Review Article

Generation of efficacy data on 60 years and older population using SARS-CoV-2 vaccines

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Abstract

As of March 31, 2021 nine vaccines against coronavirus-2019 disease (COVID-19 flu) were approved globally, which include ChAdOx1 (AZS1222) (AstraZeneca/Oxford, UK), COVAXIN (Bharat Biotech, India), BNT162b2 (Pfizer-BioNTech, USA), mRNA-1273 (Moderna, USA), ADENO 26 CoV2.S (Johnson &Johnson, USA), Sputnik V (Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia), CORONA VAC (Sinovac Biotech, China), BBIBP-Cor V (Sinopharm, China), and ZF2001 (Anhui Zhifei Longcom, China and Institute of Microbiology, China). All are two-dose vaccines except two, namely ADENO 26 CoV2.S that requires one dose only and ZF2001 that requires three doses. In India, during the same period, only two vaccines namely of AstraZeneca/Oxford by the name COVISHIELD in India, and COVAXIN of Bharat Biotech, Hyderabad were approved. As there is yet no effective therapeutic substance to contain the disease, mass vaccination is the only effective alternative to fight the pandemic. Due to the nonavailability of an adequate supply of ChAdOx1 (AZS1222) vaccine, countries using this one are resorting to delaying the use of the second dose, which must be deployed before the antibody titer is waned off after the first dose. There is a need to experimentally determine how much delay can be made between the two doses for other vaccines also. It was found later that AstraZeneca/Oxford vaccine provided protection after the first dose, up to 90 days, and therefore, the second dose was adopted to be used after 12 weeks. As people over 60 years are more vulnerable to the disease, data need to be generated for each vaccine on this population on whether there is any need to reschedule the dosage gaps as also if new three-dose regimens are more efficacious.

Keywords: Approved SARS-CoV-2 vaccines, COVID-19 vaccines, vaccination efficacy

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INTRODUCTION

The Regulatory authorities the world over have approved[1-4] the emergency use of the nine SARS-CoV-2 vaccines as of March end 2021 to protect the population from coronavirus 2019 disease (COVID-19 flu). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA (+ss RNA) virus. The approved vaccines against the virus are (1) ChAdOx1 (AZS1222) AstraZeneca/Oxford (UK)-invented, Chimpanzee adenoviral vector-based replication-deficient recombinant viral vector containing the c DNA-based expression cassette coding for the SARS-CoV-2 S protein, and the

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vaccine is known as COVISHIELD in India requiring two doses, initially recommended 28 days apart; (2) Bharat Biotech's use of propiolactone-deactivated whole-viron SARS-CoV-2 strain named as NIV-2020–770, which is multiplied in Vero cells. The vaccine is named COVAXIN by Bharat Biotech and requires two doses, 28 days apart for protection. The company has changed the name of the viral strain to BBV152. (3) Sinovac Biotech, China using deactivated whole-virion SARS-CoV-2 strain named as CN02 and multiplied in Vero cells and the vaccine is named as CORONA VAC, requiring two doses, 14 days apart; (4) Sinopharm, China using deactivated whole-viron SARS-CoV-2 strain named as HBO2 and multiplied in Vero cells, and the name of the vaccine is BBIBP-Cor V requiring two doses, 21 days apart; (5) Anhui Zhifei Longcom Biopharmaceutical Co. Ltd., China in collaboration with the Institute of Microbiology at the Chinese Academy of Sciences developed a protein subunit vaccine by the name ZF2001(trade name ZIFIVAX), which is based on a design of a tandem-repeat of a dimeric receptor-binding domain (RBD) selected from the C-terminal domain of S1 subunit in S protein of the virus. The recombinant RBD-dimer is produced in the Chinese hamster ovary cell system and formulated with aluminum hydroxide as an adjuvant. The vaccine is applied in three doses 0, 1, 2 months apart;[5] (6). Pfizer-BioNTech, USA manufacturing lab-synthesized mRNA coding for full-length S protein with proline substitutions, captured inside nanoparticles using multiple amphiphilic substances and requiring two doses, 21 days apart, and the vaccine is named as BNT162b2; (7) Moderna, USA manufacturing lab-synthesized mRNA coding for full-length S protein with proline substitutions, captured inside nanoparticles using multiple amphiphilic substances and requiring two doses, 14 days apart and named as mRNA-1273. The synthesized mRNA, as well as the amphiphilic substances used by Moderna, are different from those of Pfizer; (8) Johnson & Johnson, USA manufacturing recombinant replication-deficient human adenovirus serotype 26-vector-based DNA cassette containing the c DNA-based coding sequence for stabilized full-length SARS-CoV-2 S protein and the name of the vaccine is ADENO 26 CoV2.S, requiring application of one dose only; and (9) the two-Adenoviral vector-based r DNA vaccine, using adenovirus type 26 having an insertion of c DNA-based nucleotide sequence coding for the full-length spike protein of SARS-CoV-2 virus (Ad26) and the adenovirus type 5, also having an insertion of c DNA-based nucleotide sequence coding for the full-length spike protein of the virus (Ad5). Both the adenoviruses are replication-incompetent. The combo vaccines were invented by the Gamaleya Research Institute of Epidemiology and Microbiology, Moscow. The vaccine initially named as Gam-COVID-Vac was renamed as Sputnik V and is required in two doses, 21 days apart. Three of these vaccines, listed at (2), (3), and (4) are whole-virion inactivated vaccines; three are recombinant Adenoviral DNA-base replication-deficient DNA vaccines, shown at (1), (8), and (9); and two are m-RNA based, nanoparticle encapsulated SARS-CoV-2 vaccines as at (6) and (7). The vaccine at (5) is a recombinant protein-subunit vaccine.

It is not easy to contemplate which ones are the most efficacious ones, which ones are comparatively safer, and which ones are the best ones for individuals, especially in situations where several mutated, more infective viral particles are in circulation. Multiple other types of injectable COVID-19 vaccines are in the pipeline. Besides, vaccines based on the newer delivery system such as oral, nasal, and skin-patch-based delivery are also under development.[6]

Certain vaccines are in the advanced stage of Phase-III trials, which include those from Novavax Inc, USA (vaccine name NVX-CoV 2373), which is a protein subunit vaccine;[1] Sanofi–GSK vaccine also known as VAT00002 and VAT00008;[7] the Cuban Soberana 02 vaccine;[8] and the recombinant DNA-based protein subunit vaccine manufactured by Biological E Ltd, Hyderabad, which was developed by the company in collaboration with a Group comprising Baylor College of Medicine, USA; Texas Children's Hospital (Center for Vaccine Development), USA; and Dynavax Technologies Corporation, USA. The terms of collaboration are not known. It is a recombinant protein subunit vaccine, where the protein subunit is produced in recombinant *Pichia pastoris*. The name of the vaccine is NEGVAC or CORBEVAX. The Indian National Expert Group on Vaccine Administration for COVID-19 flu had recommended the vaccine for approval after due diligence, and had sought clinical trials; the vaccine is in an advanced stage of Phase-III trials.[9,10]

The World Health Organization (WHO) had approved the emergency use of the COVID-19 vaccines manufactured by Pfizer/BioNTech, Astrazeneca-SK Bio, Serum Institute of India, Johnson & Johnson, Moderna, and the Sinopharm.[11]

In the meantime, the COVID-19 flu continues to maintain its pandemic the world over. The world scenario on the COVID-19 pandemic as of May 28, 2021[12] indicated the total infected from the disease was 169,648,054; the total deaths were 3,525,426, and the total recovered from the disease was 151,512,824. India ranked third in terms of death, registering the number of deaths as 3,18,895 with total active cases of 27,55,457 and recovered cases of 1,11,32,082. The counties registering deaths more than India

were the USA (554889 deaths) followed by Brazil (456,753 deaths). After India, the fourth country having large deaths was Mexico (222,657 deaths). The rise in the disease state in India is alarmingly high and warrants special attention, even though the deaths per one hundred thousand population in India was about 22.91 as compared to the USA of 182.64, Brazil of 213.51, and Mexico of 584.54.

World over patients with hypertension, diabetes, coronary heart disease, cerebrovascular illness, chronic obstructive pulmonary disease, and kidney dysfunction have worse clinical outcomes[13] when infected with SARS-CoV-2.

There is yet no precise and effective therapeutic substance to contain the disease. Mass vaccination is the only effective alternative to fight the disease. The immediate need is therefore to increase the herd immunity of every community and therefore all eligible individuals must be vaccinated. This is a stupendous task. One way is to authorize the use of all the SARS-CoV-2 vaccines in India by the Indian Regulatory Authorities, which have been approved elsewhere by the Regulatory Authorities of other countries, and seek the imports of such vaccines through the WHO, which authorizes WHO Certification to the vaccines qualifying for approval and use; this would ensure and provide an adequate check on the quality of the imported stuff, whereas the supply shall immediately increase. The essence of success lies in the fast vaccination of the eligible population.

The paper aimed to ascertain how fast the eligible world population in the senior age group above 60 years be protected by vaccination; what is an experimentally determined time gap between the two-dose vaccines; and what are the deciding parameters to ensure the protection of individuals above 60 years from the disease. It is also to ascertain if there are any emerging safety issues, emanating from the use of the deployed vaccines. This age group of the population is more vulnerable to the disease. The emphasis is on the Indian population, which is in a highly chaotic stage at the present moment. Further, it also needs to be ascertained if a three-dose schedule would be more protective than the present two-dose schedule.

MATERIALS AND METHODS

The study was carried out based on a table study of relevant literature accessed through the internet by using the Google search engine.

The issues

All the approved vaccines have been rated as reasonably safe for deployment by the Regulatory Authorities of different countries, approving them. The efficacy of each one is, however, considerably different as had been determined from various studies, which has varied[14-18] from over 50% to over 90%. The mRNA vaccines have provided the highest percentage of protection among the recipients, above 90%, and the protein subunit vaccine from China had also registered higher protection,[4] whereas the other types provided much lesser protection. There is no information on what is the protection rate in individuals above 60 years of age for each type of vaccine. The mRNA vaccines are highly priced by the owners/suppliers; these are IPR protected and the prices are dictated by the owners. The other ones are moderately priced. Presently, the supply is inadequate and the available production is purchased by the governments; but sooner vaccines would be available in private markets also when more vaccines are approved and supply from the existing and new manufacturers increase.

Government vaccination programs are aimed at increasing the herd immunity of the community. Any vaccine that is more than 50% efficacious can contribute to raising the herd immunity of the population and governments can fight the pandemic using such vaccines. However, a vaccine with just above 50% efficacy shall take more time to raise the herd immunity than the one that imparts more than 90% efficacy as increased efficacy will contribute to reducing infection among the vaccinated population. Data published from Israel had shown[19] that even when about 90% of people aged 60 years and older in the country had received the first dose of Pfizer's two-dose vaccine, there was a 41% drop in confirmed COVID-19 infections in that age group. The situation must have improved further after two doses were received. One impediment of generating herd immunity is the continuous evaluation of newer, more infective, mutated strains, which problem is also to be scientifically tackled. Although the drop in the newer infection rate is the aim in government programs, senior citizens individually could be curious to ascertain if they have been protected after receiving an approved vaccine in the scheduled doses. Individual protection is important to individuals. There is yet no fool-proof method to ascertain this. Evaluation of the levels of clonal IgM/IgG to the nucleocapsid protein of the SARS-CoV-2 virus is indicative of whether there was an exposure to the virus. Methods for measuring the levels of neutralizing immunoglobulins in the vaccinated individuals against the spike protein of the virus are in place to ascertain if protection is imparted. The development of neutralizing antibodies (nAbs) to the spike protein, especially the RBD of the virus is the aim of vaccine-induced protective immunity. In a study[20] involving 19860 individuals recovered from COVID-19 flu, the measurement of total antibodies had shown that

about 70% of the individuals had moderate (1:320) to high (1:2880) titers and that over 90% of this population had neutralizing antibodies, specific to spike-proteins of the virus. Among the nAbs formed, which include IgG, IgM, and IgA, there has been a preponderance and dominance[21] of IgA antibodies, manifested as the early virus-specific antibody response, and its concentration in the serum attained the peak in about 3 weeks after the symptoms were manifested in the infected individuals. The results provide evidence that IgA antibodies may play a dominant role in the control of infection.

The concentration of neutralizing IgG antibodies is however used to assess the extent of protection, based on a cut-off that is pre-determined from the analysis of the sera of recovered COVID-19 patients. It can be apprehended therefore that measurement of the levels of circulating neutralizing antibodies of IgG types against the virus might provide a respite to ensuring protection. However, there is yet no well-defined, unanimous, globally accepted, foolproof method of determining whether, after vaccination, individuals have been protected. This information is important and more relevant for the aged individuals who are more than 60 years in age.

Due to the nonavailability of an adequate supply of vaccines, countries are resorting to delaying the use of the second dose, for certain types of vaccines, such as the AstraZeneca/Oxford vaccine. Such delays under the circumstances may be justified provided the second dose is applied within a period when the neutralizing antibody titer emanating from the first dose is not waned off significantly. This change in the re-scheduling maybe for bringing in more eligible people within the preview of the first dose to increase the number of the protected population against the disease. The French National Academy of Medicine in a press release[22] on January 11, 2021 had recommended a delay between two doses up to 3 weeks. However for this, experimental national and international data need to be generated for each type of vaccine deployed. Following the sanction of the ChAdOx1 nCoV-19 vaccine[23] for emergency use authorization in adults by the UK Medicines and Healthcare products Regulatory Agency in December 2020, the Indian Regulatory Authorities authorized[2] the emergency use of this vaccine in India, which was being presented as COVISHIELD vaccine, manufactured by the Indian major vaccine manufacturer, Serum[24]Institute of India, Pune. The Indian Regulatory Authorities had authorized the use of the COVISHIELD vaccine in January 2021—two doses, 28 days apart; in February—two doses, 4–6 weeks apart; in March—two doses, 6–8 weeks apart and in May—two doses, 12–16 weeks apart. The latest dosage schedule is being followed in India. It appears that the dosage schedule was accepted, based on the dosage schedule for the vaccine, enumerated by the UK Regulatory authorities[25] for the ChAdOx1 nCoV-19 vaccine and later, also accepted by the WHO.[26] This phenomenon implies that the injected recombinant Adenoviral vaccine cassette remains in circulation for long within the body of the recipient. There is no information on how long these viral particles remain in circulation and whether remaining in a longer period of circulation has any adverse effects. There is a need to determine by suitable reverse transcription polymerase chain reaction (RT-PCR) methods, how long does the circulating vaccine particles remain within the body of the recipient. Although the recombinant Adenoviral vaccine cassette is stated to be replication-deficient, the particles enter into the nuclear compartment of the cells of the recipient and force the nuclear transcription machinery for the transcription of the adenoviral DNA materials into mRNA, which travels to the cytoplasm and again forces the host-translational machinery to produce the recombinant proteins, which are the antigens for the vaccine. This process continues, till the injected viral particles are destroyed by the host–immune system.

Oxford Vaccine Group, AstraZeneca along with their other collaborators had published on the single-dose administration and the influence of the timing of the second booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine,[27]based on which the present timing gap for the two doses have been evolved, and have been adopted in India for deploying the COVISHIELD vaccine. One standard dose of the vaccines is about 5×10^{10} viral particles, contained in 0.5 mL volume, which is injected intramuscularly in the deltoid muscle of the recipient. The overall efficacy of the vaccine was critically assessed,[28] and was found to be 70.4% (95.8% CL54.8–80.6); it was also found that the recipients of the first lower dose (half the standard dose) followed by the second standard dose attained higher protection efficacy at 90% (95% CL 67.4–97.0), whereas the efficacy was only about 62.1% (95% CI 41.0–75.7) in the recipients who had two standard doses, 4 weeks apart. From the results of the publication, there are strong indications that the vaccine, presently deployed in the single standard dose of 5×10^{10} viral particles per dose may perhaps be reduced to half the dose, to 2.2×10^{10} viral particles per dose, as the investigators had shown that the first lower dose, followed by the second standard dose had yielded more efficacy than the use of two standard doses. There are no published data however on this conjecture. The reason why the issue is scientifically relevant is that if two half doses could be more efficacious than two standard doses; there would then be

no need to inject more viral particles, which are extraneous materials. There are issues that have surfaced later that rare clotting disorder is associated with the ChAdOx1 nCov-19 vaccine.[29] The recombinant adenoviral DNA cassette particles of the vaccine, which are the vaccine components, and which are replication-deficient, on entry into the cytoplasm of the cells of the vaccine recipient, overpower the cellular functions, and enter into the nuclear compartment of the cell, and forcefully use the nuclear materials to transcribe its recombinant mRNA, which then migrates into the cytoplasm, and gets forcefully translated into the recombinant viral protein, which is the active ingredient for vaccination. This viral protein leaves the cell and sneaks into the body fluid of the vaccine recipient, where it encounters the immune system of the vaccine recipient. The immune system gets activated and produces neutralizing immunoglobulins in the Th-2 pathways, and activates the CD4+ and the CD8+ T cells in the Th-1 pathways. As soon as the immune system is fully activated, the circulating recombinant vial proteins get neutralized and opsonized by the macrophages and other immune cells, and the cells containing the infected viral particles are disintegrated by the activated CD8+ T cells, and the liberated viral vaccine particles are engulfed by the activated macrophages. The vaccine particles are thus cleared from the body of the vaccine recipient. If the injected dose of the vaccine can be reduced, this would perhaps reduce the possibility of developing rare clotting disorder, as the quantities injected would be lesser.

There is also a need to look into the issue of whether there is any change in the results of efficacy (for betterment) of the vaccines, which are authorized in India, when these are deployed by making a change in the existing time gaps between the two shots. This can be done in Phase-IV trials.

There is another complex issue that has surfaced over time from the multiple COVID-19 infections. The original[30] SARS-CoV-2 virus has mutated over the years from December 2019 onwards and the mutated strains are developing capacities to evade the vaccine efficacy. India is fighting certain mutated variants of concern, which are in circulation. There continues to be the emergence of new information quite fast about the variants of SARS-CoV-2, with uncertainties about the speed of their transmissibility, virulence, immune escape, creation of health complications, and even increased deaths, besides uncertainty in inadequate understanding of how to tackle such mutants. These include the dominant clade[31] belonging to the identified lineage B.1.617, and possessing mutations in the spike(S) protein of the virus within its RBD. The common signature mutations identified are D111D, G142D, L452R, E484Q, D614G, and P681R. Many of the other mutated strains, which are in circulation in the human population[31] elsewhere, are also in preponderance in India[32,33] some of which could pose a serious disease risk. Under these circumstances, vaccination of the population is considered to be one important step in the right direction. Although an effective vaccine to neutralize all the mutant strains is not available yet, the vaccines available presently would impart some protection in both the Th-2 as well as the Th-1 immune pathways. Availability of multiple choices of vaccines would enable more protection of the population. Presently other dominant variants, which are causing severe COVID-19 disease are B.1.1.7 (UK strain, also identified as "alpha" by WHO); B.1.351 (South African strain, also identified as "beta" by WHO); and P.1 (Brazilian strain, also identified as "gamma" by WHO). Among the identified B.1.617 linage (dubbed as a double mutant), the subgroup designated as B.1.617.2 is in preponderance in India, causing more disease virulence, and is labeled as "delta" by the WHO, while B.1.617.1 is dubbed as the "kappa" variant. Other WHO-designated infective mutants are "delta plus" and "lambda" variants.

The extent of evasion-from-capture by the immune system of the sensitized and immunized individuals is variable and differs from vaccines to vaccines. However, for a given vaccine type, it is anticipated to be in close range in a population. Multiple mutated viral SARS-CoV-2 strains are in circulation[34,35] in the human population of which some could pose a serious COVID-19 disease risk.

The virus which has seven non-structural and four structural genes is emerging with time as more infective mutants by undergoing two main detectable and measurable changes in its genome that code for its spike protein (S protein in short). The genomic changes are manifested in (a) part deletion of the full-length amino acid sequences of S protein, and in (b) substitution of one or more amino acids in the sequence with others. The virus is not a retrovirus. It does not integrate into the host cell genome. It does not have its reverse transcriptase and other necessary machinery for integration into the genome of host cells. It uses viral RNA-dependent RNA-polymerase (RdRp) present in the infected host-cytoplasm. RdRp is a highly error-prone translator protein, which churns out erroneous newer viral mRNAs, resulting in the emergence of newer viral mutants; only the fittest ones survive and further propagate. Targeting the deactivation of viral RdRp with effective antiviral agents along with vaccination can be a more effective strategy to contain the disease. Further, the driving force for the entry of the SARS-CoV-2 mutants concerning the environment, namely the varying human

cells expressing the angiotensin-converting enzyme 2 (ACE-2), working as the entry-receptor for the virus and some other transmembrane proteinases such as the membrane-anchored metalloproteinase, known as disintegrin and metalloproteinase domain 17 (ADAM17), along with type II transmembrane serine protease (TMPRSS2) expression and associated factors are also to be more precisely understood. Such understanding would have more insight into how and why novel, more infective viral variants are emerging and getting stabilized. It might then be possible to mount effective interventions through the development of more effective vaccines and drugs. One recent investigation[36] had concentrated on studying in detail, the nature of changes in the mutated viral bodies. The investigation had revealed that the coding genes of the virus, designated as E, M, ORF6, ORF7a, ORF7b, and ORF10 are most stable, and therefore are potentially more suitable to be targeted for the development of more effective vaccines and drugs. In the meantime, use of the available vaccines seems to be the only way for acquiring certain levels of protective competence in societies to prevent the disease.

DISCUSSION AND CONCLUDING REMARKS

It is necessary to understand the dynamics of immune cells which are responsible for developing acquired immunity on being exposed to the SARS-CoV-2 virus or an antigen derived from the virus such as the vaccines. The measurement of the activated CD4+T cells, cytotoxic CD8+ T cells and the memory B cells over some time after infection would provide insight into the persistence of the magnitude of adaptive immune response and can assist the assessment of the duration of immunity against another infection. Vaccines can also be assessed in the above way to assess their protective potential. In a recent study[37] using human subjects infected with the virus, the dynamics of the above immune cells were studied. It was found that about 95% of the subjects could maintain immune memory at about six months after infection. Interestingly, the circulating antibodies against the SARS-CoV-2 did not correlate with the T-cell memory. Assessment of the protective immunity against the virus has therefore to be carried out by the measurement of the preponderance of the residual T-memory cells, CD4+ T cells, and CD8+T cells.

In a recent study on the humoral immune response to the circulating mutants of SARS-CoV-2 virus, using inactivated and RBD-subunit vaccines on volunteers, who had no previous exposure to this viral vaccine, were subjected to the deployment of either Corona Vac or ZF 2001. The study deployed 10 volunteers, who received Corona Vac two standard doses, 21 days apart. Twenty volunteers received ZF2001, of which 10 volunteers received three vaccines on 0, 30, 60 days apart, and another 10 received 0, 30, and 120 days apart. Also, the convalescent plasma collected from 10 numbers of COVID-19 flu recovered patients were collected 1.3 months after infection and the neutralizing antibody titers were compared with those in the above-vaccinated subjects. They choose the mutant 501.Y.V2 (which is a South African virulent mutant, belonging to B.1.351 linage) to evaluate the comparative vaccine efficacy. The results indicated that the RBD-subunit vaccines showed markedly higher tolerance to 501.Y.V2 than the convalescent plasma or the Corona Vac recipients; this was thought to be due to the presence of high diversity of anti-RBD neutralizing antibodies. It was also found that the extended gap between the second and the third doses of ZF2001 had led to better neutralizing activity and tolerance to 501.Y.V2.Together, the results indicated that a third dose boost may be better than the two-dose vaccine. As the more virulent mutant SARS-CoV-2 virus strains generally undergo mutations in the N-terminal domain of the RBD of the spike protein, the third dose would contribute to more production of highly diverse neutralizing anti-RBD antibodies, and would be more capacitated to deal with the mutant strains. These results suggest that the efficacy of the Oxford AstraZeneca ChAdOx1 nCoV-19 (AZD1222) vaccine, which is based on the coding of the full length of RBD of the spike protein of the SARS-CoV-2 virus, would yield better protection, if the gap between the two doses is increased, and a third dose is also applied after an experimentally determined time gap between the second and the third dose. The above results also suggest that in situations requiring to handle mutant virulent strains, the ChAdOx1 nCoV-19 (AZD1222) vaccine would better perform than those of Pfizer and Moderna vaccines, as the latter two are designed to impart protection against a designed specific stretch of recombinant synthetic m RNAs, where the possibilities of variation in the expression of the antigenic protein responsible for imparting protection by stimulating the immune system to produce specific neutralizing antibodies is limited.[38] Combination vaccination of adenoviral vector-based vaccines with mRNA-based vaccines in proper dose and vaccination schedule may be a better strategy, which needs to be evaluated in future trials. All the inactivated viral vaccines may perform with lesser efficiencies than the above vaccines, as these vaccines contain the whole virus, and therefore neutralizing antibodies would be produced against all the main viral proteins namely the spike, nucleocapsid, membrane, and envelope proteins,[39] which in effect shall result in comparatively lesser production of the neutralizing immunoglobulins against the spike protein.

From the foregoing discussion, it is apparent that a set of step-by-step instructions and standard operating

procedures (SOPs) are to be evolved for those who have been vaccinated by using any of the approved vaccines, as has been done for assessing the COVID-19 flu disease status of suspected individuals. If this is done, there would be more respite for those who would be eager to assess if they are indeed protected after vaccination.

To ensure attainment of high seroconversion and high seroprotection rate of the deployed vaccines among the senior citizens above 60y, the following suggestions are made:

Government should mount a country-wide Phase-IV trial with adequate placebo-controls to assess the efficacy of the deployed vaccines in the following interval regimen:

(a) Two shots 6 weeks apart
(b) Two shots 12 weeks apart
(c) Two shots 24 weeks apart
(d) Three shots as 0, 4, and 12 weeks apart
(e) Three shots as 0, 12, and 24 weeks apart

It is anticipated that the results shall enable to ensure the more proper schedule for increased seroprotection, especially for the elderly people. As all the vaccines are quite safe, as have been revealed from the past safety data, it is anticipated that there would be an advantage to generate data as above. This is the right time for working on the problem at the national and international levels. New information is getting revealed that weakened immune systems of individuals can take considerable time, even months to clear SARS-CoV-2 infection, if they ever clear.[40] Prolonged infection, even after the necessary intake of vaccine doses, along with not-so-perfect therapies that are currently deployed would provide enough time, which may be of advantage to the virus to use it as its evolutionary time to emerge as more virulent mutants. Although such possibilities can be ripe in immune-depressed patients of any age, senior citizens are more vulnerable to such fears as their immune systems remain sluggish than the younger people. Generally, scientists take lesser interest to include individuals above 60 years, and more so for individuals above 70 years, firstly because senior citizens often suffer from one or more ailments, the interpretations of the results are often difficult because of the existence of multiple comorbidity conditions, and that in the present-day world, the commercial use of such information is limited. However, with improved and increased health infrastructure all over the world, there has been a steady increase in the number of senior citizens in all countries, and the productivity of such a population has also increased. Therefore, in future years such information is anticipated to be more valuable.

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Conflicts of interest

There are no conflicts of interest.

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