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Invention and Apprehension in Development of Covid 19 Vaccine-A Comprehensive Review

Dr Prasanna Kumar Sahoo[1],ProfGangadhar Sahoo[2],Prof Bhagirathi Kar[3], Prof.DrRuchiBhuyan[4]

[1]Senior Consultant Pediatrics, Vyasanagar, Odisha.
[2] Dean, IMS & SUM Hospital, Siksha "O" Anusandhan (Deemed to be University), K8, Kalinganagar, Bhubaneswar751003, Odisha, India
[3] Department of Medicine, IMS & SUM Hospital, Siksha "O" Anusandhan (Deemed to be University), K8, Kalinganagar, Bhubaneswar751003, Odisha, Indi
[4] Professor, Department of Oral Pathology and Microbiology, IMS & SUM Hospital, Siksha "O" Anusandhan (Deemed to be University), K8, Kalinganagar, Bhubaneswar751003, Odisha, India

ABSTRACT

Covid-19 is an infectious disease, caused by the newly discovered coronavirus, SARS-CoV-2 and has spread rapidly throughout the globe. The World Health Organisation (WHO) declared the Covid-19 outbreak pandemic in March 2020. All the countries, including India, have adopted stringent measures to contain the disease through better diagnostic measures, treatment protocols and containment sanitation measures with limited success. Development of effective vaccines are expected to provide a lasting solution by enhancing immunity. The vaccine development procedure has been fast-tracked in order to contain the disease spread on emergency basis following stringent protocols. Apprehensions and concerns regarding the safety, efficacy and immunogenicity of these vaccines based on new and never licensed platforms do exist.

Keywords:
Covid-19, Corona, Antibody, mRNA, Vaccine.

Introduction

Corona pandemic has affected 218 countries throughout the world. Though the disease incidence has decreased to some extent the disease has neither been eliminated nor has been effectively contained. Meanwhile a new variant strain of the virus which is seventy percent more virulent than the original virus has emerged making everybody worried. This new strain was first discovered in England on 20th September and is now called the Britain Strain. An effective and successful treatment has not yet evolved. Everybody is eagerly waiting for the vaccine to get protection from the dreadly disease.

Why we use vaccines :-

Vaccines prevent infectious diseases and protect the individual against contracting vaccine-preventable diseases. Herd immunity is produced in a community when majority people of that community get vaccinated against a particular disease. This herd immunity indirectly protects unvaccinated people such as very young babies and immune compromised persons.

How vaccines work :-

Vaccines reduce the risk of infection by boosting the already existent immune system in the body to recognize and fight pathogens like bacteria and viruses entering human body. A weak or inactivated killed version of the pathogen is injected into the human body which produces a very much weak infection like the original disease. This process does not harm the body, rather it produces antibody which fights the pathogen in future.

Types of corona vaccine :-

To bring out an effective Covid vaccine several platforms are explored. They are traditional platforms, inactivated virus, live-attenuated virus, subunit vaccines, virus-like-particles and the

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newer platforms; viral vectored vaccines and the nucleic acid (DNA/mRNA) vaccines. For the first time the newer platforms are being applied in human beings. As of 5th January 2021, record number of 172 vaccine candidates are in the pre-clinical development phase, 20 are in phase 1 trials, 22 are in phase 1-2, 3 are in phase 2, 4 are in phase 2-3 and 13 in phase 3 trials[1].

1. mRNA vaccine (Pfizer and Moderna) :- These consist of messenger RNA molecules of the virus which code for the parts of the target pathogen that are recognized by human immune system. Inside the body cells, the RNA molecules are converted into antigens, which are detected by the immune cells in the body to produce antibodies[2].
2. Vector vaccine (Oxford Astra Zenica – Serum Institute of India) Covishield :- In this process the virus has been modified to contain antigens from the target pathogen. The modified virus acts as delivery systems that display the antigens to immune cells in the body. Replicating viral vectors make extra copies of themselves in human body cells. Non-replicating viral vectors do not. Chimpanzee adenovirus is used as the vector for delivering the corona virus antigen in the SII Vaccine Covishield[2].
3. Inactivated vaccine (Bharat Biotech India Ltd.) Covaxin and (Russia's Gamalaya Research Institute and marketed in India by Dr Reddy's lab) Sputnik V :- These consist of the inactivated versions of the virus which are detected by immune cells in the body to produce antibodies but they can not cause illness[2].

Efficacy and safety profile of vaccines:-

1. mRNA vaccines :- The role of mRNA vaccines used against Rabies, Influenza, Zica and HIV are being investigated. mRNA exerts its effects in the cytoplasm without entering the nucleus. Therefore there is no risk of integrating into the host genome. No major safety issues have been detected except for an increased local and systemic reactogenicity. Occurrence of neurological complications like Bell's palsy or Transverse myelitis has not been detected in the recent clinical trials[1].
2. Viral vector vaccines :- Adenoviruses have been recognized as excellent vectors to deliver genes or vaccine antigens to the target host tissues and tested in several vaccine and gene therapy studies for cancers. The advantages include broad range of tissue tropism, well characterized genome, ease of genetic manipulation including acceptance of large transgene DNA insertions, inherent adjuvant properties, ability to induce robust transgene-specific T cell and antibody responses, non replicating nature in host and ease of production in large cells. A very mild disease is caused by these adenoviruses in immunocompetent adults and by detection of crucial regions of the viral genome, the vectors can be converted to replication-defective further increasing their predictability and thus reducing unwanted side effects. The pre-existing immunity to the viral vector in humans may pose major disadvantage by blunting the response to the vaccine. To overcome this, the dose of the viral vector is adjusted using a prime-boost combination with different vectors or non-human adenovirus vectors. Adenovectors are being tested since long in vaccines against Malaria, HIV, Ebola, Zica and Hepatitis C and no major safety issues have been identified[1].

Emergency Use Authorisation in India :-

In an emergency situation eg.the current Covid-19 pandemic, for granting interim approval to a particular vaccine with evidence of reasonable efficacy and safety, tight scrutiny mechanism has been developed. This is known as Emeregency Use Authorisation (EUA). For an EUA approval to a particular vaccine, it should have adequate manufacturing information to ensure quality and

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consistency, the National Regulatory Authority (NRA) must assess and determine that the known and potential benefits must outweigh the known and potential risks of the vaccine. SII vaccine Covishield and Bharat Biotech Ltd. Vaccine Covaxin have been issued EUA in India. At a later time, Sputnic V of Dr Reddy's Lab and Zycov-D of ZydusVaxxicare may be issued EUA[1].

Trial results of vaccines in different phases :-

1. Phase 3 of COVISHIELD vaccine :- The overall Vaccine Efficacy (VE) in symptomatic Covid-19 participants with NAAT +ve test was 70.4% (54.8 to 80.6). In recipients of the low-dose (LD) followed by the standard dose (SD), LD/SD, the VE was 90.6% (67.4 to 90.0), while it was 60.3% (28.0 to 78.2) in the SD/SD group. There was no hospitalization in the vaccine group vs 10 cases in the control group. One case of Transverse Myelitis, noted after 14 days after the 2nd dose of the vaccine was possibly not related to the vaccine. Likewise 2 cases of TM , observed one each in vaccine and control group. Following the investigation by the Independent Safety and Data Monitoring Board (ISDMB), it was found to be unrelated[1].
2. COVAXIN vaccine :- This vaccine, a whole-viron inactivated SARS-Cov-2 vaccine formulated with a TLR 7/8 agonist molecule absorbed to alum (Algel-IMDG), in a phase 1 study elicited high titre of antbodies against the S1 protein, RBD and the Nucleoprotein. Pain at the injection site was the most common local adverse event. Other local and systemic AEs were equal in both the groups. In 380 recipients in the phase 2 study the vaccine was found to be safe. It is expected that the humoral and cell mediated response marked in this study will persist until 6-12 months after 2nd dose administration. The 3rd phase study including 25800 persons is in the final stage[1].
3. Sputnic V vaccine :- This vaccine is an Adeno-based (rAD26-S+rAD5-S) vaccine and is prepared using the prime-boost principle. In a phase 2 study involving 76 subjects, high anti RBD-IgGtitres and a robust T- cell response were detected. Only mild adverse events were marked. EUA was granted by the Russian Government. Subsequently analyzing the data on 18,794 recipients of both 1st and 2nd doses the VE was found to be 91.4%. In India phase 2 study with 100 subjects is complete and phase 3 study including 1500 subjects is going on[1].
4. ZyCov-D vaccine by ZydusVaxxicare :- This vaccine, a plasmid-DNA vaccine, is administered intradermally in a 3 doses schedule of 0-28-56 days. In phase 1 study it was found to be safe and immunogenic. With 1085 subjects phase 2 trial has been initiated from August 2020 and the analysis report is awaited. Permission

for phase 3 study has been issued[1].

Dosage schedule of vaccination[1] :-

Covid-19 vaccines are usually administered in a 2 dose. However, it differs from vaccine to vaccine and depends upon the manufacturer.

Covishield, Moderna and Covaxin :- 2 doses IM at 28 days interval.

Pfizer and Sputnik V :- 2 doses IM at 21 days interval. ZycovD :- 3 doses Intradermally 0-28-56 days.

Storage requirements of vaccines[1] :-

Oxford/AstraZeneca/SII vaccine Covishield and Bharat Biotech Covaxin : Storage, handling and transportation at $+2^{o}$ C to $+8^{o}$ C.

BioNTech/FosunPharma/Pfizer vaccine :-Usual Storage recommendation at -70^{o} C but can be stored at $+2^{o}$ C to $+8^{o}$C for 5 days.

The Moderna/NIAID vaccine :- Remains stable at -20^{o} C for upto 6 months and at $+2^{o}$ C to $+8^{o}$C for 30 days.

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SputnicV vaccine :- The freeze-dried formulation can be stored at $+2^{o}$ C to $+8^{o}$ C.

Vaccine Protection Efficacy Status :-

All the three vaccines, which have published phase 3 trial results have demonstrated almost 100% efficacy against severe Covid-19 infection and incidence of hospitalization was zero. Significant protection is demonstrated at least after 14 days after 2^{nd} dose of vaccination. The Pfizer mRNA vaccine has demonstrated response as early as 10 days after the 1^{st} dose. These vaccines are new with short follow up period of 2-3 months. Hence at this stage it is practically impossible to forecast how long the protection will exist. Follow up of the vaccines will provide information regarding the length of the immune response. Antibody titres may wane rather rapidly but memory B cell and memory T cell responses are likely to provide protection for a longer period at least for 6-12 months. Probably no booster dose will be needed. But it will be established only with time[1,2,3,].

Who can take Covid-19 vaccine :-

Trials have been done till now for adults above 18 years of age only. Hence it will be given at present to adults of above 18 years. As of now studies have demonstrated that Covid-19 infection is relatively uncommon in children. Even when infected, the symptoms and the complications due to disease are very mild. The role of children in transmitting the disease is not established beyond doubt but outbreaks have been reported in schools and hostels. However trials for children above 12 years have started and doses will be decided later on[1].

In immunocompromised individuals, live vaccines and replicating viral vaccines are contraindicated. The mRNA vaccine and inactivated vaccines are safe. The AZ and Sputnik V adenovirus vaccines, being non replicating viral vector vaccines, are also safe[1.2.3].

Pregnant people are at increased risk of severe illness, including illness that results in ICU admission, mechanical ventilation and death compared with non-pregnant women of reproductive age. Besides, adverse pregnancy outcomes like preterm delivery are more in comparision to pregnant women without Covid-19. None of the companies has yet done vaccine trials in pregnant women. ACOG recommends that while safe data on Covid-19 vaccine administration in pregnancy are not available, vaccination should not be withheld from pregnant women who meet criteria for vaccination. Inactivated Covid vaccines are not contraindicated. Getting vaccinated is a personal choice for pregnant women. A one-to-one dialogue between pregnant women and their clinicians may help them decide whether to get vaccinated with a vaccine, authorized for use under EUA. Similarly Covid-19 vaccines are not contraindicated in lactating mothers. The lactating women can continue breastfeeding after getting vaccinated[4,5].

Covid-19 infected persons, confirmed or suspected may possibly transmit infection at the vaccination site. Hence they are not allowed at the site. However, they can be vaccinated after 14 days of resolution of symptoms[1].

A natural infection protecting an individual in the long run is not established beyond doubt. The antibodies developed by a covid infected individual rapidly wanes over time. In the absence of a direct correlate in the form of antibody titres and considering the cell mediated immunity, waned antibody levels may not exactly mean loss of protection. However, a person who has recovered from Covid-19 disease should take the full course of the vaccine[1,2,3].

There is some concern regarding vaccination to an individual who has received plasma either as a treatment for Covid or other indication. It is quite possible that donor plasma may contain anti Covid-19 antibodies which in turn may suppress the immune response to the vaccine. Hence such type of individuals should defer vaccination to a later stage[2,3].

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Apprehension persists in some quarters that the vaccines in the current form may not be effective against the mutant variant of Covid-19 virus. With SARS-COV-2 the possibility of mutation is not uncommon. Researchers have not found any major changes in neutralization by the N501Y mutation, the main in the UK variant. Such mutation makes the receptor binding stronger, allowing better viral spread. In other variants also the case is similar. Some degree of concern do exist regarding the effectiveness of the current vaccines to combat the South African variant. The ongoing follow up studies may put forth some solution to this problem[1].

Messages are going around regarding mRNA from vaccine getting incorporated into the human genome and altering the gene structure. The mRNA vaccines are not live virus vaccines nor do they contain any adjuvant to enhance vaccine efficacy. These vaccines do not enter the nucleus and hence do not alter human DNA in vaccine recipients. mRNA vaccine carries a message to the cell to produce spike protein which induces production of antibodies. It works as per the direction and nothing else. As a result mRNA vaccines are unable to cause any genetic changes[2,3].

Conclusion :- A lot of research is ongoing to develop newer and better Covid vaccines. Nasal spray vaccine is probably the most promising one. It will produce local IgA antibodies to block the virus at the entry point itself. Additionally, it will reduce nasal colonization to prevent disease transmission[3]. No vaccine gives 100% protection. To add to it, the vaccinated person may not develop disease but may get such infection and transmit it to other contacts. Once about 70% population has antibodies by way of disease or vaccination and Herd Immunity develops the virus will cease to spread[2,3]. The population is to continue wearing mask, observing physical distance and sanitizing hands for some more time.

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