Review Article

SARS-COV-2 Vaccines : A Systematic Review

Rajat Varshney[1], Shelly Dutta[2], Anshuman Srivastava[2], Amitesh Aggarwal[3], Subhash Giri[4], Ashish Goel[5]

COVID-19 has emerged as a major pandemic in recent times which has caused great distress worldwide and resulted in high mortality. As a result, substantial efforts are being made into developing effective treatment and vaccines against the virus. Currently, numerous vaccines developed against COVID-19 have got emergency approval in various countries and many others are still in clinical development. This review provides an overview of experimental and clinical data of common vaccines in use and highlight potential safety issues with their use. Furthermore, we also highlight current data about the safety and efficacy of vaccines among vulnerable groups of our society.

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SARS-COV-2 is an enveloped, spherical RNA virus. The virus contains a helical nucleocapsid which is enclosed bya viral membrane consisting of the following 3 proteins : (i) transmembrane (M) glycoprotein (ii) Spike (S) glycoprotein (iii) envelope (E) protein[1,2]. The spike protein binds to the receptor on host cell membrane and aids in entry of the viral genome into the host cell. It contains two subunits, membrane-proximal S2 subunit and membrane-distal S1 subunit. Receptor binding domain (RBD) present on S1 subunit binds to ACE2 receptors present on the host cell membrane. Binding of S1 subunit leads to change in configuration of S2 subunit that is responsible for membrane fusion and viral entry into the cell[3,4]. M and E proteins are small proteins that are embedded in the viral membrane and are responsible for structure and infectivity respectively[4].

Immunogenicity of Viral Proteins :

"Immunogenicity is the ability of a substance to induce a cellular or humoral immune response while antigenicity is the ability to be specifically recognized by the antibodies generated as a result of the immune response to the given substance" (Ilinskaya & Dobrovolskaia, 2016)[5]. SARS-COV-2 M and E proteins have poor immunogenicity due to their small size. N protein contains immunogenic properties butanti-N immune sera have no protective role against SARS cov infection probably due to being a non-membrane protein. S protein being immunogenic and reported a protective role of anti-S anti sera against covid infection, is the major protein target of COVID vaccines[4].

Editor's Comment :

- Spike protein(S) is the main immunogenic protein in SARS-COV-2 and is the major target of all covid vaccines.
- SARS COV 2 vaccines are based on various platforms. Commonly used platform are: mRNA based, DNA based, protein subunit based, Inactivated virus based, viral vector based.
- All vaccines were found to be effective in elderly with lower frequency of adverse events as compared to general population.
- There is a paucity of data in vulnerable groups such as children, pregnant women. Some studies are underway and further studies are needed for this section of society.

Vaccination Strategies :

As of 23 March as per the WHO COVID vaccine tracker, 83 vaccines are in the clinical phase while 184 vaccines being in the pre-clinical phase[6]. These vaccines are based on many platforms with S protein being a target antigen. Common types of vaccines are:

- RNA based vaccine
- Viral Vector based vaccine
- Inactivated Virus based vaccine
- Protein subunit based vaccine
- DNA based vaccine

RNA based Vaccines: mRNA encoding Spike glycoprotein(S) serves as the basis of these vaccines. These are formulated in lipid nanoparticle which protects it against enzymatic degradation. These vaccines are administered intramuscularly. Macrophages and antigen presenting cells (APCs) present near the administered vaccine engulf the mRNA. The mRNA within the cells encodes spike glycoprotein which is presented on the membrane by

Department of Medicine, UCMS and GTB Hospital, Delhi 110095
[1]MBBS, Junior Resident
[2]MD, Assistant Professor
[3]MD, FICP, Professor
[4]MD, Director, Professor
[5]MD MPH, Professor and Corresponding Author

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APCs and further leads to humoral and cellular immune response[7]. Pfizer-Biontech COVID-19 Vaccine and Moderna COVID-19 vaccine currently in use are based on this platform.

Viral Vector based Vaccine:Some genetically altered non-pathogenic viruses are used as vectors to carry antigens of disease-causing pathogen. These non-pathogenic viruses express antigen of disease causing pathogen on their membrane and elicit an immune response against the pathogen. Many vaccines use recombinant adenovirus containing DNA that encodes spike protein of SARS-COV-2. Recombinant Ad vector induces a robust immune response (specifically involving CTL after infecting host APCs and inducing Spike glycoprotein) due to their high transduction efficiency, transgene expression and broad gamut of viral tropism[8]. Oxford Astrazaneca Ch AdOx1 nCoV- 19 Corona Virus Vaccine, Janssen Ad26. COV2.S Vaccine, Sputnik V are based on this platform.

Inactivated Virus based Vaccine:In these types of vaccines, inactivated whole SARS-COV-2 virus is used. These inactivated viruses can produce both structural and non-structural proteins thus conferring broader antibody and T-cell response[4]. Covaxin developed by Bharat Biotech is based on this platform.

Protein Subunit based Vaccine:A subunit vaccine contains a specific viral antigenic fragment that is produced by recombinant technology and does not contain any component of infectious virus. This eliminates any concerns of incomplete inactivation of the virus as in live-attenuated vaccines. S protein is mainly used in the development of subunit vaccines. Various vaccines containing it are in clinical and preclinical developmental stage. These may contain the whole S protein or merely the S1 sub unit or receptor binding domain of S1 subunit[9]. N- terminal domain of S1 subunit and S2 subunit is less immunogenic thereby a less favourable target for vaccine development[10]. Spike protein exists in two conformational states, pre-fusion and postfusion. For the production of protective immune response, the antigen must remain in its pre fusion state[11]. Novavax, pittcovaxx vaccines are based on this platform.

DNA Vaccines : These vaccines contain DNA particles that encode spike protein. DNA after being injected subcutaneously gets transfected in APCs. These APCs express antigen coded by DNA after loading on MHC1 and MHC2. These APCs can migrate to draining lymph nodes and produces a robust immune response after priming CD8+ and CD4+ immune cells[12]. ZyCov-D, INO-4800 are DNA based vaccines currently in clinical development.

Efficacy of Vaccines :

Vaccine efficacy is the percent reduction in the incidence of symptomatic disease in a group who received a vaccination compared to those who did not in a clinical trial. It is calculated as 100 × [1 – (the attack rate with vaccine ÷ the attack rate with placebo)]. A vaccine having an efficacy of 90% does not mean that 90% of people who got the vaccine will not get the disease. It means that if a cumulative disease attack rate is 1% in the general population, it will be reduced to 0.1% in vaccinated group[13].

Antibody Dependent Enhancement (ADE) Response due to COVID Vaccines :

ADE response is antibody dependent enhancement that could occur due to formation of non-neutralizing antibodies against the virus and can paradoxically produce enhanced response of the virus. None of the vaccines have so far shown to develop ADE response. The RBD of the virus can produce these neutralizing antibodies, although the other regions are protected by glycosylation. This prevents the generation of non - neutralizing antibodies that may exhibit ADE[14].

Vulnerable Groups :

Children —

As of now, most of the studies conducted to determine efficacy and adverse events of vaccines are done in those with age >18 years. Only Pfizer's COVID vaccine was studied in those with age >16 years and is approved for use in those with age >16 years[15-17].

Pregnant Women —

There is paucity of data regarding the safety and efficacy of these vaccines in pregnant and lactating females. This can be attributed to most trials excluding this population from their study. Clinical trials regarding this are underway. Data of those who became pregnant after receiving the vaccine is also being assessed by the manufacturers[21]. Developmental and toxicology study which looks at the adverse effect of a drug on pregnancy in animal model has been conducted for Moderna vaccine only and it showed no adverse effect on pregnancy[22]. A report on developmental and toxicology study conducted by Pfizer–BioNTech is expected to be sent to FDA in near future[21].

Elderly —

Notably, the older adults form the major chunk of the population that has been affected gravely by COVID-19 causing higher morbidity and mortality in them[23]. Developing a safe and effective vaccine for this group was definitely the need of the hour. All vaccines were effective in elderly individuals. A lower frequency of adverse reactions was noted in elderly as compared

Comparison of Common Vaccines :

	Pfizer(15)	**Moderna**(16)	**Covishield**(17,18) **Astra Zeneca**	**Covaxin*** (19) **Bharat Biotech**	**J & J***(20)
Efficacy	94.6%, 7 days after 2nd dose	94.1 %, 14 days after 2nd dose	66.7%, 14 days after 2nd dose	Interim vaccine efficacy 81%	66%, 28 days after vaccination
Type	mRNA	mRNA	Genetically altered Adenoviral vector carrying SARS CoV-2 DNA for spike protein	Inactivated virus providing structural and non-structural protein for broader response	
No of Inj	2	2	2	2	1
Storage	-90°C to -60°C	-25°C to -15°C	2°C to 8°C	2°C to 8°C	2°C to 8°C
Age	16 and above	18 and above	18 and above	18 and above	18 and above
Dose	0.3ml 3 week apart IM	0.5ml 28 days apart IM	0.5ml 4-12 week apart IM	0.5 ml 28 days apart IM	0.5 ml single dose IM
Contraindications:	•allergic to the lipid nanoparticles	•allergic to the lipid nanoparticles	•allergic reaction after a previous dose of this •allergic reaction to any ingredient of this vaccine	•Have any history of allergies. • Have fever. • Have a bleeding disorder or are on a blood thinner. • Are immune-compromised or are on a medicine that affects your immune system • Are pregnant. • Are breastfeeding. • Have received another COVID-19 vaccine. • Any other serious health related issues, as determined by the Vaccinator/Offer supervising	•hypersensitivity to vaccine component
Side effects	•Injection site pain (83%) •erythema (5%) •injection site swelling (6%) •headache (42%) •fatigue (47%) • fever (4%) •lymphadenopathy (0.3%)	•Injection site pain (91.6%) •injection site erythema •injection site swelling •headache (63%) •fatigue (68.5%) • fever •myalgia (59.6%) •nausea •Lymphadenopathy (1.1%) •Hypersensitivity reaction (1.5%) •Bell's palsy(<0.5%)	Very Common (>1 in 10 people) • tenderness, pain, warmth, • redness, itching, swelling or •bruising where the injection is given •Joint/Muscle ache •Fatigue •Fever •Headache •Nausea Common(up to 1 in 10) Lump at the injection site Flu like symptoms Uncommon (1 in 100) Dizziness Decreased appetite Abdominal Pain Enlarged Lymph Node Excessive sweating/itchy skin/ rash	• Injection site pain • Injection site swelling • Injection site redness • Injection site itching • Body ache • Headache • Fever • Malaise • Rashes • Nausea • Vomiting	•Injection site pain (48.6%) •headache (38.9%) •fatigue (38.2%) •myalgia (33.2%) •nausea • fever •injection site erythema •injection site swelling •Hypersensitivity reaction

*phase 3 data currently not available

to the general population.This may be due to the lower ability to mount an acute inflammatory response with increasing age[24]. Vaccine efficacy in the elderly group given covishield could not be assessed due to insufficient data[17]. Immunogenicity in elderly receiving covishield, as assessed by anti-IgG against spike protein, was robust and comparable to that in general population[25]. Pfizer and Moderna COVID vaccines have reported efficacy of 94.7% and 86.4% in individuals aged 65 and above.

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