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Review Article

Several Vaccinations are Available for the Prevention of the SARS-CoV-19 Virus and its Overall Utility in Males and Women of Reproductive Age

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Abstract

Ever since Covid-19 was marked as a global pandemic and health concern, there have been many attempts to prevent the disease from spreading. Countries all around the world are using different biotechnological techniques to mass produce and manufacture safe and efficient vaccines. Currently available in the market to immunize people against the deadly corona-virus are messenger RNA, viral vectors and live attenuated vaccines, commonly known under their brand names of Pfizer, BioNTech, Oxford AstraZeneca, and Sputnik V, amongst others that are available. Though it is known that these vaccines provide sufficient efficacy against the virus, there isn't sufficient documentation regarding the effect of these covid-19 vaccines on child bearing. In the creation of every vaccine, there is a set of procedures that must be followed. The exploratory stage comes first following vaccine design, followed by pre-clinical trials. Once the safety of the drug has been shown in animal models, it is tested in people in three stages: phase 1, phase 2 and phase 3. After that, it goes through a rigorous examination to evaluate its efficacy before being approved for mass manufacturing. This is a lengthy procedure that takes anywhere from 10 to 15 years to complete. These phases have been shortened in the development of a vaccine for Covid-19, and vaccinations have already been given to the general public. The long term effects of the vaccine is not known and it is not yet elucidated whether these vaccines have an impact on overall fertility in men and women of reproductive ages. Our review article discusses the various vaccines present for Severe Acute Respiratory Syndrome Corona-virus 2 (SARS-CoV-2) and reviews the efficiency of the vaccine in child bearing in both men and women. From our review of different literates, it is evident that the effects of childbearing in men and women that have been vaccinated against corona-virus are poorly understood. This paper acts as a primary guide to encourage future work in this particular area and come to a substantial answer for the same.

Keywords: *Covid-19; Vaccines; Fertility; Childbearing Age*

Introduction

Since the production of the first vaccine in the world in 1796 by Edward Jenner, that is, the smallpox vaccine [1], there have been various different kinds of vaccines such as inactivated vaccines, viral vector vaccines, DNA vaccines, and so on, that are available in the market today [2]. Edward Jenner highlighted that by vaccinating individuals with cowpox virus, the body produces an immunological response to fight the smallpox virus [1]. Each vaccine is designed to produce an immunological response to a foreign entity. These vaccines are developed so that the immune system produces sufficient antibodies to ward off pathogens in an infected individual [2].

Since covid-19 was determined as a global pandemic, many laboratories and manufacturers around the globe have been working tirelessly to develop a vaccine suitable for Severe Acute Respiratory Syndrome Corona-virus 2 (SARS-CoV-2) virus, also known as the coronavirus or covid-19. The outbreak started in December 2019, in Wuhan, China, and soon spread across the continents infecting millions of people. Like the two other coronaviruses (Severe Acute Respiratory Syndrome (SARS) from 2002-2003, and Middle East Respiratory Syndrome (MERS) from 2012 to date) [3], the SARS-CoV-2 virus causes respiratory infections, and patients generally show mild to moderate flu like symptoms that can be treated at home. In some cases, infected patients are asymptomatic and do not show any symptoms at all [4]. However, approximately 15% of covid-19 positive patients develop severe pneumonia and around 5% develop acute respiratory distress syndrome, multiple organ failure, or septic shock [5]. Presently, treatment consists of symptomatic relief and oxygen supply for severe patients. Anti-viral drugs like Remdesivir are constantly being tested for its usage in covid-19 positive patients, however to date; none have been approved for its use. This prompts the development of vaccines that block viral entry into host cells and target specific proteins on the virus [6].

Manufacturing an effect vaccine for SARS-CoV-2 virus is challenging as there is a constant genetic mutation in RNA causing new infections to develop, and hence, creating global wide panic [2]. Research from the previous two epidemics caused by coronaviruses (SARS and Middle East Respiratory Syndrome (MERS)) has helped scientists determine how these coronaviruses effects the body and how the immune system responds to the foreign entity [7]. Even though this research is available, people around the world are still suffering from infection by SARS-CoV-2 virus which is noticed by the numerous deaths across the globe.

Due to financial and economical strains, there are no vaccinations available for the treatment of other coronaviruses like MERS-CoV and SARS-CoV. Apart from finances, gaining a long-lived immune response to these coronaviruses and vaccination design proved to be difficult, and setbacks in terms of vaccination safety was observed in animal models [8]. Due to these factors, developing vaccination for SARS-CoV-2 possess difficulties. At present, there are only a handful of vaccines available in the present day market to treat SARS-CoV-2 virus; inactivated vaccines, protein based vaccines, messenger RNA (mRNA)/DNA vaccines, and viral vector vaccines. The unique replication system of SARS-CoV-2 virus results in challenges during vaccine production.

Production of vaccines for viral infections continues to be challenging and time-consuming. This is especially observed in SARS-CoV-2 virus, as it has uncertain pathogenesis, limited data on animal models as well as humans. Determining the right dosage and schedule for the SARS-CoV-2 virus vaccine is also vague as data on humans is limited. Most countries are still in phase II of clinical trials. Some vaccinations that have been developed require just a single dose to produce an immune response, while others need a booster shot after 4 - 6 weeks.

The effect of covid-19 vaccines on child bearing is not clear or documented. Our review article discusses the various vaccines present for SARS-CoV-2 and reviews the efficiency of the vaccine in child bearing in both men and women.

Different coronaviruses

Coronaviruses belong to the family Coronaviridae and are segregated into four categories namely alpha, beta, delta, and gamma coronaviruses. They are enveloped, ss-RNA viruses with a helical nucleocapsid. SARS-CoV-2, SARS CoV and MERS-CoV all belong to the beta genera and are transmitted to humans through bats. A crucial protein that is expressed on the surface of these coronaviruses is the Spike protein (S-protein) that is a glycoprotein with a trimeric envelope. The spike protein is the main target for antibodies from vaccines to bind to the host cell. It compromises two main sub units that control receptor binding and is involved in membrane fusion, namely S1 subunit and S2 sub unit respectively [9].

The receptor-binding domain (RBD) varies among the different coronaviruses due to different host cell entry receptors. SARS-CoV and SARS-CoV-2 share the same receptor for entry that is the angiotensin converting enzyme 2 (ACE2), whereas the receptor for MERS-

CoV is dipeptidyl peptidase 4 (DPP4). Since both SARS-CoV and SARS-CoV-2 share the same receptor and there is similarity in the RBD sequences, it was thought that both the virus receptors would bind. However, this was not the case. It was further noted that SARS-CoV is more aggressive and lethal when compared to the highly contagious SARS-CoV-2 virus [9].

Which countries are manufacturing Covid-19 vaccines?

It is interesting to note that developed countries like the United States of America, England, and Russia are the main source of vaccine development and manufacture. Other developing countries such as India and China are also in the race of manufacturing effective vaccines for the prevention of severe infection with SARS-CoV-2 virus. But what about the rest of the world? Mass vaccine production comes with different hurdles that are tackled between 10 - 15 years prior to availability of vaccine in the general population. The fastest a vaccine has been approved (before the covid-19 vaccine) was the mumps vaccination which was manufactured in 5 years. This shows that effective and safe vaccine development takes time and has to undergo different phases like the exploratory stage and then pre-clinical studies. Once the effectiveness and safety of the vaccine is above satisfactory in animal models, clinical trials (3 phases) on humans is carried out to test for the immunogenicity and safety [9]. To date there are several vaccines that are undergoing clinical trials, but only a handful have been approved by the World Health Organisation (WHO) for emergency use.

Different types of vaccines

The different kinds of vaccines that have been manufactured with the aim of immunising individuals from the deadly corona virus are as follows.

Sl. No.	General Vaccine Name	Vaccine Type	Country of Origin	No. of doses	Interval between doses	Route of administration	Efficacy	WHO Approval	CDC Approval
1	Pfizer and BioNTech	mRNA vaccine BNT162b2	USA and Germany	2	21 days	Intramuscular-deltoid muscle	52% after 1st dose 95% after 2nd dose	Approved	Approved
2	Moderna	mRNA-1273 vaccine	USA	2	28 days	Intramuscular-deltoid muscle	94.5% after 2nd dose	Approved	Approved
3	Janssen	Adenovirus encoding S-protein Ad26. COV2.S	USA	1	N/A	Intramuscular	66.3% after 14 days in a symptomatic patient	Undergoing investigation	Approved
4	Oxford AstraZeneca	Chimpanzee adenovirus vectored vaccine	UK	2	28-84 days	Intramuscular	76% after 1st dose 82.4% after 2nd dose	Approved	Undergoing investigation
5	Sputnik V	Two different adenoviruses (rAd26 and rAd5)	Russia	2	21 days	Intramuscular	91.6% after 2nd dose	Approved	Not yet approved
6	Covaxin	Inactivated whole virion technology	India	2	28 days	Intramuscular	81% after 2nd dose	Undergoing investigation	Not yet approved
7	CoronaVac	Inactivated vaccine	China	2	21 days or more	Intramuscular	Not clear	Not yet Approved	Not yet approved

Table 1: *Summary of a few Covid-19 vaccines available around the world.*

Inactivated vaccines

This type of vaccine uses a 'weakened' or inactive form of the virus. The whole virus is weakened by using heat, radiation, chemicals or physical measures which increases stability of the vaccine, but in turn requires stabilization of the virus. This allows the body to produce antibodies to fight any virus without causing any disease. Inactivated vaccines produce a weak immune response and so a booster dose in a few weeks may be required to maintain immunity. Studies in mice, rats, rabbits, and primates, revealed that BBIBP-CorV was responsible for an immune response which resulted in the production of antibodies to protect the host from infection by SARS-CoV-2 [10].

Animal trials on mice, rats, rabbits and Rhesus macaques showed that primates that were vaccinated by the inactivated virus developed immunity and was protected from SARS-CoV-2 virus, as opposed to primates that developed interstitial pneumonia when administered with a placebo 2 [11]. To produce a strong and effective immune response, BBIBP-CorV is given as two doses, and said to be efficient and stable and but the viral structure needs stabilisation [12]. Further studies on vaccine safety were carried out in China, that showed that BBIBP-CorV (inactivated coronavirus vaccine) is well tolerated and provides protection against severe infection by SARS-CoV-2 in individuals between the age group of 18 - 80 years [13].

Subunit-based vaccines

Only a few specific antigenic epitopes are used in the development of subunit vaccines through recombinant DNA technologies, which causes a reduction in adverse reactions due to vaccine. A difficulty faced by this vaccine is that due to its specificity, choosing an antigen becomes a bit problematic [14]. Viruses like particles are composed of numerous proteins that have the ability to assemble into nana structures. Upon recombinant expression, these nanostructure then surround the capsid proteins inside themselves [15]. Because virus like particles lacks their own genome, they prove to be stable when compared to non-replicating vectors [16]. Scientists around the globe are working on the 'spike' protein that is visible in SARS-CoV-2. The spike protein is the primary coronavirus surface antigen used presently in clinical trials. Spike protein is essential to enter cells and is observed on the outer layer of SARS-CoV-2. Virus replication is inhibited by antibodies that target this protein and block the virus from entering the cell [17].

The SARS-CoV-2 receptor-binding domain (RBD) vaccine is suitable to prevent coronavirus infections as it has a strong binding affinity with ACE2 receptor [18]. To enhance the safety of SARS-CoV-2 vaccine, pulmonary nanoparticle surfactants that are used to amplify immunity against influenza are being incorporated into these vaccines [10].

Messenger RNA (mRNA) vaccines

The fundamental viral antigen or spike protein is currently thought to be a key element in the production of covid-19 vaccines. mRNA that codes for the spike protein is injected into the body so that the host cell is tricked into making spike protein by translating the mRNA of spike protein, which will then be released by the cell and will cause an immunological response. This advancement in science is relatively new. mRNA-1273 (Moderna) vaccine is a lipid nano element that encodes SARS-CoV-2 spike protein [10].

BNT162b1 (Pfizer) is another recombinant mRNA vaccine, that is administered as two doses within a period of 3 weeks and encodes the spike protein receptor-binding domain (RBD) of the covid-19 virus. An advantage of this kind of vaccine is that a large scale production of mRNA vaccines can be done due to a relatively easier means of manufacture. Distribution of self-amplifying and encapsulated RNA has helped make and effective mRNA vaccine with increased success rates [19]. mRNA Covid-19 vaccines developed by Pfizer and Moderna in USA are the first mRNA vaccines that have been cleared for usage in humans to vaccinate individuals against covid-19.

DNA vaccines

Apart from mRNA vaccines, artificial DNA vaccines that contain the recombinant spike protein or that code for the spike protein are injected directly into the hosts body to activate the immune system. Some vaccinations just use the tip domain of the spike protein as this

area targets the receptors on human cells [10]. INO-4800 (recombinant DNA based engineered design) is required for the encoding and expression of the spike protein in vitro by using a viral based vector. It has been noticed that antibodies that fight SARS-CoV-2 virus further inhibits spike protein from binding to the ACE2 receptor. Studies on mice and guinea pigs suggest that INO-4800 is a potential covid-19 vaccine, as antibodies targeted to SARS-CoV-2 were seen in the lungs post immunization [20].

Viral vector vaccines

A viral vector generally integrates a viral vaccine so that the genome of one virus (example adenovirus) transmits the antigen of the other virus. A few examples of this method includes ChAdOx1, aAPC, Ad5-nCoV, and Ad26-S. Downside to this vaccine is that it needs thorough purification for virus action [21]. Oxford Astra Zeneca vaccination that is developed to fight against SARS-CoV-2 virus utilises a modified adenovirus vector which is obtained from chimps to carry the spike protein gene. It is modified so that production inside the human body is avoided. Once these viral vectors invade host cells through vaccination, spike protein production will begin and will mimic a natural infection hence causing an immune response wherein there is a large production of antibodies against the spike protein [10].

When administered to BALB/c mice, MERS-CoV spike protein that expresses recombinant adenovirus vaccines causes the stimulation of IgA, IgG in blood, and lung memory T cells that creates a long time immunity to MERS virus. This indicates that recombinant adenovirus vaccines cause a defense against MERS-CoV virus in humans [22]. CanSino Biologics and Beijing Institute of Biotechnology in China engineered a vaccine using adenovirus type 5 (Ad5)-nCoV which utilises replication damaged Ad5 to express SARS-CoV-2 spike protein [23].

Live weakened vaccines

The use of live viruses in the covid-19 vaccine is not recommended as it poses higher risks of infection to the individual [14]. In order to manufacture live vaccines, removal of the envelope protein in the virus and inactivation of the exonuclease effects of protein 14 (nsp14) through reverse genetic techniques is required [24]. For the prevention of tuberculosis, the Bacilli Calmette-Guérin (BCG) live vaccine has been developed. Researchers have concluded that a good immune response which could potentially decrease SARS-CoV-2 infection rate can be achieved by administering the BCG vaccine to individuals (10).

Apart from the BCG vaccine, the avian infectious bronchitis virus (IBV) vaccine (strain H), has been said to be beneficial in the treatment of SARS as the safety associated with the H strain blocks immune responses including production of antibodies. Hence, after determining its efficacy in monkeys, the IBV vaccine could be an additional choice for SARS-CoV-2 virus [25]. Both BCG and IBV vaccines are generated by cultivating viral particles under suboptimal environments.

What other measures are being used to control SARS-CoV-2?

In some countries, where there is a shortage of vaccines, or in emergency situations, other vaccines like BCG or oral polio vaccine are being repurposed and used in the treatment of coronavirus as an alternative measure of controlling covid-19. BCG vaccine which is used in the treatment of tuberculosis stimulates broad components of the immune system. It has been seen that BCG vaccinated individuals have some protection against a few diseases like bladder cancer and influenza. At present there are few trials that are being undertaken to determine whether BCG is efficient enough in the treatment of covid-19. Apart from the BCG vaccine, the MMR and the oral polio vaccines are also being investigated [11].

Pfizer and BioNTech vaccine

The Pfizer and BioNTech vaccine (BNT162b2) is one of the first mRNA vaccines developed by the USA. During the initial testing after the first shot of the vaccine was administered, a partial immune response was observed, suggesting that a booster shot be given after a few weeks. This resulted in a stronger immune reaction after the second dose of vaccine was given. Taking both doses of the vaccine helped

in the prevention of covid-19 symptoms. According to the Center for Disease Control and Prevention (CDC), the second booster dosage of the vaccine should be given after an interval of 3 weeks, and not exceed the 6 weeks mark. The CDC also stated that it is not advisable to give the second shot of the vaccine before 3 weeks, but in exceptional circumstances, it may be given up to 4 days ahead of schedule [26]. The vaccine is recommended to the general population above the age of 16 years at a dosage of 30 µg, however they have recently started clinical trials on children below the age of 16 years. The vaccine provides immunogenicity and protection for approximately 119 days with an efficacy of 95% after the second booster dose is administered.

Moderna vaccine

Developed in the USA, Moderna (mRNA-1273) is another type of mRNA vaccine that is available to the public. This vaccine is injected at a dosage of 50 µg to individuals above the age of 18 years. Like the Pfizer vaccine, mRNA-1273 provides immunogenicity and protection for approximately 119 days after first vaccine dose is given and is 94.5% effective in preventing covid-19. Adverse reactions to Moderna vaccine is said to be more when compared to Pfizer. Advantages of this vaccine is that it is not very temperature sensitive which makes transport and storage (-20°C) easier than the Pfizer vaccine which needs to be stored at -75°C. Both Moderna and Pfizer vaccine have been given permission by the food and drug authority (FDA) to use in emergency cases [27,28].

Janssen Vaccine

The Janssen vaccine manufactured by Johnson and Johnson in the USA, is a non-replicating adenovirus vector type vaccine (Ad26) that encodes the S-protein and is administered intramuscularly as a single shot. This vaccine can be stored for 3 months in a refrigerator, and unto 2 years in a freezer, which makes its transport, storage, and usage suitable and simple [29]. Due to blood cloths and a lower platelet count observed in six women aged between 18 - 48 years, the US regulatory bodies paused the manufacture and distribution of the vaccine [30]. Symptoms occurred 6 - 13 days post vaccination. After careful and strict investigations, the vaccine has been brought back to the market for its use in vaccination against Covid-19, as its benefits outweighs its risk [30].

Oxford AstraZeneca vaccine

The Oxford AstraZeneca vaccine (ChAdOx1 nCoV-19 (AZD1222)) is a chimpanzee adenovirus vectored vaccine that is administered in adults above the age of 18 years [31]. The vaccine is not temperature dependent and can be refrigerated making its transport easy. Apart from this, the cost of the vaccine is cheaper than other vaccine competitors [32]. Hence many countries around the globe (such as the UK, South Africa and Brazil) are using this vaccine to protect themselves from the deadly SARS-CoV-2 virus. In India, The Oxford AstraZeneca vaccine is administered under the brand name of "Covishield".

This vaccine is given as two full doses over a period of 28 - 84 days, which results in a stronger memory immune response after the second dose is given as the immune system is given plenty time to mature. If the booster vaccine is given too early, the immune response is smaller as it has not had time to mature yet [33]. Studies show that the AstraZeneca vaccine provides efficacy of 76% after a single dose of the vaccine is given, and this protection is observed up to 90 days post first dose of vaccine. The study further showed that the concentration of the dose was not as important when compared to the time interval between the two doses. Research on Ebola and Influenza support this notion. Efficacy of the virus is lowered (54.9%) if both the doses were given less than six weeks apart [34].

It is important to note that in March 2021, many countries in Europe suspended (not stopped) the administration of the Oxford AstraZeneca vaccine, as thromboembolic events were seen in a handful of patients, of which one was followed by death after vaccine administration in Denmark [35].

Sputnik V

Originating from Russia, Sputnik V is composed of two different adenovirus vectors (rAd26 and rAd5), combined with the spike protein from the SARS-CoV-2 virus that are delivered 21 days apart in two separate doses to aid the body in procuring an immune response. It is believed that this vaccine is more potent as they incorporated the use of two separate adenoviruses, instead of the same adenovirus given in both doses. Delivering the same adenovirus could lead to an immune response against the adenovirus after the second dose is given and in turn destroy the vector [36]. According to interim phase III trials [37], the vaccine was found to be 91.6% effective in preventing symptomatic infection, and no serious adverse effects were found. Most common adverse effect was pain at injection site coupled with headaches and fever which was common amongst people [36]. Scientists that developed Sputnik V are currently working to reduce the vaccine to a single dose, to manufacture one version of the vaccine that can be stored at -18°C, and the second lyophilised version to be stored between 2 to 8°C. This would help in transportation and ease distribution of the vaccine in other countries [36].

Apart from Sputnik V, Russia has also developed two other vaccines (EpiVacCorona and CoviVac) that are allowed for emergency use, though large scale trials are still pending. EpiVacCorona [38] is manufactured from synthetic peptide antigens that are capable of causing an immune response and are found in SARS-CoV-2 virus. No live virus particles are used in manufacturing this vaccine. CoviVac utilises whole virion technology that includes inactivated cold virus. This allows for a wider immune response which results in defence against multiple SARS-CoV-2 variants [36].

Covaxin

Developed by Bharat Biotech in collaboration with the Indian Council of Medical Research, Covaxin (BBV152) is the first vaccine developed in India to fight against the deadly corona virus. The vaccine uses whole virion technology that consists of SARS-CoV-2 viral particle that is completely inactive and surrounded by a protein shell consisting of RNA in the core. It has been inactivated so it cannot replicate inside the body of the person being injected or cause an infection [39]. The vaccine is administered as 2 doses taken 28 days apart.

Given India's weather conditions and frequent electricity cuts, the vaccine was developed so that it is stable and can be stored in a refrigerator at 2 - 8°C [40]. According to phase I trials, Covaxin was deemed safe with enhanced immune response [39] However, when compared to Covishield (Indian made vaccine of Oxford's AstraZeneca), Covaxin showed a lower immune response after first dose, as seropositivity to the anti-spike antibody was lower in patients that were administered Covaxin [41].

CoronaVac

Sinovac Covid-19 vaccine or more popularly known as CoronaVac is manufactured by Sinovac Biotech in China. This vaccine is made from inactivated SARS-CoV-2 virus. CoronaVac vaccine can be kept in a refrigerator at 2 - 8°C, which makes its transportation and storage easy [42]. Scientists in China initially gathered samples of SARS-CoV-2 virus and cultured them in large quantities with the help of vero cells. After this, the virus is allowed to incubate in beta-propiolactone. This inactivates the virus by binding to their genes, which is later mixed with an adjuvant that is aluminium based [43]. This vaccine is still not approved by the World Health Organisation (WHO) for use in emergency cases as there are many conflicting data on the efficacy of the Chinese based vaccine.

Common adverse reactions to Covid-19 vaccines

As with any vaccine, swelling, pain and redness at the injection site can be observed after the first or booster dose of covid-19 vaccines. Other common side effects include allergic reactions to the vaccine, muscle pain, fever, chills, itching, headaches, fatigue, joint pains, nausea and vomiting. In severe cases, anaphylactic shock, and thrombosis was reported [28,35]. Authorities have advised healthcare professionals to keep a "close observation" for at least 15 minutes after injection of the vaccine [34].

Future scope of fungal vaccines

In diseases which cause immune deficiency, like acquired immune deficiency syndrome (AIDS), cancer patients undergoing radio/chemotherapy, and now patients who have been severely infected with SARS-CoV-2 virus, there is a high risk of being infected by fungal infections [44]. Parallel to the hike in Covid-19 cases, India is now facing deaths caused by a cohort of filamentous moods known as the "black fungus" or scientifically known as mucormycosis. This fungus can be fatal and infects the sinuses which make it difficult to treat [45]. A majority of infection is viewed in patients with diabetes mellitus who are newly recovering from SARS-CoV-2 virus. Different theories are being explored as to this new disease: some scientists believe that Covid-19 virus suppresses the immune system, which helps the fungus thrive and spread in the host's body, while some doctors believe that the fungus spreads from the overuse of steroids [45]. Black fungus is known to invade and infect blood vessels in the host body which leads to thrombosis, necrosis, infraction to tissues, and finally death [44]. This rise in fungal infections in patients who are recovering from Covid-19 is causing epidemics in some places in India, and the need for vaccination against this fungus is of great importance. There are three main types of vaccines available for the prevention of fungal infections: live-attenuated, conjugate and subunit/recombinant vaccines [44].

Live-attenuated vaccine

Live attenuated vaccines provide stronger and longer immune responses in patients with a compromised immune system. However, in some patients with a suppressed immune system, additional care must be taken so that other diseases are not caused. Numerous findings have elucidated the efficiency of this type of vaccine, so that they may be used on people with a healthy immune system in endemic areas to prevent fungal infections [44]. Pan-fungal vaccine plan, which includes the heat-killed Saccharomyces cerevisiae (HKS) vaccine, has a crucial role in providing protection against several fungal infections like C. posadasii and A. fumigatus. The HKS vaccine is administered sub-cutaneous and is effective against virulent strains of the fungus. For treatment of viral diseases and cancer, scientists have reviewed a whole recombinant HKS, which together with cytotoxic drugs can provide wider range of clinical responses. The major drawback is the specificity of the vaccine [46,47].

Conjugate vaccine

When a poor and strong antigen are covalently attached to each other, normally a polysaccharide to protein, respectively, this results in a conjugate vaccine that can generate a good immunological response [48]. Conjugate vaccines target the polysaccharide epitopes, that is visible in all fungi, making it possible to commercially produce pan-fungal vaccines. This is of utmost concern in patients with immunocompromised bodies [48]. One of the earliest conjugate fungal vaccines designed was against C. neoformans. The vaccine combined a capsular polysaccharide (glucuronoxylomannan) and tetanus toxoid that were linked together covalently. and also used an adjuvant (monophosphoryl lipid A) [49].

Subunit/recombinant vaccine

Containing polysaccharides or purified recombinant proteins of fungi, this type of vaccine is commonly researched on. The aim of this vaccine is the transfer and expression of a gene that encodes an immunogenic antigen, which will allow for an immune response [50]. The transferred gene encodes a virulent part of the fungi and these antigens are combined with adjuvants (most commonly used in aluminium salts), which are normally bacterial toxoids in order to achieve a good immune response. The main advantage associated with this kind of vaccine are their safety in immunocomprised patients, as they do not contain any pathogenic agents [44]. Candida species secrete aspartyl proteinase-2 which is a virulence factor that is strongly expressed and shows protection against vaginal candidiasis in rats and phase I human trials. Though this vaccine is safe, there are many disadvantages to it such as the synthesis of the vaccine that includes glycosylation, expensive clinical trials, and health status of the patient [50].

Challenges in Covid-19 vaccine development

Vaccine production and manufacture usually takes at least 10 - 15 years, but in the case of the ongoing Covid-19 pandemic, developing a vaccine to fight the disease has been accelerated. This accelerated and shortened timeline to around one year will pose its own challenges, as long term effects of the vaccine is not known [9], as well as clinical trails have only been performed on a small sample of people, so unwarranted side effects may not show in a smaller sample size as compared to larger samples. Moreover, with a quicker vaccine development, patients with different co-morbidities and those with different demographics are not carefully considered in the vaccine design. Post vaccination check-ups are required to monitor for any adverse reaction to the vaccine, so that these may be avoided in future manufacturing [51].

DNA and RNA vaccines in the past have not been very effective in treating diseases, so it is imperative to keep a close watch on people who have received m-RNA Covid-19 vaccines. At the same time, in the case of viral vector vaccines, a reduced immune response is seen in patients who already have immunity to adenoviruses. Another challenge faced by pharmaceuticals is that there is a limitation of the effectiveness of vaccines when the virus mutates [51]. Even though some challenges are associated with vaccine development, the benefits outweigh the risks, and there is a high demand for vaccines globally.

Conclusion

The SARS-CoV-2 virus has infected millions of individuals throughout the world, with thousands of people dying as a result of the infection. Covid-19 has wreaked havoc on people's lives and shook the world, putting our health-care infrastructure and staff to the test on a regular basis. At the moment, the only way to treat positive individuals is to manage their symptoms and, in certain circumstances, provide extra oxygen. Apart from that, people are encouraged to eat properly, exercise regularly, and take required vitamins as part of a holistic strategy to preventing infection by this virus. For manufacturing purposes, no antiviral medication has been deemed safe or effective. Several attempts have been made and are being made to avoid Covid-19 by vaccines in the last several months. For the production of Covid-19 vaccines, viral vectors, m-RNA vaccines, and live inactivated vaccines are the most preferred options. Though these vaccinations are quite effective at avoiding severe illness infection, there is no certainty that infection will not occur. The vaccine's sole purpose is to prevent serious illnesses and deaths caused by the virus.

There is a fixed standard of procedure involved in any vaccine development. The first step after vaccine design is the exploratory step, followed by the pre-clinical studies. Once safety is achieved in animal models, it is then given to humans in three different phases: phase 1, phase 2, and phase 3 trials, after which it undergoes stringent evaluation to determine its efficacy before it is given a green signal for mass production. This whole process is quite tedious and spans roughly between 10-15 years. In the case of development of a vaccine for Covid-19, these steps have been cut short and vaccines are already administered to the general population.

A noteworthy point to keep in mind is the adverse reactions seen with the vaccine. In most cases, these side effects are negligible like redness or pain at the injection site however in some cases, like seen in the Janssen vaccine, blood cloths were observed. However, people should be advised that these extreme side effects are rare, and do not outweigh the benefits the vaccine brings. We are gradually reducing the infection and mortality rates associated with Covid-19 by encouraging people to obtain the vaccination. It should be mentioned that the vaccination's long-term effects are unknown, therefore it cannot be ruled out that the vaccine will not create difficulties during pregnancy or delivery. More study is needed to emphasize the negative effects of these vaccinations on childbearing.

Bibliography

1. Esparza J., *et al*. "Beyond the myths: Novel findings for old paradigms in the history of the smallpox vaccine". *PLoS Pathogens* 14.7 (2018): e1007082.

2. Shereen MA., *et al*. "COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses". *Journal of Advanced Research* 24 (2020): 91-98.

3. Fauci AS., *et al*. "Covid-19—navigating the uncharted (2020).

4. Sharma O., *et al*. "A Review of the Progress and Challenges of Developing a Vaccine for COVID-19". *Frontiers in Immunology* 11 (2020): 2413.

5. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *The Lancet* 395.10223 (2020): 497-506.

6. Cao X. "COVID-19: immunopathology and its implications for therapy". *Nature Reviews Immunology* 20.5 (2020): 269-270.

7. Liu C., *et al*. "Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases (2002).

8. Amanat F and Krammer F. "SARS-CoV-2 vaccines: status report". *Immunity* 52.4 (2020): 583-589.

9. Sharma O., *et al*. "A Review of the Progress and Challenges of Developing a Vaccine for COVID-19". *Frontiers in Immunology* 11 (2020): 2413.

10. Shahcheraghi SH., *et al*. "An overview of vaccine development for COVID-19". *Therapeutic Delivery* 12.3 (2021): 235-244.

11. Caddy S. Developing a vaccine for covid-19 (2020).

12. Wang H., *et al*. "Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2". *Cell* 182.3 (2020): 713-721.

13. Xia S., *et al*. "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial". *The Lancet Infectious Diseases* 21.1 (2021): 39-51.

14. Clem AS. "Fundamentals of vaccine immunology". *Journal of Global Infectious Diseases* 30.1 (2020): 73.

15. Syomin BV and Ilyin YV. "Virus-like particles as an instrument of vaccine production". *Molecular Biology* 53.3 (2019): 323-334.

16. Mukherjee R. "Global efforts on vaccines for COVID-19: Since, sooner or later, we all will catch the coronavirus". *Journal of Biosciences* 45 (2020): 1-10.

17. Walls AC., *et al*. "Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein". *Cell* 181.2 (2020): 281-292.

18. Tai W., *et al*. ". Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine". *Cellular and Molecular Immunology* 17.6 (2020): 613-620.

19. Wang F., *et al*. "An evidence based perspective on mRNA-SARS-CoV-2 vaccine development". *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* 26 (2020): e924700-924701.

20. Smith TR., *et al*. "Immunogenicity of a DNA vaccine candidate for COVID-19". *Nature Communications* 11.1 (2020): 1-13.

21. Choi Y and Chang J. "Viral vectors for vaccine applications". *Clinical and Experimental Vaccine Research* 2.2 (2013): 97.

22. Kim MH., *et al*. "Superior immune responses induced by intranasal immunization with recombinant adenovirus-based vaccine expressing full-length Spike protein of Middle East respiratory syndrome coronavirus". *PLoS One* 14.7 (2019): e0220196.

23. Bhagavathula AS., *et al*. "Vaccines and drug therapeutics to lock down novel coronavirus disease 2019 (COVID-19): a systematic review of clinical trials". *Cureus* 12.5 (2020).

24. Graham RL., *et al*. "A decade after SARS: strategies for controlling emerging coronaviruses". *Nature Reviews Microbiology* 11.12 (2013): 836-848.

25. Zhang L and Liu Y. "Potential interventions for novel coronavirus in China: A systematic review". *Journal of Medical Virology* 92.5 (2020): 479-490.

26. Livingston EH. "Necessity of 2 doses of the Pfizer and Moderna COVID-19 vaccines". *The Journal of the American Medical Association* 325.9 (2021): 898-898.

27. Mahase E. "Covid-19: UK approves Moderna vaccine to be given as two doses 28 days apart (2021).

28. Meo SA., *et al*. "COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines". *European Review for Medical and Pharmacological Sciences* 25.3 (2021): 1663-1669.

29. Sadoff J., *et al*. "Safety and efficacy of single-dose Ad26. COV2. S vaccine against Covid-19". *New England Journal of Medicine* (2021).

30. Mahase E. "Covid-19: US suspends Johnson and Johnson vaccine rollout over blood clots (2021).

31. Knoll MD and Wonodi C. "Oxford–AstraZeneca COVID-19 vaccine efficacy". *The Lancet* 397.10269 (2021): 72-74.

32. Mallapaty S and Callaway E. "What scientists do and don't know about the Oxford-AstraZeneca COVID vaccine". *Nature* 592.7852 (2021): 15-17.

33. Mahase E. "How the Oxford-AstraZeneca covid-19 vaccine was made". *British Medical Journal* (2021): 372.

34. Wise J. "Covid-19: New data on Oxford AstraZeneca vaccine backs 12 week dosing interval (2021).

35. Wise J. "Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots (2021).

36. Baraniuk C. "Covid-19: What do we know about Sputnik V and other Russian vaccines?" *British Medical Journal* (2021): 372.

37. Logunov DY., *et al*. "Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia". *The Lancet* 397.10275 (2021): 671-681.

38. Dobrovidova O. "Latest Russian vaccine comes with a big dose of mystery (2021).

39. Ella R., *et al*. "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial". *The Lancet Infectious Diseases* 21.5 (2021): 637-646.

40. Thiagarajan K. "What do we know about India's Covaxin vaccine?" *British Medical Journal* (2021): 373.

41. Singh AK., *et al*. "Antibody Response after First-dose of ChAdOx1-nCOV (Covishield) and BBV-152 (Covaxin) amongst Health Care Workers in India: Preliminary Results of Cross-sectional Coronavirus Vaccine-induced Antibody Titre (COVAT) study". *Med Rxiv* (2021).

42. Mallapaty S. "China COVID vaccine reports mixed results—what does that mean for the pandemic?" *Nature* (2021): 15.

43. Phase III. Sinovac COVID-19 vaccine, CoronaVac.

44. Nami S., *et al*. "Fungal vaccines, mechanism of actions and immunology: a comprehensive review". *Biomedicine and Pharmacotherapy* 109 (2019): 333-344.

45. Dyer O. "Covid-19: India sees record deaths as "black fungus". Spreads Fear (2021).

46. Liu M., *et al*. "Saccharomyces as a vaccine against systemic candidiasis". *Immunological Investigations* 41.8 (2012): 847-855.

47. Liu M., *et al*. "Immune responses induced by heat killed Saccharomyces cerevisiae: a vaccine against fungal infection". *Vaccine* 29.9 (2011): 1745-1753.

48. Karch CP and Burkhard P. "Vaccine technologies: from whole organisms to rationally designed protein assemblies". *Biochemical Pharmacology* 120 (2016): 1-14.

49. Devi SJ. "Preclinical efficacy of a glucuronoxylomannan-tetanus toxoid conjugate vaccine of Cryptococcus neoformans in a murine model". *Vaccine* 14.9 (1996): 841-844.

50. Santos E and Levitz SM. "Fungal vaccines and immunotherapeutics". *Cold Spring Harbor Perspectives in Medicine* 4.11 (2014): a019711.

51. Span P. "Older adults may be left out of some COVID-19 trials". *The New York Times* (2020).

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