Review

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On the way to COVID-19 vaccine development: tireless efforts and outcomes

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SUMMARY

Novel corona virus disease (COVID-19), since its emergence in November 2019, took the toll of a huge number of human lives. It is a β-corona-virus also known as SARS-CoV2. The safest and most effective way to prevent the disease is definitely vaccination amongst the large population. To the best of our knowledge, more than 200 vaccine candidates for COVID-19 were developed by the scientists of research institutions and pharmaceutical companies and nearly 52 candidates were in human trials. Till now, only 15 vaccines are being offered to the general population in the world, out of which 2 vaccines are RNA, 6 are conventional inactivated, 5 viral vector and 2 protein subunit. Here, we tried to unfold the events and efforts behind the successes of new innovations of COVID-19 vaccines, the world has achieved yet.

INTRODUCTION

Novel corona virus disease (COVID-19) has affected the normal life of mankind all over the world. Since its emergence in November 2019, it has spread to 188 countries and 25 territories around the globe.[1] It took the toll of a huge number of human lives even in developed countries. WHO declared it as a Public Health Emergency of International Concern.[2] It is a β-corona-virus also known as SARS-CoV2. The full genome of SARS-CoV2 was sequenced in January, 2020.[3] The incubation period of the virus ranges from 2-14 days with a median of 5.1 days. The symptoms include fever, dry cough, fatigue, shortness of breath, chills, muscles pain, headache, gastric disturbances and weight loss.[4] World Health Organization (WHO) suggested people to increase immunity by adapting balanced diet, regular exercise and to avoid watching television news regularly and repeatedly to get rid of the panic that affects mental health badly. Physical distancing, maintenance of personal hygiene, wearing masks, sanitizing hands and disinfecting of the surfaces are considered as major steps to protect individuals from infection.[5] Nevertheless, to
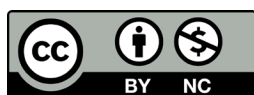
prevent the spread of this pandemic, vaccination might be the most effective therapy to generate herd immunity in the population.[6] Last one year, scientists all around the world are taking the challenge to discover harmless and effective vaccines to save the humanity from the deadly virus. The urgency to develop COVID-19 vaccine led to compressed schedules that shortened the standard vaccine development time-line without hampering the progress through several phases of clinical trials to test for safety, immunogenicity, effectiveness, dose levels and adverse effects of the candidate vaccine.[7] The Coalition for Epidemic Preparedness Innovations (CEPI) is rendering efforts to finance and coordinate research on a vaccine for COVID-19. Besides CEPI's funded initiatives, researchers are also working to develop relevant candidates and solutions, to find out successful vaccines. Within December 2020, more than 200 vaccine candidates for COVID-19 were developed by the scientists of research institutions and pharmaceutical companies and nearly 52 candidates were in human trials. Recently, 15 vaccines are being offered to the general population in the world, out of which 2 vaccines are RNA, 6 are conventional inactivated, 5 viral vector and 2 protein subunit.[8] Till date, whatever the scientists accomplished and developed vaccines against Covid-19, may not be of full proof and unquestionable, but these tireless efforts may save millions of lives throughout the world. In this juncture, we have tried to unfold the events and efforts behind the successes of new innovations of COVID-19 vaccines.

CHOICE OF COVID-19 ANTIGEN

SARS-CoV-2 virus contains four structural proteins namely, spike (S), nucleocapsid (N), envelope (E), and membrane (M) proteins which are encoded by the 3'-end of the viral genome. It has a large (30+ kb) single stranded positive sense ss-RNA genome encased by a helical neucleocaspid. Genome has an outer envelope comprised of matrix protein, envelope protein and spike protein (S).[9] S-protein contain receptor binding domain that binds human angiotensin converting enzyme-2 (hACE2) and penetrate into the cell. Among all 4 structural proteins, S-glycoprotein, being large multifunctional trans-membrane protein, plays the vital role in viral attachment, fusion and penetration into the host cell. S-1 subunit of S-protein has N terminal domain and receptor binding domain

(RBD).[10] The primary endeavour of the scientists is to produce S-protein neutralizing antibodies in the vaccinated humans and they focussed S protein as target antigen for vaccine development.[11,12]

TYPES OF COVID-19 VACCINE

There are three main approaches to designing any vaccine viz. (i) whole virus or bacterium, (ii) the parts of the virus that triggers the immune system, or (iii) just the genetic material of the virus. Conventionally vaccines prepared and administered in humans are either live attenuated viruses, or inactivated viruses, or protein or protein-polysaccharide conjugated subunit or virus-like particles.[13] In recent years bioengineering technological knowledge are applied to manufacture vaccines from composed of nucleic acids (DNA or RNA), viral vectors or recombinant proteins.[14] All such procedures are applied to develop vaccine against SARS-CoV2. At present, 442 interventional studies have been registered for Covid-19 vaccine in the Clinical Trial of NIH, US National Library of Medicine.[15]

1. Protein sub-unit vaccines

Many efforts have been directed towards the development of the vaccines against COVID-19, to avert the pandemic and most of the developing vaccine candidates have been using the S-protein of SARSCoV-2.[16] Novavax (NVX-CoV2373) is a nano-particle based immunogenic vaccine, based upon the recombinant expression of the stable pre-fusion, coronavirus S-Protein. In the animal models, a single immunization resulted in the high level of anti-spike protein antibodies which blocked the hACE2 receptor binding domain and could elicit SARS-CoV-2 wild type virus-neutralizing antibodies.[17]

2. Viral vectored vaccines

Vaccine based on viral vectors offers a long term and high level of antigenic protein expression. These vaccines trigger and prime the cytotoxic T-cells and ultimately lead to the elimination of the virus infected cells.[18] These vaccines are highly specific in delivering the genes to the target cells, highly efficient in the gene transduction, and efficiently induce the immune response. Covishield or Vaxzevria (ChAdOx1 nCoV-19) was developed

Table 1: Development of Covid-19 vaccines

Vaccine	Brand name	Vaccine type	Developed & manufactured by	Trial location	Authorized for use in
Pfizer-BioNTech	Comirnaty	m-RNA	BioNTech (Germany) & Pfizer (USA)	Multinational	84 countries including USA, EU, UK, Japan etc.
Oxford-AstraZeneca	Covishield & Vaxzevria	Viral vector	Oxford University & AstraZeneca & Serum Institute of India	Multinational	UK, USA, EU, Japan, Canada, Bangladesh, Australia etc.
Johnson & Johnson	Janssen COVID-19	Viral vector	Johnson & Johnson (Netherlands & USA)	Multinational	USA, Brazil, South Africa
Moderna	Moderna COVID-19	m-RNA	Moderna (USA)	USA	45 countries including USA, Canada, EU, UK, Singapore etc.
Sputnik V	Sputnik V & Gam-COVID-Vac	Viral vector	Gamaleya Research Institute of Epidemiology and Microbiology (Russia)	Russia	45 countries including India, Brazil, China, South Korea, Hungary etc.
Covaxin	Covaxin	Inactivated virus	Bharat Biotech & ICMR (India)	India	India, Nepal, Iran, Zimbabwe, Mauritius, Mexico, Philippines etc.
BBIBP-CorV	Sinopharm COVID-19	Inactivated virus	Sinopharm (China)	Multinational (Argentina, UAE, Pakistan, Peru etc.)	China, Nepal, UAE, Pakistan, Mexico etc.
CoronaVac	CoronaVac	Inactivated virus	Sinovac Biotech (China)	Brazil, Chile, Indonesia, Philippines	Brazil, Turkey
Novavax	Covovax & NVX-CoV2373	Recombinant nanoparticle vaccine	Novavax (USA)	UK, South Africa	UK, Canada

at Oxford University and consists of a replication-deficient chimpanzee adenoviral vector containing the SARS-CoV-2 structural surface glycoprotein antigen gene. The previous animal studies have suggested that a single shot should induce the immune response.[19] An interim analysis of ongoing four randomized clinical trials in Brazil, South Africa and UK suggested that ChAdOx1 nCoV-19 has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19.[20]

3. mRNA vaccines

mRNA is a promising, non-infectious and a non-integrating platform with almost no potential risk of mutagenesis. The immunogenicity of the mRNA can be minimized and modifications can be made to increase the stability of these vaccines. Moreover, the anti-vector immunity is also avoided as the mRNA is the minimally immunogenic genetic vector, allowing repeated administration of the vaccine.[21] Moderna (mRNA-1273) vaccine is composed of synthetic mRNA encapsulated in Lipid

Nano Particle which codes for the full-length, pre-fusion stabilized S-protein of SARS-CoV-2. It can elicit a highly S-protein specific antiviral response. The geometric mean of RBD specific antibody titers showed a rapid increase in all the participants. Sero-conversion was observed after 15 days and the median magnitude of antibody responses was similar to the magnitude in convalescent sera. It is relatively safe as it does not contain the inactivated pathogen or the sub-units of the live pathogen and found to be well tolerated in the 25 μg and100 μg dose cohorts.[22] Another m-RNA vaccine is Comirnaty (BNT162b1), developed by Pfizer-BioNTech. It is a codon-optimized mRNA vaccine that encodes for the trimerized SARS-CoV-2 RBD, a critical target of the virus nAb. The vaccine showed an increased immunogenicity due to the addition of T4 fibritin-derived fold on trimerization domain to the RBD antigen.[23]

4. DNA vaccines

DNA vaccine encodes for the antigen and an adjuvant which induces the adaptive immune response. The transfected cells express the transgene which provides a steady supply of the transgene specific proteins which is quite similar to the live virus. Furthermore, the antigenic material is endocytosed by the immature Dendritic Cells which ultimately present the antigen to the CD4+ and CD8+ T cells in association with MHC II and MHC I antigens on the cell surface hence stimulating effective humoral as well as cell-mediated immune responses.[24] Inovio Pharmaceuticals has developed the DNA plasmid vaccine INO-4800 from Lassa virus, Nipahvirus, HPV, HIV and Filovirus. The presence of functional antibodies and T cell response in the preclinical trials suggest that the vaccine can produce an effective immune response within 7 days post-vaccination.[25] Zydus Cadila has developed ZyCoV-D vaccine, a genetically engineered DNA plasmid based vaccine encoding for the membrane proteins of the virus.[26]

3.5 Live Attenuated Vaccines (LAV)

Live vaccines are derived from wild viruses or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. Covaxin (BBV152) was developed by Bharat Biotech and Indian Council of Medical Research (ICMR). It is the whole virion inactivated vaccine. It contains 6 μg of whole-virion inactivated SARSCoV-2 antigen (NIV-2020-770).

VACCINATIONS

After completion of phase III trials, 15 vaccines have exhibited significant efficacy (95%) in preventing symptomatic Covid-19 infections and authorized by national regulatory authority for public use. UK was the first country in the world to approve Pfizer-BioNTech's Covid-19 vaccine on December, 2020. According to recent data, 704,983,864 individuals have received at least one dose of a Covid-19 vaccine throughout the world, which is only 9.0% of world population.[27] Even if sustained immunity is attained after infection by Covid-19, estimates are that 60–70% of a population would need to be immune to achieve herd immunity against SARS-CoV2. US-FDA approved only three Covid-19 vaccines for USA, namely Pfizer-BioNTech, Moderna and Johnson & Johnson. Most of the countries have given the priorities of vaccination to their elderly persons, healthcare workers, state employed workers, police and susceptible population.

DISCUSSION AND CONCLUSION

The safest and most effective way to prevent the disease is definitely vaccination amongst the large population. In spite of the tireless efforts a definite goal has not been reached yet. According to WHO, vaccine must provide a highly favourable benefit-risk contour, with high efficacy, only mid or transient adverse effects and no serious ailments. [28] Vaccine must be suitable for all ages, pregnant and lactating women and should provide a rapid onset of protection with a single dose and confer safety for at least up to one year of administration. Dream vaccine should be inexpensive, easily transferable with minimal cold chain requirements. Nevertheless, majority of the vaccine trials were done on healthy population of age group 18-65 years. The duration of immunity after vaccination is yet to be known. Following SARS-CoV infection, IgG and neutralizing antibody was detectable for 1-3 years following infection indicating vaccine-induced protection may not be long-lasting and re-immunization may be required.[29] It is better to remain alert; maintain physical distancing;, early detection and self-isolation, if infected; along with being vaccinated to control the spread of this viral disease.

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