

# COVID-19 Vaccines: Speedy Development and their Use to be Saviour of Humanity

V. P. Kamboj<sup>1</sup>

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**Abstract** COVID-19 disease is caused by a novel coronavirus (SARS-CoV-2), and it was declared as a pandemic by WHO within two and half months of detection of first case. The pandemic situation induced unprecedented cooperation amongst countries, academia, public sector institutions and industry in sharing knowledge, resources and strategies. In this article, development of vaccines and their delivery system is discussed. The regulatory toxicology and clinical trials are the most important factors to ensure safety and formation of neutralizing antibodies for efficacy. The article creates awareness about the global cooperation and efforts in developing the vaccines speedily for the society. Finally, results show that all the COVID-19 vaccines trigger an immune response to enable your body to fight and kill virus and none of them cause COVID-19 disease.

**Keywords** Coronavirus (SARS-CoV-2) · Vaccine · mRNA vaccines · Delivery system · Herd immunity · Global cooperation · Speedy development

## Significance Statement

The article creates awareness about the global cooperation and efforts in developing the vaccines speedily for the society. It is also aimed to encourage people to take vaccine by knowing the benefits and limits of COVID-19

vaccines so as to generate herd immunity and have coronavirus-free society globally.

COVID-19 disease is caused by a novel coronavirus (SARS-CoV-2) which emerged in Wuhan, China and was noticed on 30th December, 2019. The virus spread like wild fire and engulfed virtually all the countries of the world (187 out of 192) in a couple of months due to fast modes of travel used these days by people; virus has now spread to all the countries.. COVID-19 was declared as a pandemic by WHO on 11th March, 2020. The fast spread of the virus brought fear due to memories of the earlier Spanish flu pandemic of 1918–19 which infected 500 million people (1/3rd of world population) and caused 50 million deaths and subsequent epidemics of recent times namely SARS-CoV-1 (of 2002–03) which affected 8422 persons in 32 countries [1] but mainly China with fatality rate of 11% and MERS virus (of 2012) infecting 2494 persons in 27 countries but mainly Saudi Arabia with high mortality rate of 34.4% [2].

This fear of fatality seen during the earlier pandemic and epidemics and the non-availability of therapeutics and prophylactics (drugs and vaccines) and even of ventilators, oxygen support system, hospital beds, diagnostics and even masks and sanitizers to meet demands of increasing number of patients un-nerved nations. The Govt. suspended all modes of transportation and enforced lockdown of all institutions and establishments including shops and events of social gatherings within their countries. The lockdowns affected employment and economy of countries badly which will take some time to recover. India, after lifting of lockdowns, encouraged and supported indigenous industry and R&D institutions to develop technologies for manufacture within the country. These measures made the country self-sufficient ('Atmanirbhar') by September, 2020 and began exports to other needy nations. These measures

✉ V. P. Kamboj  
kambojvp@yahoo.com

<sup>1</sup> CSIR-CDRI: CSIR-Central Drug Research Institute and Biotech Park, Lucknow, India

also helped nations to contain the virus spread to a great extent.

The situation induced unprecedented cooperation amongst countries, academia, public sector institutions and industry in sharing knowledge, resources and strategies. The genome sequence of the virus was made available online by 15th January, 2020, i.e. within a fortnight of virus disease detection. More than 1,200 drugs and vaccines were identified for repurpose and tested *in vitro* in cell lines and then in animal models but with limited success. Only four drugs were given emergency use authorization by WHO and some countries. All of them failed in treating COVID-19 patients in WHO Solidarity multi-country trial for drugs. By that time, a pharma firm selling one of these drugs had made a couple of billion dollars and is still continuing to push its drug, through aggressive marketing, in developing countries.

### Vaccine Leads and Development

It is well known to academia and industry that drugs will only cure but the availability of vaccines will provide immunity to large populations to reduce infections and eliminate the virus by generating herd immunity. Pertinently vaccines will not only prevent infection of an individual but save community or society by producing herd or community immunity if around 70–80% persons have been immunized/vaccinated because the infection is intercepted and the remaining people are safe without getting vaccine. Vaccine will also save people from the recurrence of this coronavirus (SAR-CoV-2) infections in future. The available knowledge of vaccines and the knowledge gained from SARS-CoV-1, MERS and Ebola virus have encouraged vaccine development. By January 2020 end, the lead from Oxford University, UK motivates AstraZeneca pharma towards it and a little later the lead from BioNTech of Germany attracts Pfizer pharma to join with this very small company to convert the leads to vaccines in the shortest possible time. Almost all major companies start exploring vaccine strategies utilizing the available knowledge and outsourcing leads from academia/small companies to identify over 200 vaccine candidates; nearly, 50 are currently in clinical development. The major focus is on surface protein of virus namely spike protein which attaches to host target organ cells to induce infection and cause COVID-19 disease. The strategies adopted for producing this protein are mRNA gene, its code, synthetic gene, mutated gene to enhance protein production, spike protein produced outside in insect cells, DNA regulating spike protein gene, etc., and delivery by novel platforms to generate specific antibodies against this coronavirus, because these could be patented. Very few industries attempt technology by which most of the available

vaccines have been produced and that is attenuation and inactivation of the virus because of being not patentable but generating immunity against future infection with this virus.

### Novel Delivery Systems

mRNA vaccines, before COVID-19 disease, have not been successful clinically in preventing any disease. The advances in science and technology during the last ten years or so have resulted in their clinical success. The delivery systems being deployed for the delivery of COVID-19 vaccines are adenovirus platforms used successfully to develop flu vaccine. The trusted adenovirus (human Ad 26, 5 and chimpanzee ChAdOx 1) and the new and novel nanoparticles (both organic and inorganic) have provided successful platforms for the delivery of mRNA and spike proteins and their efficiency in generating immunity in human. These platforms provide immunogenic support as well. Novel immune genes have been used with inactivated virus and spike protein per se vaccines to boost immunity.

### Regulatory Toxicology

The advantage in developing the vaccines is that only one or two doses are needed to immunize a person. Thus, the regulatory toxicology in rodents and non-rodent species (i.e. non-human primates) and likewise regulatory pharmacology needed is for 1–2 weeks only and a follow-up of one month to ensure safety and formation of neutralizing antibodies. The immunity induced can be monitored continuously along with other mandatory preclinical and human studies.

### Clinical Trials

Considering the non-availability of treatments and availability of only palliative therapy, the regulations of almost all the countries provide for accelerated approvals in the development of vaccines for such dreaded diseases but without compromising on the rigours of quality of protocols for ensuring safety and efficacy. The regulatory authorities conduct rolling reviews in such a situation and that is submission of data as produced and providing speedy clearances after the submission of total data. The protocols are approved for simultaneous initiation of Phase I and II clinical trials and that is safety and safety plus initial efficacy in a limited number (50–100) of adult healthy human volunteers (18–60 years of age); hundreds of human volunteers are used in phase II clinical studies. The monitoring of neutralizing antibodies in animals and human is continued to know the duration-life/half-life of

antibodies in the body. These studies are over in about three months and the regulatory clearance given speedily due to rolling review of data. The leading vaccine developers and that is Oxford/AstraZeneca(UK), Pfizer/BioNTech (USA/Germany), Moderna (USA) and Bharat Biotech/ICMR (India), Sinopharma and Cansino (China) initiate Phase III [3, 4] randomized, double-blind placebo-controlled clinical trials in large number (20,000–50,000) of healthy human volunteers in July–September. The companies in USA, UK and Europe happen to be lucky because disease was at peak level and the trials therefore could be completed speedily. However, the disease incidence shows decrease in India by that time and thus has delayed efficacy results.

### Indian Efforts

Indian Govt. through the Dept. of Biotechnology and other S&T dept. supports academia and industry in R&D translation and clinical trial of all vaccines being developed in India. The support begins with the isolation of SARS-CoV-2 virus from an asymptomatic patient at Pune and its transfer (in early April, 2020) to industry, Bharat Biotech International Ltd. (BBIL), Hyderabad. BBIL grows and replicates the virus, inactivates it with a chemical (beta propiolactone) and complete regulatory preclinical studies in animals demonstrating safety and immune response and gets permission to initiate Phase I & II clinical trials in healthy adult human volunteers with its vaccine (BBV 152) in July, 2020. The company completes these studies satisfactorily and gets permission to initiate randomized double-blind multicentre Phase III trial in November. Based on the safety and good immune response (neutralizing antibodies), data in animals and human Phase I & II studies and limited Phase III trial data are granted emergency approval on 3rd January, 2021 to market the product (under trade name “COVAXIN”) for use in adult healthy 18–60 years old persons. Serum Institute of India which has been conducting Phase III bridging clinical trial in India with Oxford/AstraZeneca vaccine upscaled and produced in India also gets permission to market (under trade name “Covishield”) on basis of earlier data and without completing phase III trial in India. BBIL submits the interim analysis of Phase III study data on 3rd March, 2021 demonstrating 80.6% protection efficacy of its vaccine. Another indigenously developed COVID-19 vaccine ZyCoV-D (DNA vaccine) is granted permission to initiate Phase III clinical trial in January, 2021. Russian vaccine Sputnik V indigenously produced is also under Phase III clinical trial in India. Another five vaccines, ranging from attenuated to inactivated, viral vector, sub-unit glycoprotein, mRNA including two for intranasal single dose, with different delivery systems, are under development

(preclinical to Phase I/II clinical trial). Indian industry has therefore done exceedingly well in developing COVID-19 vaccines.

It is pertinent to mention here that some leading virologists of our country issue statements in media that they are unhappy with the clearance given to India developed vaccine without making results of phase III clinical trial public thereby probably doubting the integrity of Indian science, scientists, data examining experts and the regulator. It appears that they are not aware of accelerated approvals under emergency conditions of public health situations if the data that have been generated so far are satisfactory. It is pertinent to mention that another vaccine upscaled and produced in this country and undergoing phase III trial in India also gets marketing permission similarly without completing clinical trial. These unforeseen media reports about India developed vaccine create suspicion amongst health care workers (first users of vaccine) and public. It may be noted that the concerned India developed vaccine has shown 80.6% efficacy in phase III clinical trial in human in recently published interim analysis. Unnecessary and unfortunate statements by some politicians and religious leaders against the use of vaccines also deter some people not to use vaccines. Fortunately, the campaign to promote use of vaccines has been led by our Prime Minister, Chief Ministers, Union Health Minister, Member (Health), NitiAyog (monitored R&D translation and clinical trials), other leaders and academia for the welfare of the people. The Govt. of India has stood by the side of industry from R&D through clinical trials in providing funding. Academia of public sector institutions, likewise, have provided technical support. WHO and other international agencies have appreciated India’s efforts and are looking towards India to supply vaccines to needy countries.

### Vaccine Approvals and Marketing

Russia takes the lead to market its vaccine under trade name “Sputnik V” for public use with data on safety, efficacy and neutralizing antibodies after the completion of Phase I & II clinical trials and initiation of Phase III clinical trials with regulatory permission in Russia on 11th August, 2021. WHO and other leading companies also have criticized the speedy introduction without ensuring safety and effectivity. The appreciation of the wide use efficacy of this vaccine now by CDC, USA head and use in different countries justifies the judicious decision of Russia’s drug regulator considering the surge of COVID-19 disease and associated mortality in the country. Pfizer/BioNTech, vaccine “BNT162b2” (11 December, 2020), Moderna vaccine “mRNA-1273” (19 December, 2020) [5], AstraZeneca/Oxford vaccine “AZD1222” (30 December, 2020) follow introducing their vaccines under Emergency

Use Authorization in USA of former two companies and in UK of 3rd company on the dates mentioned above; in December, 2020. BBIL/ICMR and Serum Institute of India introduce their COVID-19 vaccines “*COVAXIN*” and “*Covishield*”, based on safety and neutralizing antibody data in animals and Phase I/II human clinical studies and some data only of Phase III clinical study, under emergency use authorization in India on 3rd January, 2021; *Sinovac* of Sinopharm is approved in China on 8th February, 2021. Johnson & Johnson single dose vaccine “*ENSEMBLE*” is approved under EUA in Europe on 11 March, 2021. These vaccines have now been approved for use by a large number of countries. The COVID-19 vaccines, therefore, have got the clinical use approvals in about 9–10 months because of speedy completion of clinical trials due to large number of people suffering with disease and some mortality and emergency situation of fast spreading of coronavirus as compared to 9–10 years needed normally for vaccine development and approval for marketing.

Never in history before, so many vaccines (13 novel vaccines as of 23 March, 2021) have been developed for any disease. And over 40 vaccines (10 in Phase II/III or III) are still under different phases of clinical trial. The sooner these vaccines reach the market, the better it will be for humanity to get immunized against COVID-19 disease. Never in history before, to the best of my knowledge, public sector institutions/academia, industry and Govts. of nations (whose industry was developing vaccines) have supported industry from R&D through clinical trials and advance purchase of vaccines to minimize/reduce industries development risks and advance production of vaccines. These supports helped the industry to make available the vaccines for public use immediately after getting EUA.

### How Vaccine Works/Produces Immunity

COVID-19 vaccines have been made from inactivated or attenuated (weakened) virus or laboratory-made parts of its surface spike protein or mRNA gene that regulates this protein. When the vaccine is injected into human, it triggers the immune response and consequently immune system produces SARS-CoV-2 coronavirus-specific antibodies as also develops long lasting immunity in the form of T cell [6] and B cell responses. The antibodies prevent entry of virus into cells/organs by surrounding and killing virus and if entered killer T cells enter infected host organ cells and kill virus. These antibodies are produced by B lymphocytes of immune system transformed into large plasma cells. B lymphocytes also produce small B stem cells which retain immune memory of this particular virus and activate the immune system to prevent future infections if caused by this particular coronavirus. Thus, the vaccine will start

protecting a person, 55–60 days onwards after the first injection of vaccine, not only from the ongoing coronavirus COVID-19 disease but also future infection/disease with this virus dependent upon immune memory life of the vaccine which is not yet known of the current COVID-19 vaccines. It may be mentioned that all the COVID-19 vaccines are prophylactic and not therapeutic (curative).

### Limits of Vaccine

No vaccine protects from ongoing/current infection or cures from disease but protects from future infections after body has acquired pathogen specific antibody titres. No COVID-19 vaccine is 100% protective. Pertinently, primary failure or even secondary failure after antibody titres wane from protection level is well known for vaccines; these data of COVID-19 vaccine are not yet available. Vaccine will protect from future COVID-19 disease but not infection from the coronavirus, and therefore, the vaccinated person may be an asymptomatic carrier or may even get mild disease or even severe disease in case of vaccine failure.

### Herd Immunity

The humanity will be safe globally if either the virus mutates and becomes non-infectious to get eliminated naturally. Or nearly about 70–80% of the population of the entire world is vaccinated to generate herd immunity to eliminate virus by intercepting transmission. This postulation is as per polio vaccine because no knowledge is yet available as to how much population needs to be vaccinated to generate herd immunity against coronavirus. India has already moved ahead in providing vaccines to 84 countries (free supplies to 12), both developed and developing after meeting Indian demand. Other countries are awaiting supplies from India. People all over the world are appreciating the Indian contribution. The COVID-19 vaccines may therefore prove to be the saviour of humanity from this dreaded disease.

### Why we should Take Vaccine

We have faith in vaccines because we get our children vaccinated with three vaccines within 12 h of birth, follow the vaccination schedule thereafter and take 11 vaccines provided under ‘Indradhanush programme’ by 2 years of age of the child and thereafter as per schedule up to 12 years of age to protect children from many diseases. We know that one killer disease smallpox and one debilitating disease polio have been eliminated globally with the use of vaccines. The only way to prevent the spread of SARS-CoV-2 virus and end this pandemic is not only to get

vaccinated ourselves with the COVID-19 vaccine provided when your turn comes but also motivate and encourage your relations, friends and well-wishers to take vaccine so as to secure yourself and the society from coronavirus to create herd immunity to end the pandemic.

We should have full faith in our industry for the quality and efficacy of COVID-19 vaccines. Both the vaccines developed, produced and marketed in India namely “COVAXIN” and “Covishield” are equally effective. There should be no doubt in one’s mind towards their quality and efficacy. India has already supplied these vaccines to 84 countries (ETHealthworld Lates, 31st March, 2021) under the programme “Vaccine Maitri”. Other countries are eagerly looking towards India to supply vaccines to them. It may be noted that India is the largest producer of quality vaccines and supplies to 130 countries as also meets 70% of UN supplies. It is surprising to note that we are hesitant to take a COVID-19 vaccine when the world is looking to us for supply. Two more vaccines namely ZyCoV-D developed indigenously and Sputnik V produced in India are likely to be added to our armoury shortly. By the end of the year, five more indigenously developed COVID-19 vaccines in India will be available to us. As of 24th March, 2021, thirteen COVID-19 vaccines are globally available. It may be pertinent to mention that there is no other disease against which so many vaccines have been developed in the world and many more are in the pipeline. The secretary to the Govt. of India, Dept. of Biotechnology in a recent interview on 3rd April, 2021 has called it “Vaccineyaan”, a new booster on the Indian horizon and moving towards “Vigyanyaan” to meet international demand/need of vaccines.

It is once again reiterated that all the COVID-19 vaccines are safe and effective and please get vaccinated as your turn comes to ensure COVID-19-free society. All the COVID-19 vaccines trigger an immune response to enable your body to fight and kill virus and none of them cause COVID-19 disease.

It is also emphasized that even after vaccination, continue using face mask, keep social distance of six feet and frequent hand wash with soap when out of your home till community immunity is achieved or virus mutates to become non-infectious.

The article is written in simple language to educate or create awareness about the global cooperation and efforts in developing the vaccines speedily for the society. It is also aimed to encourage people to take vaccine by knowing the benefits and limits of COVID-19 vaccines so as to

generate herd immunity and have coronavirus-free society globally.

Every effort has been made to make this write-up inclusive but data are being generated so fast that no claims are made to its exclusivity. Non-inclusion of any data or error is unintentional and regretted.

### Message

Get vaccinated, stay safe and stay healthy. Continue following COVID-19 appropriate norms/behaviour.

### Note

This write-up is part of 75 weeks science education programme of the Department of Science & Technology, Govt. of India and Azaadi ka Amrut Mahotsav initiative of the Govt. of India in celebration of 75th year of India’s independence.

**Acknowledgements** Author acknowledges the National academy of Sciences, India for its support to him.

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