Review Article

Global efforts on vaccines development against SARS-CoV-2 and Indian endeavor

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Abstract

By the end of September 2021, worldwide there were 22 approved SARS-CoV-2 vaccines of which nine were inactivated whole virus-based, six were replication-deficient viral vectored, four protein subunit based, one DNA vaccine, and two mRNA vaccines. Developmental efforts were also to manufacture the whole virus attenuated vaccines, viral vector replicating vaccines, bacterial vector-based vaccines, and viral particle-based vaccines. Host-cell-based vaccines were also being explored. As of October 05, 2021, there were 318 novel vaccine development approaches of which124 had entered into the clinical development stage, the rest 194 were in the preclinical stage. As of October 22, 2021, there were 243.44 million COVID-19 patients worldwide, of which 220.6 million recovered, and about 4.95 million died. The largest deaths per one million population were recorded at 5659 in Peru, and the smallest of 3 were in China. The total vaccine doses deployed worldwide were 6795 million, with 38% of the world population fully vaccinated, and 50% partly. India had taken multiple proactive steps, which included the development of local capabilities in various aspects including manufacturing of vaccines, testing methods and devices development, mass vaccination, mass testing, and production of personal protective equipment and materials. India had lost 324 people per one million, which was much lower than those witnessed in several countries like the Czech Republic, Brazil, Argentina, Spain, Columbia, Romania, the USA, Belgium, Mexico, and Italy. The virus is anticipated to stay in nature and people would have to live with it. Mass vaccination of people all over the world as fast as possible, and deploying booster doses on vulnerable people including those aged 60 years and above, are thought to be most protective for the people against the disease.

Keywords: COVAXIN, COVID-19, COVISHIELD, SARS-CoV-2, vaccination, variants of concern, ZyCoV-D

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INTRODUCTION

Global efforts for making a vaccine against the SARS-CoV-2 virus began shortly after the outbreak of COVID-19 flu, first time reported by China[1,2] in December 2019, followed by the publication of the nucleotide sequence data of the virus by the Chinese scientists[3] in January 2020. By July 31, 2020, at least as many as 169 new initiatives for the development of a novel vaccine against SARS-CoV-2 were being pursued and of these efforts, at least six vaccines had reached the stage of Phase-III clinical trials.[4] By October

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05, 2021, the efforts were further intensified, and as many as 194 diverse vaccines against SARS-CoV-2 came up to the stage of preclinical development, and another 124 numbers were undergoing registered clinical trials[5] totaling 318 novel approaches for vaccine development. The global efforts continue to move at unprecedented speed!

During the same period, Indian efforts include indigenous development, manufacture, and use of two vaccines namely COVAXIN by Bharat Biotech; and ZyCoV-D by Zydus Cadila; manufacture and sale of COVISHIELD by Serum Institute of India(manufacture and sale based on licensing agreement of Serum with Astra-Zeneca/ Oxford University, UK); and distribution, manufacture and sale of SPUTNIK V through Dr. Reddy's Lab(based on licensing agreement of Dr. Reddy's Lab with Gamalia Institute, Russia). India has also authorized the sale of mRNA-1273 vaccine manufactured by Moderna, USA; and Ad26.COV2.S vaccine, manufactured by Johnson &Johnson, USA. Another six vaccines namely COVOVAX [a protein subunit vaccine] by Serum Institute; four protein subunit vaccines by the name BECOV2A, BECOV2B, BECOV2C, BECOV2D by Biological E Limited, Hyderabad; and HGCO19 (m RNA Vaccine) by Gennova Biopharmaceuticals, Pune are under clinical trials.[6]

CORONAVIRUSES

Coronaviruses belong to the family of *Coronaviridae*, subfamily *Orthocoronaviridae*, of the order Nidovirales. Coronaviruses include 4 genera namely Alpha Coronavirus (Alpha -CoV), Beta Coronavirus (Beta-CoV), Gamma Coronavirus (Gamma-CoV), and Delta Coronavirus (Delta-CoV). The Alpha-CoV and Beta-CoV infect mammals; the Gamma-CoV infect avian species, and the Delta-CoV infects both mammals and avian species. The genera infecting humans and animals cause different kinds of diseases, especially respiratory diseases; Beta-CoV is most harmful to humans.[7,8] The viral genomes span between 26 and 32-kilo bases. These viruses were known for a long time to cause diseases in mammals and birds, and in humans, some of these caused mild respiratory infection. Being RNA viruses, these undergo mutation over time. Coronavirus was not known to cause severe human diseases before 2003. In 2003, a new coronavirus was identified that caused Severe Acute Respiratory Syndrome (SERS)[9] in humans. The virus was named as SERS-Co V. Further studies indicated that the human mutant had jumped from bats through undefined intermediate hosts; the viral isolates from human and civet cat were found[10] to be phylogenetically within the SARS-like coronaviruses. Later in 2012, other sets of new lethal coronaviruses were identified in the Middle East, which was identified and named as Middle East Respiratory Syndrome Corona Virus (MERS-Co V), and that the new virus was also thought to be zoonotic, jumping from camels to human.[11,12] In December 2019, another devastating epidemic in the form of COVID-19 flu originated at Wuhan city of China; this virus has brought about severe stress on human health the world over. This novel coronavirus is named as SARS-CoV-2. All the above three viruses are phylogenetically related, and this one is more related to SARS-Co V than to MERS-Co V. The frequent mutation of this virus has started scaring humankind. Its infection causes the disease called COVID-19 flu. The virus is highly infectious.

The frequency of mutation of RNA viruses during replication was reported to be in the range of 10^{-3} to 10^{-5} substitutions per nucleotide.[13] The average mutation rate of Human coronavirus 229E[14] was reported[15] to be 3.28×10^{-4} per multiplication. At present multiple mutated versions of the virus causing COVID-19 disease are in circulation; by September 2020, more than12000 mutants of the virus were reported.[16] The original Wuhan SARS-CoV-2 RNA virus of 29903 nucleotides started mutating quite fast as it infected more people. The mutation sites were mostly at the receptor-binding domain (RBD) of the spike(S) protein of the virus. Curiously, most of the mutant strains had the D614G amino acid on the RBD [meaning thereby that the 614th amino acid of the spike protein of the original Wuhan virus containing aspartic acid (D) was replaced by glycine (G) after mutation]. Further, there had also been point mutations including transition as well as transversion at multiple other sites of the 29903 nucleotide bases of the viral backbone; some of the identified mutants had part-deletions of the viral genome. Every point mutation in the genome as also part deletions or additions of nucleotides gives rise to a new mutant and requires a new name for exact identification.

Because of the susceptible nature of the SARS-CoV-2 genome, which is easily amenable to mutation, there are apprehensions that over some time more numbers of lethal coronaviruses may emerge from the vast natural pool of the coronaviruses (which may be named as SARS-CoV-3, SARS-CoV-4, etc). In the natural environment, these viruses keep multiplying in their chosen natural hosts, sometimes multiplying together with other viruses and gaining access to newer genetic materials. The resulting newer mutants acquire newer properties and perhaps ease their capacities of jumping from unknown animal hosts to humans although the precise nature of the issue is yet speculative. But this is a possibility, and this might happen, especially from the human needs of food proteins obtained

from the wild and domesticated birds and animals, many of which also harbor coronaviruses besides others. Since at present there are no effective therapeutic substances to contain the coronaviruses except a couple of newly evolved vaccines, there is a pressing need for understanding how coronaviruses multiply in the different host environment and how the zoonotic species jumping phenomenon takes place, to mount strong antiviral strategies in the future years.

Countries have resorted to mass vaccination of their citizens, using the approved vaccines, as vaccination has been the safest and the most sought method for controlling the SARS-Co-V-2 virus–generated pandemic the world over. In the meantime, the global work culture in multiple job-fronts is changing, and an emerging trend is being surfaced implying that much of the work can efficiently be carried out from locations away from the usual workplace efficiently by teleworking mode including video conferencing and deploying other similar technologies.

All the approved vaccines are somewhat effective, with their efficacy varying between above 95% to just above 50%, among the tested recipients. None is 100% effective to cure the infected. The infection and the cure have two components, one emanating from all the mutated SARS-CoV-2 variants, and the other requires an understanding of the health, age, and genomic status of the infected individuals. More scientific understanding is therefore required, and to come out with a novel vaccine that can be deployed to contain all the factors, and to cure the infected from all the mutants of the SARS-CoV-2 virus that produces COVID-19 flu. Further, since the lungs are the main organ that manifests the worst damage because of which maximum deaths occur, other known measures to protect the lungs from other viral infections should also be concurrently strategized while using approved COVID-19 flu vaccines.

INTENT OF THE STUDY

The study intends to review and ascertain the nature of SARS-CoV-2 vaccines developed globally and in India; the nature of the spread of the viral infection, the capacity to identify and name the nature of the infecting virus, and also to briefly review how India had been able to fight back to contain the disease among the Indian population.

METHODOLOGY OF THE STUDY

The study is based on a search of web pages of published literature on the internet of the Google Search Engine. The websites of the World Health Organization (WHO), major manufacturing units of SARS-CoV-2 vaccines as also government websites of major developed and developing countries were consulted. Also, the websites of the Indian government departments involved in the administrative function, vaccination, R&D support, and funding of research on vaccines against the virus were consulted. The author has a background of hands-on experience in research and development, production and administration of drugs and pharmaceuticals, diagnostics, certain vaccines, and clinical chemistry reagents for several decades.

Chemical nature of the evolving/evolved vaccine antigens

The global initiatives on the development of COVID-19 vaccine candidates in both clinical and pre-clinical development are being continuously tracked and updated by the World Health Organization (WHO) through its incessant initiative.[5] The 318 novel approaches for vaccine development as of October 05, 2021, could be classified to be belonging to various vaccine categories, depending on the selection and design of the vaccinating antigens. Figure 1 depicts the nature of vaccines evolving/evolved globally.

It was assessed by the author that as of September 30, 2021, worldwide there were twenty-two approved vaccines. The country-wise trade names of these approved vaccines along with the names of the companies who invented/introduced these vaccines into the market are furnished below. Of these approved vaccines, nine were inactivated

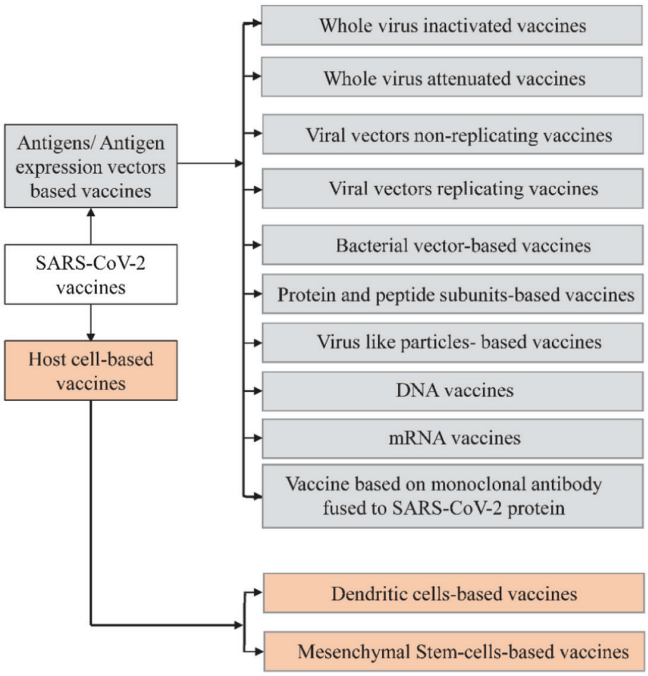

Figure 1: Schematic representation of various SARS-CoV-2 vaccine platforms

whole virus vaccines [India: COVAXIN by Bharat Biotech; China: CORONA VAC by Sinovac Biotech, BBIBP-Cor V and WIBP-CorV both by Sinopharm, and Minhai-Kangtai by Shenzhen Kangtai Biological Products Co. Ltd; Russia: CoviVac by Chumakov Centre, Inst. of Russian Acad. of Sci.; Iran: COVIran Barekat by Shifa Pharmed Industrial Group (a subsidiary of Barkat Pharma Group), and FAKHRAVAC by Organization of Defensive Innovation and Research; and Kazakhstan: Qaz Vac by Research Institute for Biological Safety Problems]. There were six replication-deficient viral vectored vaccines [UK: ChAdOx1 nCoV-19 (AZD1222) by Astra Zeneca/Oxford, UK; India: COVISHIELD [ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)] by Serum Institute of India under license from AstraZeneca/Oxford, UK; Russia: SPUTNIK V and SPUTNIK LIGHT by Gamaleya Research Institute of Epidemiology and Microbiology; USA: ADENO 26 CoV2.S by Johnson and Johnson; China: CONVIDECIA by CanSino Biologics]. Among the protein subunit vaccines, there were four products:[China: ZIFIVAX (ZF2001) by Anhui Zhifei Longcom Biopharmaceutical Co. Ltd.; Russia: EpiVac Corona (Aurora-CoV) by Vektor State Research Center of Virology and Biotechnology; Cuba: ABDALA by Centre for Genetic Engineering and Biotechnology, and SOBERNA 02 (Soberana 2, FINLAY-FR-2) by Finlay Institute]. There was only one DNA vaccine:[ZyCoV-D by Zydus Cadila, India]. Only two mRNA vaccines, both from the USA were approved, which were BNT162b2 by Pfizer-BioNTech, and mRNA-1273 by Moderna, Inc.

All of these vaccines were approved for use by at least one Regulatory Authority of one country. Including these 22, as of October 05, 2021, there were in total 318 novel approaches, of which 194 were in the preclinical stage while 124 had reached the clinical development stage. More vaccine development approaches would evolve. The wish and consensus of newer approaches are that there has to be such an effective vaccine, which would be so universal that it would bring an end to the pandemic.

In a review of 30 studies on approved vaccines, where the investigation was focused on determining the vaccine efficacy/effectiveness (VE) on the SARS-CoV-2 infective mutants, it was found that in fully vaccinated individuals(vaccinated between the period from January 1 to May 14, 2021), the VE against symptomatic and asymptomatic infections in almost all the studies[17] was close to between 80–90%. It was therefore concluded that fully vaccinated individuals were less likely to become infected from COVID-19 flu. The vaccines used in these studies were mostly the mRNA vaccines and in some cases the adenoviral vector vaccines of Astra-Zeneca or Johnson and Johnson. No other types of SARS-CoV-2 vaccines were used. In another study focusing on the safety and efficacy of eleven COVID-19 vaccines, where the results were published up to December 31, 2020, it was found that in 10 such studies, the 28-day seroconversion rate of vaccinated individuals exceeded 80%. In two studies among the eleven, using a level of 10,000-scale clinical trials, the vaccines were found to be effective in 95% and 70.4% of the recipients, respectively. The study included the results of a wide range of vaccine types including inactivated vaccines, recombinant adenoviral vectored vaccines, recombinant viral spike protein vaccines, and mRNA vaccines. It was concluded[18] that most of the vaccines appeared to be effective and safe. The authors suggested that the long-term efficacy and safety of SARS-CoV-2 vaccines need to be studied. These study results provide ample evidence that vaccination is one of the most effective methods for containing the pandemic. And there are certain vaccines such as the mRNA vaccines, which are more efficacious in containing the spread of the disease.

The information on the number of countries that had one million people or more infected from the disease as of October 22, 2021, has been compiled from the published data and presented in Table 1. The countries have been listed and organized in order of diminishing number of infected cases, up to one million cases in one country.[19] The table also provides information on individuals recovered, the deaths occurring countrywide, as also the status of vaccination of the people fully or partially beside the number of vaccine doses deployed[20] by each country up to October 22, 2021 [Table 1].

It was the intention to analyze and find if any trend of insight could be had from these data. It is found from the information in the table that more than 5950 infected died per one million population in Peru, being thus far the highest death rate in the world. This death rate is also much higher than the death rate in other South American countries. In South America, multiple infective variants are in circulation. In Peru, the Lambda variant, earlier known as C.37 has spread rapidly.[21] WHO has designated it as a "variant of interest", which means that it may be more infective and dangerous than the original Wuhan strain. This variant has been found to exist in more than 80% of the infected.[22] But this is not as infective as the Delta variant. More death in Peru is not therefore because of the preponderance of the Lambda variant, though the infection with this variant could also be dangerous if treatment options are inadequate. The country imposed the earliest and strictest lockdowns in March 2020, which lasted until the end of June 2020. Peru's government sealed the country's borders, curfews were imposed, and people could only leave their homes for essential goods. Yet the disease

Table 1: Countrywise total COVID-19 flu diseases up to October 22, 2021 in descending number for 32 major countries

A	B	C	D	E	F	G	H	I	J
1	USA	46.18	35.90	753,749	2,260	411.0	57%	66%	124
2	India	34.14	33.51	453,076	324	1003.2	21%	52%	73
3	Brazil	21.70	20.88	604,764	2,819	261.0	52%	74%	124
4	Russia	8.17	7.12	228,453	1,565	99.4	33%	36%	69
5	Turkey	7.77	7.20	68,472	801	114.8	57%	66%	138
6	France	7.12	*6.90*	117,411	1,794	97.7	68%	76%	146
7	Iran	5.84	5.39	124,928	1,463	77.6	33%	60%	94
8	Argentina	5.28	5.14	115,796	2,532	56.9	56%	71%	127
9	Spain	5.00	4.85	87,102	2,532	71.2	79%	81%	151
10	Colombia	4.99	4.83	126,959	2,461	44.7	39%	57%	89
11	Italy	4.73	4.52	131,724	2,183	88.4	71%	77%	147
12	Germany	4.45	4.19	95,753	1,138	110.6	66%	69%	133
13	Indonesia	4.24	4.08	143,153	516	175.6	24%	41%	65
14	Mexico	3.77	3.13	285,669	2,186	113.5	41%	55%	89
15	Poland	2.96	2.68	76,359	2,020	38.5	52%	53%	101
16	South Africa	2.92	2.81	88,835	1,474	20.5	19%	24%	35
17	Philippines	2.75	2.64	41,520	372	54.4	23%	26%	50
18	Ukraine	2.73	2.36	63,003	1,452	15.4	15%	19%	35
19	Malaysia	2.41	2.30	28,234	858	48.7	73%	79%	152
20	Peru	2.19	N/A	199,945	5,956	32.6	44%	56%	100
21	Netherlands	2.07	*1.97*	18,290	1,064	23.9	68%	75%	138
22	Iraq	2.04	1.98	22,901	553	8.5	8.3%	13%	22
23	Thailand	1.83	1.71	18,625	266	66.6	38%	55%	96
24	Czech Rep	1.72	1.67	30,593	2,850	11.9	57%	58%	112
25	Japan	1.72	1.69	18,173	144	183.3	69%	76%	145
26	Canada	1.69	1.64	28,667	751	58.0	74%	79%	154
27	Chile	1.68	1.63	37,640	1,947	34.2	76%	85%	180
28	Bangladesh	1.57	1.530	27,801	167	58.4	12%	24%	36
29	Romania	1.53	1.30	43,844	2,299	11.4	30%	35%	59
30	Israel	1.32	1.30	8,039	862	15.8	63%	69%	175
31	Belgium	1.31	1.20	25,835	2,217	16.8	74%	75%	146
32	Pakistan	1.27	1.21	28,344	125	99.3	17%	31%	46
33	Sweden	1.17	*1.13*	14,956	1,469	14.3	66%	70%	139
34	Serbia	1.09	0.95	9,388	1,080	6.7	42%	44%	97
35	Portugal	1.08	1.03	18,125	1,784	16.1	86%	88%	157
36	China	0.097	0.091	4,636	3	2240.6	75%	79%	160
	World	243.44	220.60	4,948,431	634.8	6795.0	38%	50%	89

A = Serial number; B = Names of countries arranged in decreasing number of COVID-19 infected individuals, expressed in million numbers, up to countries that registered up to one 1 million cases; C = COVID-19 infected, in million numbers; D = Recovered, in million numbers; E = Total deaths in numbers; F = Death per one million population; G = Millions of vaccine doses used; H = Percentage of the population fully vaccinated. I = Percent of population partially vaccinated. J = Number of vaccine doses used per 100 people.

spread violently and killed many. Death per one million people in Peru superseded many Latin American countries including Brazil, Argentina, Colombia, and Mexico. The main reasons, therefore, seem to be the fast spread of the disease due to the poor living conditions of poor people, living in overcrowded homes, thereby spreading infection fast; inadequacy of Peru's healthcare system, which probably was insufficient to handle a large number of critically ill patients; inadequacy in oxygen supply, and slow vaccination of people.[23]

A sizable number of countries had registered death per one million population as over 2000; these countries include the Czech Republic, Brazil, Argentina, Spain, Columbia, Romania, USA, Belgium, Mexico, and Italy. No correlations among the listed parameters depicted in Table 1 could be found for such high deaths in these countries from the above data. Probably with fast and more vaccination, the future death rates in these, and other countries would be reduced significantly. However, it is to be borne in mind that the virus would exist in the environment, and therefore people would have to be alert and would have to resort to the measures to minimize the spread of infection among the vulnerable population till more people are vaccinated.

Of the four viral variants of concern, the Delta variant is spreading quite fast globally. The R_0 value of this most infective variant is very high; its highest value thus far reported is 7.41. Based on this value, it appears that over 86.5% of the population needs to be vaccinated before which the required herd immunity would not be achieved to contain the disease. Further, since the vaccines used globally are considerably different from one another like the use of deactivated whole virus vaccines as the conventional types to the most modern mRNA vaccines (which are much more protective), it is the opinion of the author that till at least

90% of the world population are fully vaccinated, the viral infection shall continue to be manifested at different parts of the world. Therefore, till that time all the precautions of preventing the spread need to be adhered to.

Indian efforts to combat COVID-19 flu

Following the COVID-19 pandemic in India, after India declared for the first time a complete lockdown for 21 days[24] on March 25, 2020, immediately thereafter, on March 27, 2020, the Prime Minister's Citizen Assistance and Relief in Emergency Situations Fund (fondly known as PM CARES Fund) was created[25] to fight the emerging pandemic. No vaccines were available at that time. In the meantime, on 27th January 2020, the first case of COVID-19 flu was presented to the Emergency Department of the General Hospital, Thrissur, Kerala, the case was confirmed by RT-PCR method on January 30, 2020, by the NIV, Pune.[26] The first reported[27] case of death from COVID-19 flu was on March 12, 2020, from Karnataka.

Later, when vaccines were invented, followed by studies of their safety and efficacy information maturing in late December 2020, the Government of India came out with operational guidelines[28] on vaccination (as of December 28, 2020) for the eligible and more deserving candidates against COVID-19 flu. The guidelines spelled out how the vaccination will be offered to people; the initial priorities were to vaccinate first the healthcare workers, frontline workers, and population above 50 years of age, followed by population below 50 years of age with associated comorbidity conditions. The remaining populations were to be vaccinated later, based on the disease characteristics and vaccine availability. Over time as more experience was gathered and the availability of vaccines increased, the guidelines were modified and enlarged. The revised guidelines, effective from June 21, 2021, provide the commitments[29] of the government to vaccinate every Indian falling in the category of Front Line Workers working to manage COVID-19 flu, citizens more than 60 years of age, citizens more than 45 years of age and eventually citizens more than 18 years of age, free of cost. There is yet no announced policy on the vaccination of citizens below 18 years.

Indian initiative to tackle COVID-19 flu including vaccines development efforts

Indian commercial establishments in collaboration with institutions and international establishments were to develop novel vaccine technologies locally as also to team up to obtain technologies from abroad and utilize the local manufacturing infrastructure to produce the vaccine in the country. Indian Government came up with multiple funding initiatives to support such endeavors.

On March 20, 2020, a project entitled "India COVID-19 Emergency Response and Health Systems Preparedness Project [P173836]" was announced by the government,[30] which project was to be implemented involving the Ministry of Health and Family Welfare (MOH&FW), Indian Council of Medical Research (ICMR) and the National Centre for Disease Control (NCDC). The financing of the project was to be by the International Bank for Reconstruction and Development, Washington DC, USA, which is also called the World Bank.

In April 2020, Government of India from the MOH&FW had initiated proactive steps[31] including setting up of (a) a Task Force for Focused Research on Corona Vaccine in April 2020, to encourage domestic R&D on Drugs, Diagnostics, and Vaccines; (b) a National Expert Group on Vaccine Administration for COVID-19, constituted in August 2020, to formulate a comprehensive action plan for vaccine administration; and (c) an Empowered Group on Vaccine Administration for COVID-19 constituted in January 2021, to facilitate optimal utilization of technology to implement vaccination against COVID-19 flu.

The country-wide vaccination in India commenced on January 16, 2021. Initially, all Health Care Workers were targeted. Gradually, the program was expanded with time to include vaccination of Front Line Workers, citizens more than 60 years of age, citizens more than 45 years of age, and eventually citizens more than 18 years of age. From January 16, 2021, to April 30, 2021, a hundred percent of vaccine doses manufactured in India were procured by the Government of India and provided free of cost to State Governments. The program was revised, and with effect from May 01, 2021 Government of India was procuring 50% of the vaccine produced in the country and was continuing to provide them to States free of cost for administering to priority groups. The State Government and private hospitals were then also empowered to directly procure from the remaining 50% vaccine pool. This policy worked up to the third quarter of July 2021. In the meantime, several states had communicated that they are facing difficulties in managing the funding as also in procurement and logistics of vaccines, which factors were impacting the pace of vaccination of individuals. Consequently, with effect from June 21, 2021, new vaccination guidelines were announced by the government, which guidelines are presently in use. The main elements of the Revised Guidelines are as under:

1. The government of India will procure 75% of the vaccines being produced by the manufacturers in the country, and shall provide these free of cost to

States/UTs, who in turn shall use these for vaccination of people free of costs through the Government Vaccination Centres.
2. Vaccination needs to be prioritized so that these are first applied to Health Care Workers, followed by Front Line Workers, followed by citizens more than 45 years of age, followed by citizens whose second dose has become due, and then to citizens 18 years and above.
3. Within the population group of citizens more than 18 years of age, States/UTs may decide their prioritization factoring in the vaccine supply schedule.
4. The government of India will provide States/UTs advance information of vaccine doses to be supplied to them, following which the States/UTs should further allocate doses well in advance to districts and vaccination centers.
5. To incentivize production by vaccine manufacturers and encourage new vaccines, domestic vaccine manufacturers are given the option to also provide vaccines directly to private hospitals. This would be restricted to 25% of their monthly production. States/UTs would aggregate the demand of private hospitals keeping in view equitable distribution between large and small private hospitals and regional balance. This would enable the smaller and remoter private hospitals to obtain a timely supply of vaccines.
6. The price of vaccine doses for private hospitals would be declared by each vaccine manufacturer, and any subsequent changes would be notified in advance. The private hospitals may charge up to a maximum of Rupees 150 per dose as service charges.
7. All citizens irrespective of their income status are entitled to free vaccination. Those who can pay are encouraged to use private hospitals' vaccination establishments.

The MOH&FW had later issued a guidance protocol[32] on COVID-19 vaccination. The protocol included guidelines for identification of workplaces for COVID-19 vaccination; identification of eligible and willing beneficiaries at workplaces; registration of workplace as COVID vaccination centers (CVC) in Covid Vaccine Intelligence Work (Co-WIN) portal; linkage of workplace COVID vaccination centers (CVC)with public and private CVCs; linkage of workplace CVC with cold chain points; engaging health infrastructure and health care workers of workplace CVC; deployment of vaccination team at workplace CVC; adverse event following immunization(AEFI)management; vaccination at workplace CVC; monitoring of vaccination at workplace CVCs; and financial guidelines for vaccination at workplaces.

MOH&FW has informed[33] that through the National Vaccination Program as of October 17, 2021, the number of citizens who are the recipients of the first dose was 694,733,920, the number of recipients of two doses was 281,855,620, and that the total vaccine doses deployed were 976,589,540. The total vaccine doses deployed crossed one billion number on October 22, 2021 [Table 1]. Mass vaccination of Indian citizens for protection against the SARS-CoV-2 virus is a great national responsibility, which is discharged by the Indian government quite proactively.

To get vaccinated, one has to register on the government's Cowin platform.[34] There were initial difficulties in using the platform, but sooner the system became easier and useful. Everyone vaccinated received a certificate indicating the vaccines used and the dates of vaccination. Vaccination started in India on January 16, 2021.

Mass vaccination of Indian citizens for protection against COVID-19 flu is a feat that needs to be recognized and applauded, taking note of the resource—constraint public environment, the existence of multiple heterogeneous cultural environments throughout the country, and a weak common national identity to wholeheartedly support the central executive system that is constantly being watched by the multiple media and is prone to criticism by the legislature and the judiciary. The Indian public-funded healthcare system comprising the government-run hospitals and medical institutions, diagnostic facilities, and R&D institutions engaged in evolving and providing innovative evolving technologies had always been on the edge for long. The COVID-19 pandemic had enthused the healthcare ecosystem under the leadership of the existing central political system, which rose to the challenge and steered the nation through the crisis through multiple actions. The all-around efforts of stimulating the ecosystem through public-private-partnership have thus far been an example that needs to be flagged and recognized.

For conducting research and development and technology applications in multiple aspects of COVID-19 flu, the Government of India from the Department of Biotechnology (DBT) came to the forefront, and it has taken an extremely enthusiastic and aggressive role to fight the pandemic caused by the SARS-CoV-2 virus through multiple proactive actions. These include activities promoting research and innovation in multiple relevant areas that could make a difference. The relevant areas of promotion include disease diagnosis, treatment, vaccination, development of therapeutics, and certain other supporting activities such as the creation of viral genome sequencing facilities including repositories and augmentation of research infrastructure development. Taking up such relevant activities was initiated in a mission-

mode program, known as the Mission COVID Suraksha.

The Mission COVID Suraksha was announced on November 29, 2020, and was intended to develop indigenously a safe, efficacious, affordable, and accessible COVID-19 vaccine, at the earliest, and several actions were initiated.[35] Following scientific and technical due diligence Bharat Biotech, Hyderabad, and three public sectors (Indian Immunologicals, Haffkine, Bharat Immunologicals) were provided funding support to set up enhanced capacities for COVAXIN production. COVAXIN was approved for use in January 2021. In order to develop other SARS-CoV-2 vaccines indigenously, requests for showing "Requests for Expression of Interest" (REOIs) were called for, and after receiving proposals and due diligence, supports have been extended to develop five vaccine candidates, which include a DNA vaccine by Zydus Cadila, Ahmedabad; protein subunit vaccines by Bio E, Hyderabad; mRNA vaccine [named as HGCO19 (COVID-19 vaccine)] by Genova, Pune; intranasal vaccine by Bharat Biotech, Hyderabad; and a virus-like particle(VLP) vaccine by Genique Life Sciences, Gurgaon. The DNA vaccine by Zydus Cadila has already been developed, tested, and approved for use. Facilities for conducting animal challenge studies, and laboratories for performing clinical immunogenicity assays, required for vaccine development were also supported through the Suraksha Mission. Enhanced capacity for the conduct of human clinical trials (Phase I, II, III) for COVID-19 candidate vaccines has also been supported in 19 hospitals.

Through two documents available on the net[36,37] of the DBT site, it is found that as of October 15, 2021, the following have been pursued:

1. The development of multiple methods of diagnosis of the COVID-19 disease has been supported including serological and molecular testing methods. Testing hubs have also been created in different parts of the country.
2. Several treatment methods such as treatment by using monoclonal antibodies, plasma therapy, repurposing of known pharmaceutical substances for treating the disease, and use of phytopharmaceutical substances have been explored.
3. For preventing the disease from spread several projects have been supported, which include promotion and support of multiple vaccine production and development platforms, creation of facilities for assay using animal models of various kinds, supporting the creation of clinical trial sites, creation of immunoassay labs, initiating BCG trials to ascertain the preventive role of vaccination on COVID-19.
4. Creation of PAN-India 1000 SARS-CoV-2 genome sequencing consortium, creation of repositories and connected facilities for epidemiological studies.
5. Supporting the scaling up of manufacturing for ventilators, personal protective equipment (PPE) such as surgical masks, non-surgical masks, gloves, goggles, face shields, gowns, N95 masks, etc, as well as disinfection and sterilization platforms at multiple locations.

Large quantities of COVAXIN doses were available in the country, primarily because of unstinted support provided by DBT for easing the manufacture of this vaccine in the country. Further, the ZyCoV-D vaccine also got developed and approved through the DBT efforts.

Simultaneously along with MOH&FW and DBT, another organization, the Indian Council of Medical Research (ICMR) came up with multiple other connected activities to fight COVID-19 flu. ICMR[38] is involved in generating, providing, implementing, and collating information on various aspects of COVID-19 flu. On information about Labs for testing the presence of the virus, ICMR provides procedures for sample collection and sample recording, informing about the government institutions/ Medical colleges having testing facilities for the virus, providing information about the private labs that are approved for COVID-19 testing, validating multiple testing formats such as the Cartridge Based Nucleic Acid Amplification Test, True Nat assay system, etc, and some more information linked with lab testing. On the status of testing of samples, it provides details on the number of samples tested region-wise in the country. ICMR is also involved in establishing COVID-19 bio-repositories; a total of 17 National COVID-19 bio-repositories have been identified by ICMR and other Science Ministries such as DBT and CSIR, and these are parts of the PAN India Genome Sequencing consortium. ICMR is also actively involved in the Clinical Phase trials of SARS-CoV-2 vaccines and publishes updates on the trial results[39] of COVID-19 vaccines being developed in India.

DISCUSSION

For containing COVID-19 flu, the epidemiology of the disease needs to be exhaustively studied, as this would provide information on the rate of infection, prevalence, cost of illness, the burden of the disease, disability-adjusted life year, etc. One basic number, called the basic reproductive number (Ro) [represented by some authors as RO] is determined, which number denotes the number of new infection cases directly generated by one infected from the disease, and where all individuals in the population are considered susceptible to the disease. The mathematical basis for calculating the R_O provides further details.[40] The value of R_O is affected by multiple factors such as the

behavior of the population infected or not yet infected, the environmental conditions, the population genetics, the disease burden, and the immunological status of the population. When R_O is greater than 1, then only the disease would spread. In a population, when R_O is larger than (1-1/R_O), the spread of the disease can be controlled by taking effective measures to contain the spread such as using protective masks, maintaining isolation, social distancing, washing hands when doubtful infective materials are touched, taking baths using soaps after returning from work or after visiting crowded places, vaccination, etc. R_O values also assist in finding what fraction or percentage of the population must be affected, beyond which the spread of the disease shall stop, a factor that is called herd immunity. For COVID-19 flu, the R_O values have been reported during the early period of infection in different situations in different parts of the world. The R_O values calculated and estimated for the Middle East countries[41] including for Iran, Kuwait, Bahrain, Qatar, Saudi Arabia, United Arab Emirates (UAE), Oman, Jordan, Egypt, Lebanon, Syria, Israel, West Bank, and Gaza Strip territory, and Cyprus for all the strains of SARS-CoV-2 virus varied from 2.60 to 7.41, with mean R_O of 3.76. The R_O for the USA and eight European countries were estimated[42] during the early epidemic period before broad control measures, to vary be between 4.7 to 7.3 in the USA, and between 3.6 and 6.1 in the eight European countries. For the Indian environment, since in India presently the WHO-classified delta variant is becoming prominent, assuming its R_O value as 7.41 (the highest value thus far reported), the fraction of the population getting infected would reach 0.865 or 86.5% where after the further spread is likely to stop. Interpreted differently, a 100% effective vaccine, when deployed on 86.5% of the population would stop the further spread of the disease in India. Since no vaccine is 100% effective, more percentage of the vulnerable population would need to be vaccinated. It is anticipated by the author that soon after over 90% of the population is vaccinated, further spread of the disease may substantially slow down. In the meantime, all the preventive measures such as the use of masks, maintaining of social distancing, washing of hands-on touching doubtful infective objects, etc need to be kept in vogue.

World over the viral mutants have been classified as (a) Variants of Concern (VOC), and (b) Variants of Interest (VOI) by the World Health Organization[43] (WHO), while the USA have classified the mutants[44] as (a) Variant of Interest, (b) Variant of Concern, and (c) Variant of High Consequence. Because of the emergence of newer viral mutants, the overall R_O values measured at different times in the population have been varying to a considerable extent. The whole-genome sequencing (WGS) data of SARS-CoV-2, generated from the isolates from different global regions have thrown insights into various aspects of the pathogen. These data are used for better diagnosis of the disease and enable mounting better disease-control strategies. This situation needs continuous monitoring of the new evolving mutants through sequencing of the evolved variants. The creation of the PAN-India 1000 SARS-CoV-2 genome sequencing consortium, the creation of repositories and connected facilities for epidemiological studies are rightful steps taken by the Indian government.

The UK government has published[45] an update on the SARS-CoV-2 variants of concern. Such information needs to be generated in India too to constantly monitor the emergence of new variants of concern. This would enable taking advanced action for containing the spread. The Delta mutant is considered to be the most infectious among the mutants. In India, the Variants of Concern, certain Variants of Interest, and sub-lineage of Delta such as Delta Sub-Lineage AY.4 are on the rise in certain regions of the country.

A highly infectious new mutant has recently been described by the researchers of South Africa, which mutant is named as B.1.1.529; this virus harbors a large number of the mutations on its spike protein genome.[46] It is spreading fast in a large number of southern African regions including South Africa, Namibia, Zimbabwe, Botswana, Angola, etc, and has been detected in many other parts of the world.[47] The WHO has classified the mutant as a variant of concern (VOC) and has named it Omicron.[48] This mutant is thought to be more infectious, meaning thereby that it infects and spreads, and multiplies faster. It is not yet known if the mutant is more lethal. In the African region, the deaths reported from COVID-19 flu are comparatively lower than in other parts of the world.[49] Although it is too early to conclude about how the new mutant Omicron shall behave in other parts of the world, in terms of rate of infection, cure, and mortality, it is the surmise of the author that it would spread fast especially among the population which is not yet vaccinated and reinfection among the already vaccinated individuals shall be more for various reasons, especially after waning off of the effect of vaccination but the death rate among the vaccinated would not increase. It is also the belief of the author[2] that in Mycobacterium tuberculosis-exposed but the non-diseased population in the world such as the South Asian Region and the African region the spread and death from this disease shall be much lower than in other parts of the world.

It is difficult to correctly and precisely predict what would be the emerging world scenario on the status of further

infection and the requirement of vaccine types and doses. However, for India, this is being attempted. As of October 17, 2021, in India the numbers of citizens who were the recipients of the first dose were over 694 million, the number of recipients of two doses was over 281 million, and that the total vaccine doses deployed were close to one billion, which number is increasing with time, and had crossed one billion doses on October 22, 2021. Indian population at the end of 2020 was about1.38 a billion, which was 17.7% of the global population.[50] Taking into consideration the 2011Indian Population census data,[51] when the population was 1.21 billion, there were nearly 64.4% of the population who were above 15 years. Taking the adult population of India in 2020 as 64.4% of the total, the number works out to 0.8887 billion. Therefore, the number of adult vaccine doses required for vaccinating all the adults of India would be 1.99 billion, say 2 billion with 12% provisions for handling and process loss. As of October 17, 2021, the number of adult individuals already vaccinated was about 282 million or about 31.6% of the eligible population, and 21.7% of the total population. Taking into consideration, the number of adults already vaccinated in India as of October 17, 2021, the number of vaccines required for the remaining eligible adults would be 1023 million doses [2000 million − 282 million − 695 million (recipients of one dose)]. Encouraged by the Government of India, the Indian vaccine manufacturers are ramping up their vaccine production capacities fast. The manufacturers are further stimulated by the talks that a large number of adult recipients may have to be given a third dose. Additionally, children may also be brought into the vaccination program. Further, Indian vaccine makers are looking for exporting a sizable portion to meet the requirements of the poor nations. Taken together, these factors are energizing the manufacturers to increase their production fast. The present production of Serum Institute of India (SII) is about 220 million doses per month and that of Bharat Biotech is about 50 million doses per month, totaling about 270 million doses per month. Both the companies are looking for exploring export possibilities. Indian vaccination rate is presently about 170–180 million doses per month, which rate seems to be the maximum maintained rate for a while with the existing infrastructure. It is anticipated therefore that out of the above-estimated production per month, about 90–100 million doses per month shall be available for exports from these two companies. It is further observed that presence of all eligible adults, about 38% have been fully vaccinated and about 80% have received the first dose.[52] This implies that at the present peak rate of vaccination, it would take another 2.5 months from December 2021 to complete the full vaccination of the eligible candidates. In other words, the period may extend up to mid-February 2022 at full speed.

In the meantime, several new and expansion endeavors[53] are in sight which includes SII's new COVOVAX [a protein-based COVID-19 vaccine developed by Novavax, USA, and known as NVX-CoV2373 internationally], in capacity of about 50 million doses per month, which is meant primarily for exports, and can be used to vaccinate adults and children; Bharat Biotech's COVAXIN expansion plan in its multiple own facilities plus it's teaming up for production from facilities of Indian Immunologicals, Hyderabad, Haffkine Institute, Mumbai, and BIBCOL, Haryana to have production of about 50 million doses per month; Biological E, Hyderabad company's new protein- subunit based vaccine (CORBIVAX) of the capacity of 80 million doses per month; and Zydus Cadila, Ahmedabad, to produce Zy Co V vaccine at 10 million doses per month. This additional production of vaccines will ease the availability situation tremendously, making more room for exports. Mass vaccination of Indian citizens for protection against the SARS-CoV-2 virus is a great national responsibility, which is being discharged by the Indian government quite proactively. It is not quite easy to reach all the eligible vaccine recipients in the country who may be living far away and maybe handicapped for various reasons to reach the vaccination sites. Reaching everyone requires the creation of an effective infrastructure on a large scale involving all the state governments, many community-based organizations, and local health centers, which is what has been majorly achieved in the Indian efforts.

There has been a significant dip in COVID-19 caseload in India although some states such as Kerala, Maharashtra, Tamil Nadu, Andhra Pradesh, and West Bengal have remained more infective. More intense mass vaccination in these states is required to enable the increase in the vaccine-preventable status of these states in particular. If this is done before the end of November 2021, it is anticipated that the possible third wave during the winter months of December 2021–January 2022 can be avoided.

The COVID-19 pandemic in India had activated the country's healthcare ecosystem under the leadership of the existing central political system, which rose to the challenge and steered the nation during this emergency period through multiple proactive actions. The nation worked together with the relevant government departments, the public-funded institutions, and the private enterprises. The all-around efforts of stimulating the ecosystem through public-private-partnership have thus far been an example that needs to be flagged and recognized.

In the meantime, concerns have been raised globally that the effect of full vaccination is waned off gradually over time.

In a study on the two-dose mRNA vaccine BNT162b2 of Pfizer up to 6 months, it was found that the antibody levels declined[54] at 12 weeks and 6 months postvaccination. Six months after the second dose the neutralizing antibody levels against the spike protein of the virus was much lower than the originally reached peak levels, and was similar to the levels in persons vaccinated with one dose or in patients who recovered from the disease. The study suggested ascertaining if booster vaccination was necessary. In another study in Israel on recipients of Pfizer's mRNA BNT162b2 vaccine, who were 60 years of age or older and had received two doses, it was found that the rates of confirmed COVID-19 and severe illness were substantially lower.[55] Since the immune mechanism of protection is essentially based on the preponderance of neutralizing immunoglobulins against the spike protein of the virus, in all the different formats of deployment of vaccination, there is a common thread of similar biological processes happening, and the mechanism of protection has to be similar. The manner of making the antigens available to the immune machinery by different types of vaccines deployed makes only the difference in the elucidation of the quantum and intensity of neutralizing antibodies as also in the production of memory cells in both the Th-2 and Th-1 pathways. Therefore, the waning of the phenomenon of antibody levels observed for Pfizer's mRNA vaccine is also anticipated to be the trend for all the other types of presently deployed SARS-CoV-2 vaccines. All the types of vaccines approved and used are reasonably safe. Deployment of a third dose may not, therefore, warrant manifestation of additional safety issues. There is consequently a need to approve the third booster dose on the recipients of 60 years and older as also on the vulnerable population, and such a program should roll out fast.

In almost all new vaccines, developed or under development the world over, the researchers look for establishing a correlate of protection, and then measure the immune responses on trial participants, with adequate numbers of placebo controls. Investigators in different trials monitored antibody responses and tried to correlate the responses with participants that remained out of disease versus those who got sick. However, the antibody titer measurement for all the trials was not the same; there had been considerable variation in the choice of the neutralizing antibodies too. Moreover, there were different standards for defining mild disease versus life-threatening disease syndrome. To rationalize the trial data, the titer of antibody elucidated by each comparing vaccine was compared with antibody levels of infected individuals in the placebo group. It was generally found[56] that postimmunization antibody titers had at least a considerably good correlation for ascertaining the protection of vaccinated individuals against the disease. However, it appears that finding robust correlates through the use of measurement of neutralizing antibodies is not the last word[57] for judging whether a vaccine is the best one or otherwise for protection. Other factors of protection such as measuring the different kinds of activated T cells and the measurements of other immune parameters such as the differences in the levels of cytokines, complements, mannose-binding lectins, macrophages, neutrophils, etc., need also to be gone into. More basic research is to be pursued to enable coming out with more innovative correlates.

CONCLUDING REMARKS

The multiple mutants of SARS-CoV-2 already in circulation are anticipated to stay in nature, and the human population has to live with it. If the spread of the disease is not substantially prevented in humans then more virulent mutants are anticipated to emerge in the future. Omicron variant is the example. This can be prevented by deploying mass vaccination of people all over the world, and deploying booster doses on vulnerable people including people over 60 years after 9–12 months of last vaccination. Concomitantly, efforts may be made to strengthen the capacity of prevention of lungs infection by viral pathogens, and suitable antiviral vaccines need to be taken, especially by aged individuals. In the meantime, efforts need to be made to invent effective therapeutic agents to contain the virus causing COVID-19 flu.

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