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Prospects of Vaccination Against COVID-19 and Road to DNA-based Vaccine: A Review

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Abstract

Covid-19 made the countries develop and adopt significant measures to control the spread of disease. For this purpose, firstly countries ordered the public to follow precautions, like, wearing a mask, sanitizer usage, and home quarantine. Then, countries endeavor for the preparation of vaccination started to not only stop the spread but to control and end the coronavirus. These efforts of vaccination started giving benefits in late 2020 and by the end of February 2021, many vaccines were approved conditionally and ready to use, while more were on the way to approval. Apparent from this, there is a great possibility that more clinically proven vaccines will be available on the market in the coming few years. Now, when there is the solution, "The Vaccine", the main point is how to meet the need for the vaccine on a global scale and capital generation for the purchase of vaccine. Till so far, mRNA vaccines are market-available, while DNA-type vaccines are under improvement, being experimented and tested. Because DNA vaccines usually only encode one protein from a pathogen; those may not be as effective if individuals need to mount an immune response to numerous proteins to gain protection, but this can be achieved by combining multiple vaccines. While mRNA vaccines guide the immune system to make a protein that will trigger an immune response without using a live virus and generate longer immunity.



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Introduction

SARS-COV-2 linked with severe respiratory distress syndrome was first witnessed in the city of Wuhan, China. To date, this virus has devoured millions of lives worldwide [1]. WHO officially announced the outbreak of SARS-COV-2 in China on 31st December 2019, initiated a lockdown in the whole of China progressively [1]. SARS-COV-2 belongs to the coronavirus family, which is enveloped viral agent, spherical in shape and range 80-100 nm in diameter. Genomic studies revealed the presence of a single RNA strand composed of 26.4 to 31.7 kilobases. This particular agent bears 96% similarity with the bat coronavirus depicting its zoonotic importance [2]. Vaccination has proven to be a beneficial source of immunity against prevailing pathogens. Since 1950, vaccination programs have refined and revamped quality of life where there has been an increase of 10% in life expectancy and about 66% decrease in infant mortality rate. Eradication of diseases like smallpox and polio (partially) worldwide was only possible due to the implementation of vaccination by every nation [3]. On a broad scale, vaccines are demarcated into 2 groups, one group having live attenuated pathogens while the other group of subunit vaccines, including toxoid vaccines, conjugate vaccines, and carbohydrate vaccines [4]. Since the genomic discovery of SARS-CoV, vaccine production and trials began immediately for the development of protein-based, RNA-based, and viral vector vaccines at a pandemic pace [5]. These vaccines bear the antigen-presenting cells (APCs), which present epitopes of SARS-CoV-2 through the major histocompatibility complex I (MHC class I) in humans. The MHC cells in the newly formed CD8+ cells to destroy the invading infected cells through their cytolytic activity. Moreover, T helper 1 cells (Th1) are activated via MHC class II, which further strengthens the “CD8” + cellular reaction. Production of T helper 2 cells (Th2) and follicular helper cells initiate the formation of viral antibodies; collectively strengthening immunity through B-cell and T-cell activities [6].

Background of Corona Virus Disease

COVID-19 was first recognized as pneumonia in December 2019, which started to spread among

people working or living near the human seafood market. Upon a throat swab test, it was recognized as a novel form of coronavirus by WHO which was named “SARS-COV-2” and infection is known as “COVID-19”. During February 2020, the average mortality rate had risen to 2.1% in China [7]. In February 2020, COVID-19 had spread to 46 countries of the world. Human to the human mode of transmission was hinted and evidence suggested that the viral agent transferred through droplets in close contact. At that time, the calculated reproductive number (R_0) was ranging from 2.20 to 3.58. The incubation period of invading virus ranged from 1-14 days and an average person suffered symptoms after 12.5 days of contact. The possibility of asymptomatic carriers was also calculated [8]. By 11th March 2020, COVID-19 was announced pandemic by the WHO. The disease was suspected to be disastrous in people associated with conditions like diabetes, chronic heart diseases, obstructive pulmonary disease, and renal failure [9]. General indications of COVID-19 may include fever, myalgia, fatigue, dyspnea, dry cough, tightening of the chest, nausea, and vomiting [10]. Severe patients may display falling blood oxygen saturation (below 93%), decreased respiration (less than 30 per minute), while critical patients may undergo respiratory failure, organ dysfunction, or septic shock [2]. Clinically, COVID-19 may manifest lymphopenia and leukopenia along with elevated creatinine kinase and lactate dehydrogenase. Abnormal levels of procalcitonin, aspartate aminotransferase, alanine aminotransferase, and D-dimer have also been observed. Levels of certain cytokines and chemokines were also affected in COVID-19 patients [11].

Vaccine Candidates and Trials

COVID-19 has proved to be a threat to public health on a global level, asserting an impending need to formulate an operative vaccine. The manufacturing of a productive vaccine is critical in the current conditions of the pandemic. Vaccine candidates can provide a good understanding of the development of immunity against the spike protein of SARS-COV-2, which can form an immunological basis for vaccine production in the future [12]. During this pandemic, it is absolute to shortlist vaccine candidates having certain qualities. The phase I trials were based on the

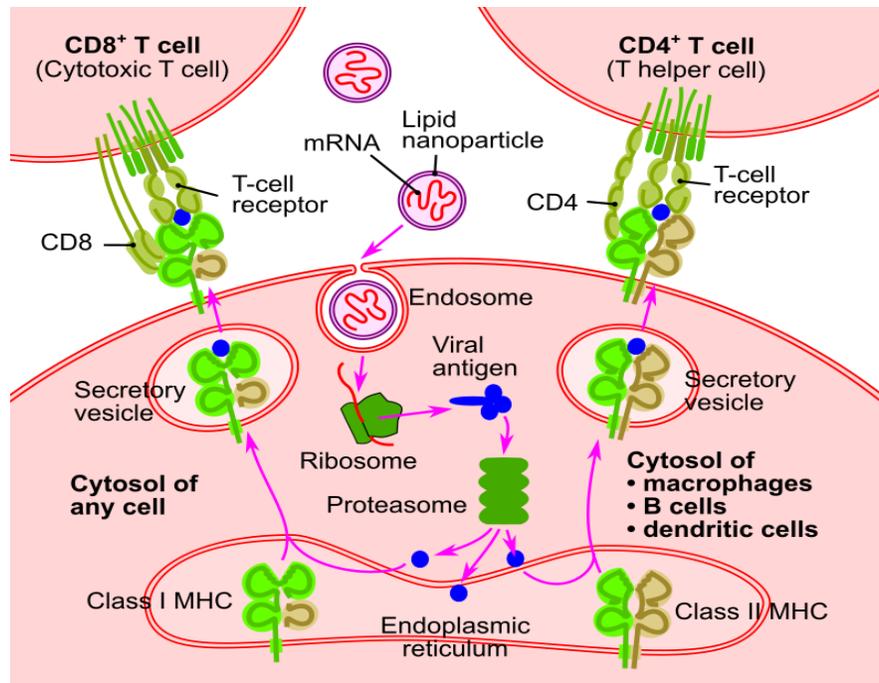


Fig. 1 An illustration of the mode of action of RNA vaccine [57].
Available from: https://commons.wikimedia.org/wiki/File:RNA_vaccine-en.svg

results obtained from animal immunogenetic tests, and the trials were expanded to test human immunogenetic qualities based on the evidence produced from animal models. Progress to efficacy trials (phases 2 and 3) bore additional evidence of the safety of animals injected with a limited dose of vaccine with fruitful effects. Health evaluation of candidates along with studies in animals provided a route to vaccine production with minimum risk and accelerated availability of the COVID-19 vaccine [13]. University of Oxford and AstraZeneca conducted trials of AZD1222 “adenovirus vaccine”. After phase-1, two-dose administration of vaccine was asserted with the standard dose of 5×10^{10} particles per dose, each administered 28 days apart. In total, 19 trials were going on all around Britain. A follow-up of 2 trials of 11,636 participants was conducted within four months consisting of 87.8% people aged between 18-55, and 60.5% participants were female. No one was admitted to hospitals for COVID-19 related symptoms, while some symptoms were seen in participants of the control group [14]. The findings of phase 1-2 clinical trials of the AZD-1222 vaccine conducted by the University of Oxford and AstraZeneca supported the hypothesis that a two-dose vaccine could increase anti-spike protein

production, Fc-mediated functional antibody responses, antibody-dependent neutrophil/ monocyte phagocytosis, complement activation, and natural killer cell activation [15]. Sinovac Biotech Co. Ltd. conducted clinical trials of their inactivated vaccine in Beijing, where they administered 16 SU or 32 SU (SARS-CoV-2 units) in the deltoid muscle, each dose 28 days apart. In total, 36 healthy candidates were chosen for trials, aged between 21-40 having a normal immune system and no chronic disease, they were divided into 3 groups of 12 candidates each. None of the candidates reported a severe reaction to the vaccine, all mild, local symptoms were resolved within 47-72 hours and all systemic symptoms subsided within 24 hours. Seroconversion of 100% was achieved in 2 groups getting 16 SU on day 42 while seroconversion of 91.1% was achieved in group 3 getting 32 SU on day 56 [16].

RNA Vaccine Development and Limitations

With the ascent of the COVID-19 pandemic, an mRNA vaccine was quick to enter clinical preliminaries [17]. For the vaccine development, RNA introduces himself as a flexible and

encouraging stage (Fig. 1). The RNA-vaccine is known for encoding the required sequence of virus. These RNA-vaccines are less susceptible to the host genomic mixing and act as anti-vector immunity, that's why these vaccines propose incredible potential as primers for the COVID-19 vaccine [18]. BNT162b1 is an mRNA vaccine that encodes the trimers of RBD; present on the spikes of the SARS-CoV-2 made of glycoprotein. This mRNA vaccine is the lipid minute formulated particle vaccine, which after vaccination results in vigorous immunogenicity [19]. Nowadays RNA vaccines proved to be more favorable than other types. It has the advantage that RNA vaccines can handle viral infection, develop immunogenicity, and quick production can be made possible [20]. DNA vaccine has developed into a nonviolent and steady technology for vaccination against SARSCOV-2 [21]. In SARS COV-2, the interference of DNA vaccine encodes the S-protein of the virus that produces T-cell and protective immunity and generates NAb responses. The limitations of the DNA vaccine are that it needs precise delivery devices for attaining a good immune response [19]. To obtain a better immune response to SARSCOV-2 infection, DNA plasmids are used to encode immunogenic antigens and deliver them to the host's cells. [22]. Because of the speedily global spread of this novel coronavirus, messenger RNA vaccines for human clinical trials are sometimes not possible to make as a safe and effective vaccine for SARS-COV-2 in this pandemic time to overcome the increasing factor of mortality because of the increasing number of deaths due to this novel coronavirus [23].

Host Infection and Immune Response

COVID-19 is considered the most arduous challenge in the world and for that, the worldwide vaccination program is applied effectively. By overriding virus-induced innate immune repression and assisting adaptive immunological activation, COVID-19 vaccination improves immunity and viral control. Immunity plays an important role in the later stages of COVID-19, as it aids immunopathology efficiently. This happens because of the maximum production of cytokines by macrophages [24]. One study was made to observe the influence of vaccines on the immune response. The people who recovered from COVID19 had 100% CD4⁺ T cells having S

protein specific, whereas 70% had CD8⁺ T cells having S protein-specific in the circulation. These findings suggest that T lymphocytes play a defensive role in the host's defense against Coronavirus-2, which causes severe acute respiratory syndrome [25]. In the host immune response, inactive immune cells in circulation lead the host to self-destruct (Fig. 2). As a result, the COVID-19 becomes more severe [26]. More observations made from people who recovered from COVID-19 recommend that the specific antibody response against the infection has a short life. In these infected persons, covid specific antibodies that have IgM and IgA effects, lasted <6 months. This causes a lack of B-cells and memory T-cells in such people. In the future, such vaccine strategies should be made, which enhance T-cell response resulting in robust long-term memory. By applying such strategies that have memory T-cells provide good safety and boosts the general and systemic T-cell response [27].

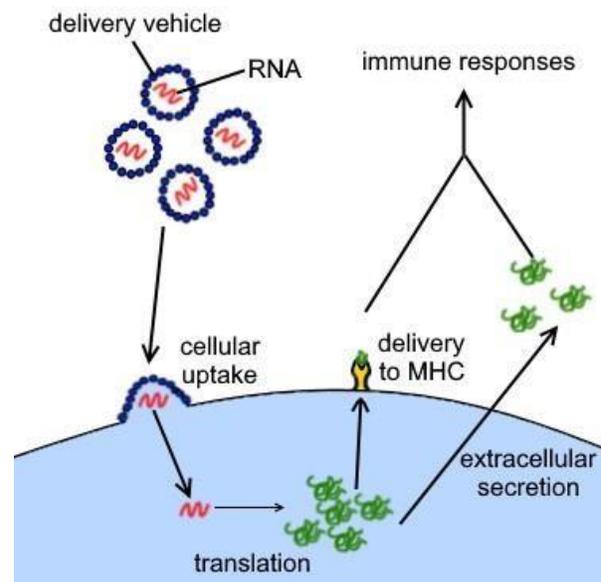


Fig. 2 RNA vaccine illustration [58]. Available from: [https://commons.wikimedia.org/wiki/File:RNA_vaccine_illustration_\(en\).jpg](https://commons.wikimedia.org/wiki/File:RNA_vaccine_illustration_(en).jpg)

Efficacy of Available Vaccines

The efforts around the globe to develop an efficient vaccine that could combat the SARS-CoV-2 are on track [28]. The aged people and people with pre-existing conditions or diseases are more prone to the virus. To get the desired outcome of the vaccine, two

Table 1 Comparative analysis of several commercial COVID vaccines.

Types of vaccines	Brands	Reported side effects	Efficacy (%)
Viral vector	Johnson & Johnson	Pain at site of injection, headaches, & flu-like symptoms [36]	66 [35]
	AstraZeneca	Diarrhea, fatigue, headache, chills, nausea [34]	70 [37]
Protein-based	Novavax	-	60-86 [35]
mRNA vaccines	Pfizer-BioNTech	Pain at site of injection, headaches, Flu-like symptoms, fever & fatigue [38]	95 [31, 39]
	Moderna	Rashes [40], vomiting, fever, headache, muscle aches [34] Nausea	94.5 [37, 41, 42]
Inactivated vaccines	Sinopharm	Headache, fever, pain at the injection site [34]	79.34 [34]
	Sinovac	-	50-91 [37]

ways can be followed: direct vaccination or vaccinating people around the vulnerable people so that the elderly people can be saved from the transmission of the virus [29]. The trials of Oxford-AstraZeneca revealed that the people who got vaccinated with a small dose shot supported by the standard dose after four-week interval showed 90% efficacy [30]. Pfizer BioNTech vaccine studies and trials showed its efficacy to be 52% between the two doses [31]. While the Sinopharm vaccine provides 79% protection against the disease and hospitalization. It was the first vaccine authorized by WHO that can be used in an emergency. Sinopharm and AstraZeneca can provide herd immunity as it gives 100% protection against severe COVID-19 [32]. The people aged above 65 years showed 94% effectiveness with complete vaccination and 64% protection when partially vaccinated with Moderna and AstraZeneca vaccines [43]. Pfizer and Moderna vaccines have been proved to be the most effective against COVID-19 (Table 1) [34].

Success of COVID-19 Vaccines Against Delta-variant

The delta is the form of SARS COVID-2. It's much more contagious than the alpha variant. First It was detected in mid-April 2020 in India after which it got spread all over the world due to traveling from India. To study the effectiveness of the vaccine against delta variant, two methods were conducted; First by using test-negative case-control design to approximate potency of disease caused by both delta and alpha variant. The second was done by estimating the cases of patients diagnosed with delta variants. According to assumption, if the vaccine is

more effective towards alpha variant, then delta variant cases could be much higher. The results were taken by genome sequencing method and PCR to test three genes such as spike, nucleocapsid, and open reading frame 1ab for identifying both variants. Bernal et al. reported that the effectiveness of the first vaccine was higher in people with alpha variant (48.7 %) and much lower in people with delta variant (30.7%) though the result of the vaccine was similar among both, and difference between the effectiveness next the 2nddose of vaccination either ChAdOx1 nCoV-19 vaccine or BNT162b2 was lower as it was 88.0% /67.0% with the delta variant and 93.5%/74.5% with the alpha variant. Overall, the reduced effectiveness with one dose can aid the effort to take two doses of vaccine [43].

Contribution by Various Countries

After the recognition of the causative agent of COVID-19, pharmaceutical groups inflate attempts for vaccine preparations. Moderna Inc. evolved its first mRNA vaccine and conducted its first clinical testing in the US. Other vaccines that are being developed by different countries are inactivated, subunit, DNA based, replicating viral vector-based, and live attenuated vaccines [44]. Canada and South Korea are conducting trials for DNA-based vaccines while Germany and UK are processing mRNA vaccines [44, 45]. In countries, like Pakistan vaccine administration is a most important challenge as several conspiracy theories stand in the way of vaccines, like the polio vaccine. Extensive lockdown is impossible because of economic reasons [46]. In February 2021, Pakistan received the COVID-19 vaccine prepared by a Chinese company, Sinopharm after being reported fewer cases in 2020 [47, 48].

Access and Equity

Globally, with an immense number of people getting the coronavirus vaccine, a couple of countries have effectively begun the execution of vaccine certification which indicates available confirmations attesting coronavirus immunization. The advantage of this certification, the government contends, is permission to travel, and ensuring personal and public safety [49, 50]. Considering all the sources, for the global distribution of the vaccination, there are some inadequate efforts to support the world widely the accession to the coronavirus vaccine (Table 1). It is estimated that almost 25% of the total populace might not probably have access to vaccines until no less than 2022 [51]. Equity in terms of vaccination is quite important. This should be prioritized and considered first and foremost. This considering is due to the uneven distribution and uneven load of the infection and mortality by discrimination of color and low-income societies. On the side of COVID-19 pandemic, this is quite important to follow up on the virus and better use of the vaccine to keep the viral influence down. This indicates that taking “vaccination campaigns” to societies has been hard-hit for a truly lengthy period [52]. According to a recent analysis, various countries have made premarket purchase commitments totaling 7.48 billion doses between November 15 and December 2020. On the front, 13 vaccine manufacturers are there to produce 7.48 billion vaccine doses. The high-income countries purchase more doses of vaccines according to the need of their population for future securement in case of this upgrown pandemic. In this regard, governments and manufacturers need to take strict notice of this. They may also need to give much-needed declarations for impartial distribution of vaccines by more transparency and accountability upon these unfavorable decisions [53].

Strategies Behind Vaccine Operation

With the advancements in molecular biology research, different strategies have been utilized to develop different vaccine types like attenuated, dead, protein type, RNA/DNA based. While some have been tested in the animal specimen, others have passed the stage to the clinical trials, and some have already come to the market [54]. The receptor-binding area of spike protein has been proven as an

Table 2 Income-based distribution of vaccines.

Countries	Doses
High-income-countries (EU)	3.85
United States	0.80
Japan, Australia & Canada	1.00
Low-income-countries	2.34

Note: The numbers of doses are out of 7.481 billion.

effective source of neutralizing antibodies [55]. The S-protein is an important target for combating the virus. It has also been observed that the antibodies produced against the S-protein are lifelong and more effective as it is observed in recovered patients [56]. Nanotechnology has also made way to target viruses using nanoparticles as gene carriers [57]. Nucleic acid vaccines are the traditional vaccines. These are the most prepared type of vaccines because of their safety and feasibility of mass production. With advantages, it also has some drawbacks like a double dose of the vaccine [30]. The whole spectrum of vaccines and vaccination strategies will eventually help to gain herd immunity against the SARS-COV-2 [54].

Awaiting DNA Vaccines

DNA vaccines are made up of genes or fragments of genes. The antigens are delivered into the body of the host using a DNA plasmid vector. It not only stimulates cell-mediated immunity but also humoral immunity. [22]. The DNA vaccines under investigation have been observed to be producing neutralizing antibody effect when the spike protein of the virus is targeted [53]. The DNA vaccines in trials have different approaches like using plasmid coding DNA and the use of hybrid transporter protein to induce an immune response. The route of administration is also uncommon, like the oral route or intradermal electroporation [54]. Most of the vaccines target the S glycoprotein of the virus. The DNA vaccine under development also targets the spike protein and showed promising results when tried on mice, guinea pigs, and macaque, as the viral load and the lung infection in monkeys was decreased when infected again after 9 weeks of vaccination. It also can neutralize antibodies [55]. The manufacturers of ZyCov-D have claimed that this DNA plasmid vaccine has shown promising results when tested in animal models intradermally. The vaccination resulted in neutralizing antibodies and Th-1 response [58].

Conclusions

COVID-19 at its full blossom has been hosted by many countries and many others are still serving the mighty Covid-19. This demands, to take up the framework of WHO's guidelines, particularly formulated regarding COVID-19 and to take precautionary measures at a satisfactory level. No question can arise at the point that vaccination preparation is a long-drawn-out process and can extend to the period of 5 to 10 years. The currently available and clinically verified vaccines, which are also supplied in countries across the globe are mRNA vaccines, like Sinopharm, AstraZeneca, Pfizer, and Sinovac. Now, the efforts to make DNA vaccines continue in a great hustle, which optimistically ensures its availability in the market, in a short time. Likewise other vaccines, COVID19 vaccines also have side effects, while allaying the COVID-19. These side effects are muscular pain, headaches, high temperature, and fatigue. Though, the vaccine preparation and human vaccination are and will remain a challenge and cumbersome process; because of the unsettled queries, superstitions of people, conspiracies against the vaccine, and low budgeted accounts of many countries and pockets of many people, but still the vaccine has successfully pinned public's hope to a corona-free future.

Conflict of Interest

The authors declare that they have no conflict of interest

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