REVIEW ARTICLE

A Review for the COVID-19 Vaccines

Monica Jain, Anil Bhandari**, Alka Bansal***, Shivankan Kakkar******

INTRODUCTION

A novel coronavirus, named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan China and caused the highly contagious disease COVID-19. In few months the COVID-19 became a worldwide pandemic. There have been worldwide 8,97,07,115 confirmed cases of COVID-19, including 19,40,352 deaths, reported to WHO, as of Jan 12th, 2021[1].

Presentation of COVID-19 disease is unpredictable for a few asymptomatic and for others it can cause symptoms starting from flu-like to acute respiratory distress syndrome (ARDS), pneumonia and death. After any infection in our body, immune system develops fighting tools to urge over the infection; and system remembers those tools in form of memory cells (T-cells and B – cells) to protect against that disease. When the familiar antigens are detected, B-lymphocytes produce antibodies to attack them. It is still not clear how long these memory cells will protect an individual against COVID-19 due to rapidly mutating CORONAVirus[3].

Till the last month prevention and cure of the COVID by means of social distancing and good quality self-hygiene measures and experimental repurposed drugs were the only measure available.

Today there is a worldwide race flagged off for a safe, and an efficacious vaccine against SARS-COV2. Four vaccines got Emergency Use Authorization (EAU) from FDA (USA) and CDSCO (INDIA), and approximately two hundred vaccines are in various stages of development and in clinical trials.

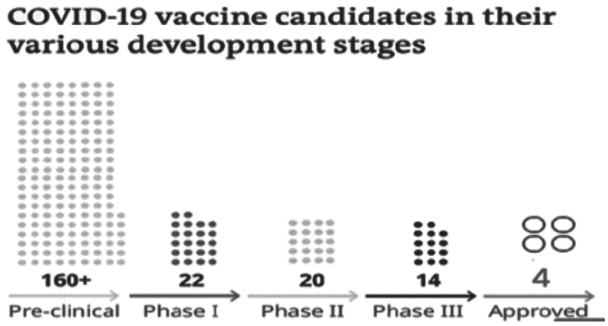

Figure 1: Vaccine candidates in their various development stages

This review will primarily focus on the four approved vaccines- Moderna's mRNA -1273, Pfizer'BioNtech; Fosun Pharma's BNT162b2, Astra Zeneca/Oxford's AZD1222 and Covaxin.

Accelerated COVID-19 Vaccine Development

A new vaccine development typically takes around 10 to 15 years[3], shown by Figure2[2]. The mumps vaccine was the quickest; in five years developed and approved for human use. The exigency of COVID-19 vaccine required a new approach; most of the vaccine candidate opted "Adaptive" and "Compressing" clinical trials models with open digital data share for peer review and quicken approval (*Operation Wrap speed*) to shorten the duration of the complete trial process for the development of the vaccine.

Figure 2: Duration of vaccine trials Standard v/s accelerated

*Senior Professor, **Resident, ***Associate Professor, ****Assistant Professor
Department of Pharmacology, SMS Medical College, Jaipur
Corresponding Author:
Dr. Anil Bhandari
Mob. : 9717545233
Email: anil.bhandari@gmail.com

Vaccine Efficacy or Vaccine Effectiveness[4]:

Vaccine Efficacy and Effectiveness is interpreted as the proportionate reduction in disease among vaccinated group. Vaccine efficacy is used when a study carried out under idea or standard conditions like clinical trial. Vaccine effectiveness is used when a study is carried out in society.

Vaccine Efficacy Effectiveness (VE) is measured by calculating the risk of disease among vaccinated and unvaccinated persons and determining the percentage reduction in risk of disease among vaccinated persons relative to unvaccinated persons.

The basic formula is written as:

Risk among unvaccinated group-Risk among vaccinated group

Risk among unvaccinated group

OR (Odds Ratio): 1-Risk Ratio

Vaccine Efficacy of 90% indicated a 90% reduction in disease occurrence among the vaccinated group.

Final objective of an efficacious Covid-19 Vaccine[5]

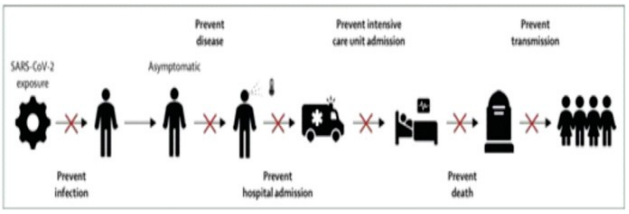

Diagram adapted from Published Online October 27, 2020 https://doi.org/10.1016/ S1473-3099(20) 30773-8

Traditional vaccine Platforms

The mainstream of vaccines presently licensed for human use are often divided into either virus -based or protein-based vaccines[6]. The virus-based vaccine haveinactivated virus that is not pathogenic or is a live-attenuated virus. Since whole-inactivated viruses never replicate so adjuvants are required to stimulate the immune system. Live-attenuated virus vaccines are designed to decline its pathogenic properties and cause no infection or low to mild infection upon injection. Protein-based vaccine comprises a protein purified from the virus or virus-infected cells, recombinant protein or virus-like particles. Virus-like particle contains the structural viral proteins necessary to form a virus particle, but lack the viral genome and non-structural viral proteins. Protein-based vaccines require the addition of an adjuvant to induce a robust immunologic response. There are a number of restrictions like large quantities of virus required, ought to be grown under Biosafety level 3 and extensive safety testing are correlated with the classic platform that make them less amenable to fast vaccine production during a pandemic[6].

Gene-based vaccine (GBV) / Novel

GBV are viral vector vaccine and nucleic acid base vaccines, is a novel vaccine platform. Viral vector vaccines contains a recombinant virus, often attenuated to weaken its pathogenicity, and carrying recombinant genes encoding viral antigen(s) which are cloned using recombinant deoxyribonucleic acid techniques[6].

Nucleic acid-based vaccines can contain DNA or mRNA and may be adapted quickly when new viruses or mutations emerge which is why these were among the very first COVID-19 vaccines to enter clinical trials. DNA vaccines contain a novel artificial DNA construct encoding the vaccine antigen; for maximum efficiency of the artificial DNA construct into cells, injection needs to be followed by electroporation. After uptake into cells, the vaccine antigen is expressed from the artificial DNA construct.

Nucleic acid-based vaccines stimulates a humoral and cellular immune reaction and required two dose one for prime and other to strengthen the immune system.

mRNA-based vaccines work on an equivalent principle as DNA vaccines; However, initial steps of nuclear translocation of the DNA construct and transcription into mRNA is bypassed[6]. Self-replication RNA vaccines are likely to induce protective immunity employing a lower dose, because more vaccine antigen is expressed per cell[7]. In view of poorly stable mRNA these constructs include modified nucleosides to stop degradation. A carrier molecule lipid nanoparticle is important to enable entry of the mRNA into cells.

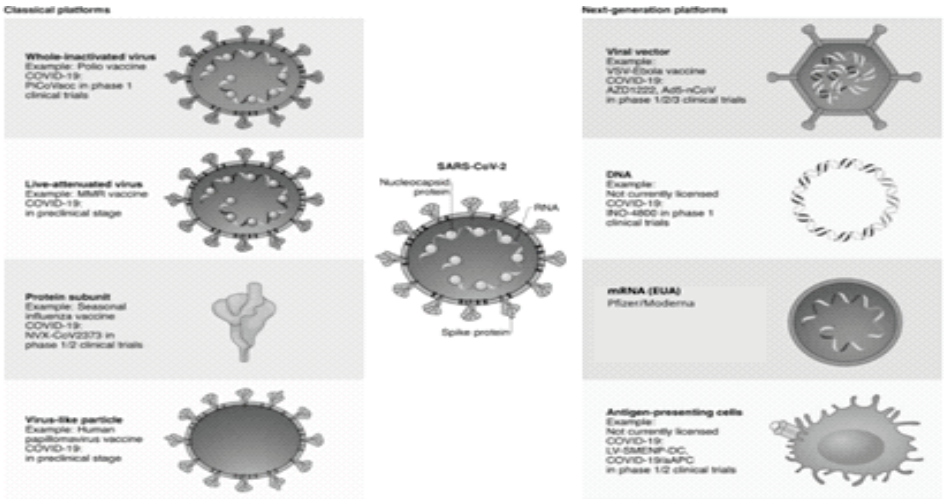

Figure 3: A schematic representation of the different vaccine platforms (Adapted with permission, from "Next-Generation vaccine platforms for COVID-19" Nature Materials-VOL19-Aug2020-810-820-Debby van Riel and Emmie de Wit).

Authorised or Approved Vaccines:

BNT162b2 (BioNTech and Pfizer) "mRNA"

This mRNA vaccine is delivered in a lipid nanoparticle to express a full-length spike protein. It is administered intramuscularly in two doses three weeks apart[8]. During a large placebo-controlled phase 3 trial[9], this vaccine had 95 percent efficacy in preventing symptomatic COVID-19 at or after day seven following the second dose[9,10].

Local and systemic adverse effects were dose dependent and comparatively common after the second dose; most were of mild or moderate severity. Among participants younger than 55 years, fever occurred in sixteen percent and severe fatigue, headache, and chills occurred in four, three and two percent, respectively[10]. Rates of adverse effects among older participants were slightly lower[9].

After the vaccine was administered to individuals within the UK and US outside a clinical trial, few instances of anaphylactoid reactions were reported[11]. Four rare cases of Bell's palsy were also noted during this trial in vaccine group[10].

Moderna "mRNA 1273"

This mRNA vaccine was developed and administered to humans within two months of publication of the SARS-CoV-2 genomic sequence. The vaccine utilizes mRNA delivered in a lipid nanoparticle to express a full-length spike protein. It is administered intramuscularly in two doses 28 days apart. mRNA 1273 having 94.1 percent vaccine efficacy in preventing symptomatic COVID-19 at or after 14 days following the second dose. Among adult above 65 years of age, vaccine efficacy was 86.4 percent.

Local and systemic adverse effects were dose dependent and relatively common after the second dose; most were of mild or moderate severity[12]. Among participants younger than 65 years, fever occurred in 17 percent, and severe fatigue, headache, myalgias and arthralgias occurred in 10, 5, 10 and 6 percent, respectively. Adverse effects were less frequent among older individuals; individuals with evidence of prior SARS-CoV2 infection also had lower rates of adverse effects than those without prior infection. Bell's palsy was reported[12] in three cases in vaccine and one in placebo group.

COVISHIELD "Adenovirus vector" CHAdOx1 nCoV-19/AZD1222[13].

(University of Oxford, AstraZeneca, and the Serum Institute of India)

This vaccine is based on a replication-incompetent chimpanzee adenovirus vector that expresses the spike protein. It is given intramuscular and is being evaluated as a single dose or two doses 28 days apart. The levels of antibody titers achieved were higher following two doses; and subsequent studies are evaluating the two-dose regimen. In a study that included older vaccine recipients

(>70 years)[14], the vaccine resulted in similar antibody responses after the second dose as in younger adults.

This vaccine had 70.4 percent efficacy[13] in preventing symptomatic COVID-19 at or after 14 days following the second dose. However, a subgroup of participants inadvertently received a lower vaccine dose for the first of the two vaccine dose, and the vaccine efficacy in this subgroup differed from the rest. Vaccine efficacy was 90.0 percent. Reasons for this difference are uncertain, although the overlapping confidence intervals indicate that the difference is not statistically significant.

In initial-phase trials, fatigue, headache, and fever were relatively common after vaccine receipt and were severe in up to 8 percent of recipients. In the phase III trial[13], there were two cases of transverse myelitis in ChAdOx1 nCoV-19 vaccine recipients. One was thought to be possibly related to vaccination and was described as an idiopathic, short-segment spinal cord demyelination; the other was in a participant with previously unrecognized multiple sclerosis and thought to be unrelated to the vaccine.

COVAXIN "Whole Virion inactivated"

Bharat Biotech-Indian Council of Medical Research (ICMR)-National Institute of Virology (NIV): Approved by CDSCO on 3rd Jan 2021[15].

This indigenous vaccine (BBV152) is a whole-virion propiolactone -inactivated SARS-CoV-2 vaccine. The vaccine strain NIV-2020-770 contains the D614G mutation, which is characterised by an aspartic acid to glycine shift at amino acid position 614 of the spike protein. The vaccine was injected intramuscular in a two dose regimen four weeks apart, and hasto be stored at 2^{O}-8^{O} C. The most common adverse event was pain at the injection site, followed by headache, fatigue, weakness, rashes, body ache and fever. No severe or life threatening solicited adverse events were reported. The Phase III efficacy trial was initiated in India in 25,800 volunteers, approximate 22,500 participants have been vaccinated across the country and the vaccine has been found to be safe as per the data available till Jan 3rd 2021.

Table1: Comparison of vaccines.

Vaccine Developer	Pfizer	Moderna	AstraZeneca	Covaxin
Type	mRNA	mRNA	Adenovirus Vector	Whole Virion inactivated
Approval	11th Dec2020	19th Dec 2020	UK 30st Dec2020 India 1st Jan2021	India 3rd Jan2021
Efficiency	95%	94.1%	70%	Yet to know
Dose/ interval	Two dose, 3 weeks apart	Two dose, 4 weeks apart	Two dose, 4 weeks apart	Two dose, 4 weeks apart
Storage	-70 C (-94*F) and will last for only 24 hours at refrigerated temperature between 2°and 8° C (36° to 46° F).	-4 -20ºC, keep in home Deep Fridge 30 days and at room temperature for 12 Hrs	Normal refrigerated temperature of 2 to 8 °C (36 to46 F) for at least six months	Normal refrigerated temperature of 2-8°C.
Side Effects	Fatigue, Headache. Fever, chills, and muscle pain, especially after second dose.	Fatigue, muscle pain, Headache and fever, Worse after second dose	Fatigue, muscle pain, Headache, and fever	Injection site pain, headache, fatigue, weakness, rashes body ache and fever
Any Significant Side effect	The CDC has identified 6 cases of anaphylaxis and 4 cases of Bell's palsy in people who received the vaccine and none in placebo group.	Four cases of Bell's palsy were reported in the clinical trials including 3 in the vaccine group and 1 in the placebo group.	One case of transverse myelitis	No significant side effect reported so far.

Important Vaccine Candidates in development phase: NVX-CoV2372[17,18] "Recombinant protein nanoparticle"

Novavaxinvestigational vaccine, NVX-CoV2373, is formed from a stabilized coronavirus spike protein using the company's recombinant protein nanoparticle technology[16]. The purified protein antigens in the vaccine cannot replicate and can't cause COVID-19. The Vaccine also contains a proprietary adjuvant, MatrixMTM. Adjuvants are additives that enhance desired immune responses to vaccine.

NVX-CoV2373 is given in liquid form and may be stored, handled and distributed at above-freezing temperature (35° to 46ºF or 2º-8ºC). The primary safety and immunogenicity analysis indicate that in healthy participants 18-59 years of age, two dose regimens of 5 mcg and 25 mcg of rSARS-CoV-2 plus the Matrix-M1 adjuvant had acceptable safety findings and induced high immune responses[17].

ZyCoV-D "Plasmid DNA vaccine"

Zydus Cadila Healthcare [19]

Approved for Clinical trial phase 3 on 3rd Jan 2021[15]

ZyCoV-D, is an indigenous plasmid DNA vaccine for COVID-19 that focus on the entry membrane protein of the virus. The plasmid DNA when introduced into the host cells through intradermal route, would be translated into viral protein and can elicit a robust immunologic response, mediated by the cellular and humoral arms of the human system.

The DNA vaccine platform is additionally known to show improved vaccine stability, and low cold chain requirement. Further, the platform makes the vaccine easy to manufacture, with minimal bio-safety requirements (BSL-1) and found to be safe in phase 2 trial[15]. The vaccine platform can allow the vaccine to be modified just in case the virus mutates. This makes the plasmid DNA vaccine ideal for access within the remotest regions of the country.

Sputnik V "Adenovirus Vector Vaccine"

The Gamaleya National Centre of Epidemiology and Microbiology, Russia

Sputnik V is human adenoviral vector-based platform; it is a two-vector vaccine against SARSCOV2. The vaccine is given intramuscular as an initial adenovirus 26 vector dose followed by an adenovirus 5 vector boosting dose 28 days later. The Sputnik V vaccine efficacy is confirmed at 91.4%[20] supported by data analysis of the ultimate control point of clinical trials. The vaccine showed mild to moderate local and systemic adverse reactions.

In India Dr Reddy's laboratories and Sputnik LLC are jointly conducting Multi-centre, phase II/III adaptive trial.

Wrapping up for Kaizen: Although vaccines clinical trials data are publicly available, however, caution on the effectiveness of immunization programs remains. How long does immunity last? Will the vaccines prevent viral transmission? Are those vaccines safe and efficacious in vulnerable population like children, immune compromised patients and pregnant women who haven't been included in the trials?

Vaccines are going to be a masterstroke for the control of COVID-19. We have to successfully implement the mass immunization program for entire adult population without compromising the vaccine effectiveness; nonetheless, worldwide supplies are going to be a conundrum.

The mass inoculation programme and its effect won't be instantaneous, as COVID-19 cases and deaths are still on rise across the planet. The non-pharmaceutical interventions to constrain the spread of SARS-CoV-2 that the worldwide population has by now become adapted to will have got to remain in situ for a little longer time.

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