].

8.2. Inactive

Although the genetic material of the virus is terminated, it may still carry several proteins that the immune system could identified and take an action; this action will be limited as the mentioned proteins could not infect cells. Based on this, mild stimulation of antibody will occur for a short time. The way of administration of these vaccines comes alongside with adjuvants and may need booster doses[42].

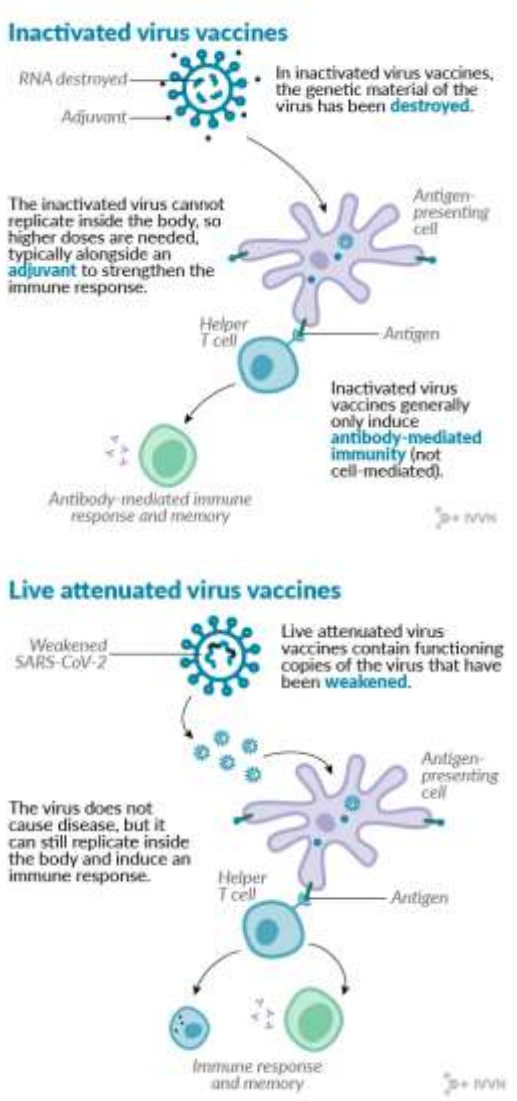

Fig (2): Mechanisms of immune response against live attenuated vaccine and inactivated vaccine [40]

9. Sino Pharm Vaccine

This vaccine used an applied technique in a wide range of vaccines like Rabies. It is simply made of virus particles grown in culture and cannot cause disease [43]. The virus was cultivated in a qualified Vero cell line for propagation, and the supernatant of the infected cells was inactivated with β-propiolactone (1:4000 vol/vol at 2 to 8 °C) for 48 hours. Following clarification of cell debris and ultrafiltration, the second β-propiolactone inactivation was performed in the same conditions as the first inactivation [44]. It was 79% effective, as announced by the manufacturer. It is authorized for people between 18 to 60 years of age [45]. It cannot be given to people 60 years or older who suffer from fever and patients with active COVID-19 until the isolation period is complete. The effectiveness for Pregnant women is not yet tested [44,45]. It is given as a single dose vial, Intra-muscular through Deltoid Muscle [44, 45].

10. Vaccine Common Side Effects

10.1. Local Reactions

The injection site may show flush, swelling, scleroma, rash, and itching.

10.2. Systemic Adverse Reactions

Headache is fallen under very common. For common ones; fever, fatigue, muscle ache, joint pain, cough, difficulty breathing, nausea, diarrhea, and itchy skin [44,45].

11. Nucleic Acid

These vaccines use either RNA or DNA, which are genetic materials that instruct a cell to produce the antigen. The viral spike protein is the one in the COVID-19 case. This will lead the human body to produce antigens and eventually start the immune response. The benefits of these vaccines are easy to manufacture and relatively cheaper than the others. The body initiates a strong immune reaction because the mass production of the antigen is done inside the human cells [36, 46, 47]. RNA vaccines require storage conditions of -70C or a similar range; such conditions might impose challenges for low-income countries [47, 48].

The advantages of this vaccine are no risk associated with it as no live components will trigger the disease. The immune response involves B cells and T cells. Relatively easy to manufacture. The disadvantage of nucleic acid vaccines is that they require ultra-cold storage; booster shots may be required, it could be approved for emergency use for human subjects, but it is still not fully licensed for use by accredited health organizations [48,49].

12. Immune Response for RNA Vaccines

RNA type of vaccines uses one of two following methods, self-amplifying RNA (saRNA)- molecular templates utilized by cellular reactors to produce proteins or the antigen of interest in messenger RNA (mRNA). The integration of these two with human genetic materials is almost zero because of their transitory character. RNA driven into cells using similar techniques being developed for DNA vaccines or can be injected by itself within nanoparticles like what applied in Pfizer's vaccine against COVID 19 [50,51,52]. Once the DNA or RNA starts producing antigens inside the cell, these antigens could fall under detection by the immune system, initiate a reaction. The reaction comes in the form of killer T cells, helper T cells, and antibody-producing B cells [51,52, 53]. Designing and producing a vaccine against one of its proteins is relatively easy as its pathogen genome has been sequenced. For example, within two months, Moderna's RNA vaccine entered the clinical trials against COVID-19 and SARS-CoV-2 genome being sequenced [54]. The manufacturing process of RNA and DNA vaccines is different. In the case of DNA, it is a straightforward procedure that begins by encoding the antigen and chemically synthesizing it, then end by inserting it into a bacterial plasmid with the help of specific enzymes. Multiple copies of the plasmid are divided within bacteria, then being isolated and purified[54,55].

This process is easier with RNA vaccines as it is done chemically, without any bacteria or cells, using only a template in the lab. One great advantage in terms of manufacturing DNA and RNA vaccines is reducing the cost significantly and by using the same facilities [55,56].

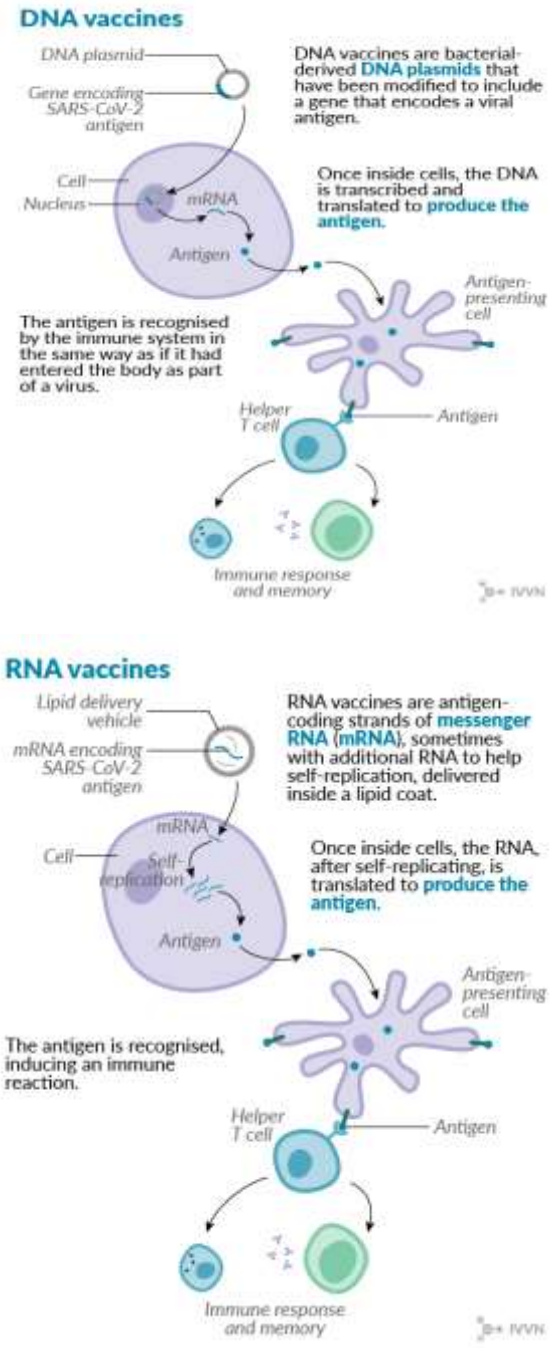

Fig (3): Mechanism of DNA vaccine and RNA vaccine within immune system [55]

13. Pfizer-BioNTech BNT162b2 Vaccine

This vaccine was developed by Pfizer and BioNTech. The vaccine is also called BNT162b2 vaccine. The interesting note about this vaccine is guaranteed FDA full approval on August 23, 2021 [57]. This approval makes it the only vaccine that could be given to people aged 16 and under. Basically, it is an mRNA genetic code of the spike protein at the top of the virus that causes COVID19. While in the body, the spike protein starts encoding, releases an immune reaction [57]. In other words, if the body interacts with coronavirus' spike protein, the body will easily identify and terminate it without causing an infection. The vaccine cannot cause COVID-19 disease; no active or whole virus is included in it. After a few days, the mRNA is naturally degraded [58]. The reports stated prevention of 95% from COVID-19 cases.

On the other hand, the general safety and efficacy of the mentioned vaccine assessed in six countries, including USA, Germany, Brazil, where the subjects over 44,000 people in 20 groups of people, 19 people out of the whole subject will be protected from infection. The protection level of Vaccine was equal in terms of ethnicities, ages, and races. This vaccine is given in two split doses. The second dose is given after 21 days as recommended; however, it can be given till 12 weeks after the first dose [57,58]. The route of administration is intramuscularly in the deltoid muscle after dilution [57]. The side effects ranged from pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever lasted for several days. It is good to mention that people experienced these side effects after the second dose [58,59].

14. Moderna Vaccine

On December 18, 2020, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for this vaccine. This authorization allows the Vaccine to be distributed in the U.S for use in individuals 18 years and older [60]. Moderna Vaccine has a messenger RNA (mRNA) molecule that contains guidelines to produce a protein from SARS-CoV-2. This Vaccine unable to cause COVID-19, as it does not contain the virus itself [61]. 30,000 people participated in the trials; 50% took the actual vaccine where the rest had placebo injections. The trials were anonymous. The people who received the vaccine showed a 94.1% reduction in the number of symptomatic COVID-19 cases. Out of 14,134 vaccinated people, only 11 got infected compared to 185 infected with symptoms out of 14,073 who received placebo [60,61,62].

The trial revealed an efficacy of 94.1%. While 90.9% efficacy was recorded in severe COVID cases, like heart disease, chronic lung disease, obesity, diabetes, liver disease, or HIV infection [61,62].

Individuals 18 years of age and older can take it according to FDA authorization [61]. Pregnant and breastfeeding women, People with known medical conditions, People who have or had COVID-19 already, had a severe allergic reaction after a previous dose of this vaccine, had a severe allergic reaction to any ingredient of this vaccine [61]. It is given as an injection intramuscular. The Vaccine consists of two split doses given one month apart [61]. Redness and swelling at the site of injection. Tiredness, Headache, Muscle pain, Chills, Fever, and nausea at the whole body [63].

15. Inovio Vaccine

It was released by Inovio Pharmaceuticals, USA. A plasmid pGX9501 designed to encode the SARS-CoV-2 S protein has been evaluated as an antigen. The INO-4800

vaccine activates both humoral and cellular immune responses; this reaction is seen within a few days after a single shot in guinea pigs and mice [64]. Phase 1 was done to assess the tolerability, safety, and immunogenicity of the vaccine. It is administered intradermally through electroporation [64,65].

Furthermore, an earlier study showed that the vaccine induced eliminating antibodies that inhibit the binding of coronavirus S protein to the ACE2 host receptor [65]. Electroporation is a technique at the vaccine application site that delivers short electrical pulses; this will cause the cell membrane to be increased by utilizing inflammatory cells and APCs permeability, and the absorption of the antigen will be enhanced [66]. Synthetic plasmid DNA encoding the S protein of SARS-CoV-2A, that comes from recombinant *Bifidobacterium longum*, is used in the bacTRL-Spike vaccine. Bifidobacterium is part of the human microbiota, a nonpathogenic anaerobic bacterium. Theoretically, this bacterium increases the immune response against viral infection and as a consequence, improves the host's endurance [66,67].

16. Viral Vector Vaccine

These types of vaccines use a different technique than most traditional ones, as antigens are not actually one of its contents. However, it uses the body's cells to make them. A modified virus (the vector) can do this by delivering genetic code for antigen [68], then infecting and guiding cells to produce large quantities of antigen, which lead to activate an immune response. In other words, the vaccine mimics the infection that occurs naturally by using certain pathogens-practically viruses. A great benefit of this vaccine is generating T and B cells reflecting robust cellular immune response. Ebola is a good example [69]. These vaccines used a proven technology, build up strong immunity. However, the earlier exposure to the vector could reduce effectiveness, manufacturing is relatively complicated [69].

17. The Process Of Triggering Immunity Of Viral Vector Vaccines

In general, antigens and molecules from Viruses' particles are able to activate an immune reaction. Viral vector vaccines use a similar method. The genetic instructions received by host cells to make the antigen from the target pathogen are stitched into the virus vector's genome [69,70]. The vector allows the vaccine to enter the cell and then inject the code for different antigens. The virus normally does not cause any harm, and cells produce antigens without developing the disease [70]. A good example of a virus that developed as vectors is an adenovirus. Viral vector-based vaccines come in two types.

18. First: Non-Replicating Vector Vaccines

These ones produce the vaccine antigen and cannot generate new viral particles.

19. Second: Replicating Vector Vaccines

These vaccines work on an infected cell by making new viral particles and replicating them to other cells making the vaccine antigen [69, 70]. Once it is inside the human body, it starts infecting cells and injecting their genetic material. Antigen made by human cells is like its own proteins at the surface [71]. The immune system will start to react once the foreign antigen is identified. This reaction aims to release antibody-producing B cells and T cells to eliminate the infected cells by examining the repertoire of proteins expressed on the surfaces of cells [71]. This approach has one challenge in case that people are exposed to the virus vector before and develop an immune response against it. As a result, this will reduce the effectiveness of the vaccine. Based on the above, if a second dose is needed, it should use a different virus vector [71].

20. How Easy Are They To Manufacture

Scalability is the main obstacle in the production of vaccines. Because the old manufacturing method grows viral vectors in cells attached to a substrate, not in free-floating cells, and is hard to do in mass production. Suspension cell lines come to service, allowing viral vectors to be grown in large bioreactors. The assembling process of the vector vaccine is sophisticated, undergoing a series of steps and components, all participating in increases the risk of contamination. This makes costs go up as they need extensive testing after every step. [70,71].

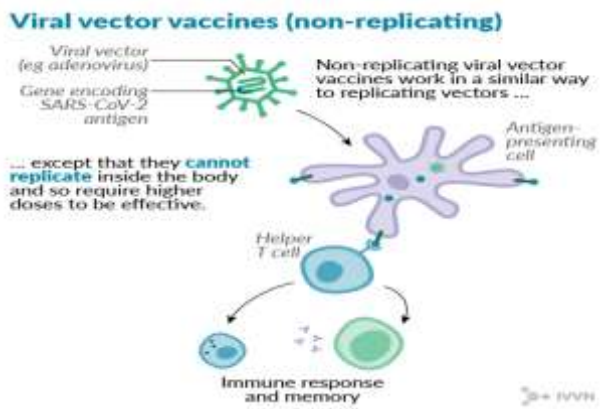

Fig (4): Showe viral vector vaccine replication and the trigger of immune response [70]

21. Oxford-AstraZeneca

This vaccine was designed at Oxford University, a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing COVID19 structural surface glycoprotein antigen [72]. April 23, 2020, a clinical trial in the UK was initiated, followed by three other randomized controlled trials across the UK, Brazil, and South Africa [73]. The immunogenicity results of vaccine from the phase 1/2 UK study, COV001, and phase 2 show a good level of safety represented by neutralizing antibodies generation of the interferon-γ enzyme, showing higher antibody tires. This effect improved by the second dose[72,73,74]. The vaccine showed a 70.4% prevention rate of COVID-19 cases as the results by UK and Brazil trials presented. This outcome was received from two different groups of people and dose regimens. While the vaccine showed higher prevention reached 73% in individuals who suffer from one underlying medical condition. The

vaccine showed no significant difference in immune responses between older adults and young, healthy individuals [72,73]. It is a two-dose course vaccine delivered by intramuscular injection. After 4-12 weeks, The second dose can be given [74]; Pain and tenderness at the injection site are the most common side effects, followed by headache, tiredness, and muscle pain. The rest side effects are similar to seasonal flu [74,75,76].

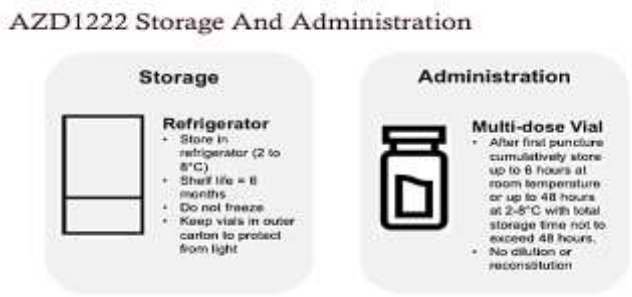

Fig (5): the guide for Oxford-AstraZeneca vaccine [75].

Oxford Uni-AstraZeneca	✓	Viral vector (genetically modified virus)	x2	Regular fridge temperature
Pfizer-BioNTech	✓	RNA (part of virus genetic code)	x2	-70C
Moderna	✓	RNA	x2	-20C
Novavax	Pending	Protein-based	x2	Regular fridge temperature
Janssen	Pending	Viral vector	x1	Regular fridge temperature

Fig (6): The comparison between vaccines [88]

22. Johnson & Johnson Vaccine

The vaccine uses existing technology that involves a virus called adenovirus that may develop respiratory infections. Adenovirus' DNA is being modified in order to make COVID-19 Virus particles and subsequently let the body build up an immune reaction [77]. This process cannot cause infection as the adenovirus is unable to multiply. As this system uses stable DNA molecules, no ultra-cold storage is required, eventually, easier to distribute [77]. 90% of the people who received the Johnson & Johnson vaccine, their bodies produced antibodies against SARS-CoV-2 only after a single dose, and greater amounts of antibodies after the second dose [78]. The vaccine manufacturer claim that one dose of their vaccine is 66% effective in preventing COVID-19 cases that ranged from moderate to severe and 100% effective in preventing COVID-19 related to death [79]. It is good to note that this vaccine developed no severe allergic reaction, and side effects were similar to those of other vaccines. Only 9% of volunteers experienced fever [78,79]. Individuals aged 18 and above are eligible to take this vaccine. It has not yet been established for other age groups or anyone who has a severe allergic reaction to any ingredient of this vaccine [77]. It is a single-dose vaccine administered in injection to muscles [77,80]. In terms of side effects, it is similar to other vaccines, posing no risk to health. It does not contradict making consultations with health professionals about medical history before taking the vaccine [77,78,79,80].

23. Novavax Vaccine

It is a protein-based vaccine engineered from the genetic sequence of COVID 19. Carrying a whole, prefusion spike protein using Novavax's recombinant nanoparticle technology [81,82,83]. The advantage of this vaccine is that it cannot cause COVID-19 or replicate. Also, it is stable between 2°C to 8°C, which means it can be shipped and distributed using existing vaccine supply chain channels [84,85,86,87]. Novavax is a patented saponin-based Matrix-M™ that stimulated antigen entry, presented cells into the injection site, and enhanced antigen presentation in local lymph nodes, boosting immune response [88]. The Novavax is given in two doses; the clinical trial done in the UK was effective by 89.3% in preventing Covid-19 among the participants in its Phase 3, and around 86% effective against the new UK variant [87,88]. Before the vaccine is being submitted for approval by a regulator. More than 15,000 people aged between 18-84 participated in Phase 3 trials, the final stage. Most of the cases were the South African variant, Novavax said, the vaccine was 60% effective for the people who did not have HIV [88].

24. Discussion

A recent report by CDC showed that Among adults aged 65–74 years, the effectiveness of complete vaccination for preventing hospitalization was 96% for Pfizer-BioNTech, 96% for Moderna, and 84% for Janssen COVID-19 vaccines; among adults aged ≥75 years, the effectiveness of complete vaccination for preventing hospitalization was 91% for Pfizer-BioNTech, 96% for Moderna, and 85% for Janssen COVID-19 vaccines [57,57, 61,62]. It is good to mention that the antiviral drugs and hydroxychloroquine show significant side effects and have been prescribed based on compassion; scientific evidence supports its effectiveness against SARS-CoV-2. When considering convalescent plasma as a treatment option, it should be hyperimmune and contain high antibody titers [57, 63]. Since there is no clue how long the antibody is still high after the infection end, there is a short time window to donate after a patient's full recovery. According to the physiopathology of COVID-19 severe patients should be privileged over critical ones in order to reduce mortality and improve outcomes [60,61].

25. Conclusion

This review found that the Sinopharm vaccine is relatively easy to manufacture and does not require strict storage conditions. Such a feature allowed this vaccine to be distributed in undeveloped countries smoothly. However, these vaccines showed medium production against the infection 60 to 70% compared to MRNA vaccine like Pfizer bio that offers high protection 99.6%. It could be true that Pfizer and Moderna vaccine show such protection, but it

required special storage conditions and a high cost of production. The future vision is that the above vaccine requires a supported dose to increase the level of immunity inside the individual body, even though some manufacturers recommend a third poster shut like Pfizer did. This review notices that all vaccines are licensed for emergency use only as they carry side effects, as we have seen earlier in this review.

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مراجعة لقاحات Covid−19

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الخلاصة :

لا يزال SAR−COV2 يمثل مشكلة ملحة، حيث أصيب 219 مليون شخص وفقد أكثر من 4.5 مليون شخص حياتهم. يمكن أن توفر غالبية العلاجات المضادة للفيروسات والالتهابات دورًا داعمًا فقط في علاج عدد محدود من حالات COVID. هذه المراجعة تبحث عن اللقاحات المتوفرة من حيث سلامتها وكفاءتها في مكافحة الفيروس. سبعة لقاحات تتشابه في آثارها الجانبية مع لقاحات الأنفلونزا الأخرى وفي حاجتها لجرعة معززة. على الرغم من استخدام العديد من التقنيات لتصنيع اللقاح، إلا أن لقاحات mRNA تظهر بوضوح معدل حماية مرتفع وصل إلى 90٪ خاصة في حالات الوقاية من الحالات الشديدة والحالات الاستشفائية. من بين كل اللقاحات المتاحة، بعد لقاح Pfizer هو استثناء لأنه منح الموافقة الكاملة لاستخدامه في الأشخاص دون 16 عامًا ولغاية 5 سنوات.

الكلمات المفتاحية: مضاد فيروسات ، كوفيد −19 ، لقاح