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REVIEW

Development of SARS-CoV-2 vaccines: challenges, risks, and the way forward

Vipin M. Vashishtha[a] and Puneet Kumar[b]

[a]Department of Pediatrics, Mangla Hospital & Research Center, Shakti Chowk, Bijnor, India; [b]Kumar Child Clinic, Dwarka, New Delhi, India

ABSTRACT

The COVID-19 pandemic mandates the development of a safe and effective Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) vaccine. This review analyzes the complexities, challenges, and other vital issues associated with the development of the SARS-CoV-2 vaccine. A brief review of the immune responses (innate, antibody, and T-cell) to SARS-CoV-2, including immune targets, correlates of protection, and duration of immunity is presented. Approaches to vaccine development including different vaccine platforms, critical attributes of novel vaccine candidates, the status of the ongoing clinical trials, and the ways to speed up vaccine development are also reviewed. Despite a historical average success rate of only 6%, and a usual gestation period of 10–12 years for the development of a new vaccine, the world is on the verge of developing COVID-19 vaccines in an extraordinary short time span.

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Introduction

The world is in midst of the pandemic of Coronavirus Disease (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The virus infection has affected virtually every country of the world with tens of millions of infections and over one million deaths.[1] The pandemic is progressing, although containment strategies have slowed the progression of the pandemic in many countries. Nevertheless, small surges have been reported in many countries after apparent control, thus suggesting a distinct possibility of more future "waves" of the contagion. The likelihood of the disease becoming endemic like influenza cannot be ruled out. Thus, the best solution is a safe and effective vaccine. About 200 vaccine candidates are in various stages of development, and over 40 of these are in clinical development.[2,3] There is optimism for the possible rollout of at least one specific vaccine by early 2021. The current review analyzes different issues associated with the development, clinical trials, and deployment of new SARS-CoV-2 vaccines.

Risks in vaccine research and development

Development of a vaccine is a costly affair, considering the long journey starting from the "proof of concept" to the phase III clinical trials followed by licensing, manufacture, and quality control. An average gestation period of a new vaccine development is about 10–11 years.[4] The fastest vaccine ever developed for a new human pathogen was possibly the Ebola vaccine. From the first cases to licensure in the US took some 6 years, although work on a vaccine had started around two decades before that.[5] Gouglas et al. recently analyzed and found that the average cost of successfully developing one pandemic vaccine from preclinical to phase II may be in billions of dollars.[6] Most of the candidates fail during one of the stages of development: they are either found ineffective, or the adverse effects are disproportionate to the benefit, often leading to discontinuation of research in that direction. It has been estimated that on an average, just 6% of the vaccine candidates that are developed became licensed.[4]

Intriguingly, even after crossing these hurdles, numerous uncertainties remain. Since the vaccine takes a long time from development to licensure, the disease is sometimes controlled by the time vaccine is ready, and it is no longer needed. This happened in the case of the Ebola vaccines, although the ready stock of the vaccine became handy for containment when a major outbreak occurred recently after the apparent elimination of the disease.[4] Similarly, SARS-CoV-1 vaccine development lost steam after the virus transmission stopped in humans. However, efforts are still on to develop a Middle East Respiratory Syndrome coronavirus (MERS-CoV) vaccine, but success remains elusive.

Immune responses to SARS-CoV-2 and their implication on vaccine candidates

Understanding the immune response to SARS-CoV-2 is crucial for vaccine development. But our understanding of the protective immune responses following SARS-CoV-2 infection is inadequate currently. There are four essential structural proteins, namely the spike glycoprotein (S), the membrane glycoprotein (M), the nucleocapsid protein (N), and the envelope protein (E). The transmembrane 'S' glycoprotein forms homotrimers that protrudes from the viral surface and consists of two functional subunits in each spike monomer: The S1 subunit is used for binding to host cell receptor, and the other S2 subunit is used for fusion between viral and host cell membrane. The 'receptor binding domain' (RBD) is in the S1 subunit that specifically recognizes human angiotensin-converting enzyme 2 (hACE2) as its receptor and uses it to enter cells (Figure 1). The 'S' protein contains a furin cleavage site at the

CONTACT Vipin M. Vashishtha vipinipsita@gmail.com Department of Pediatrics, Mangla Hospital & Research Center, Bijnor, Uttar Pradesh 246701, India.

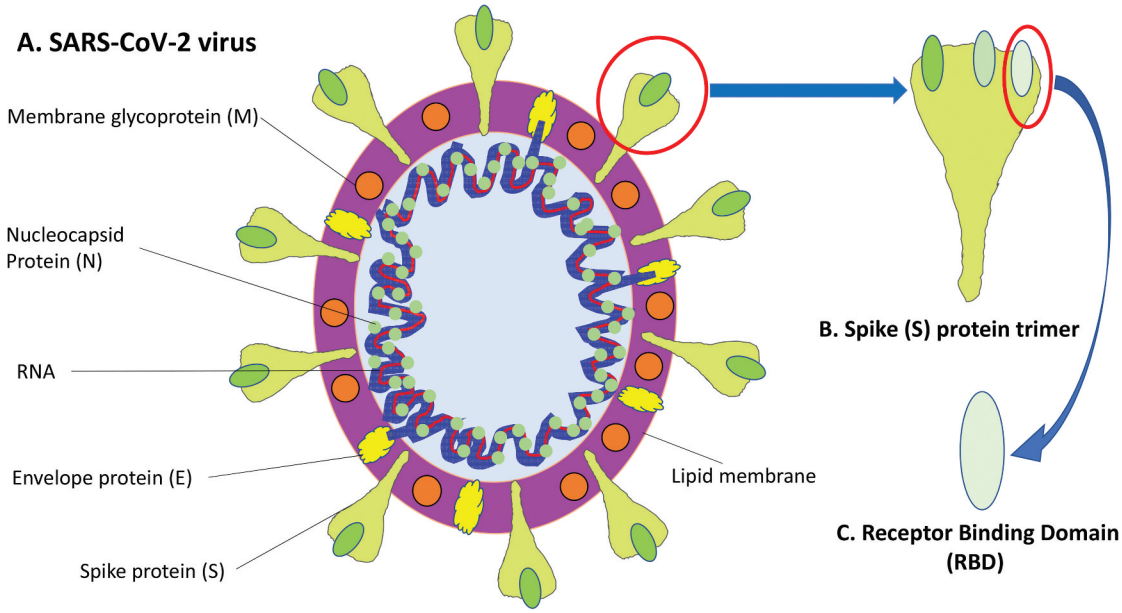

Figure 1. Schematic illustration of SARS-CoV-2 virus structure with its major proteins (a), spike protein trimer (b) with receptor-binding domain (c). The four structural proteins, the spike glycoprotein (S), the membrane glycoprotein (M), the nucleocapsid protein (N), and the envelope protein (E). The 'S' glycoprotein consists of homotrimers that protrudes from the viral surface. The 'receptor binding domain' (RBD) specifically recognizes human angiotensin-converting enzyme 2 (hACE2) as its receptor and uses it to enter cells.

boundary between the S1/S2 subunits, which sets this virus apart from other coronaviruses.[7] The SARS-CoV-2 genome also encodes 16 nonstructural proteins (NSPs) and nine accessory proteins. Antibodies directed to the 'S' protein prevent viral entry, while antibodies to other structural proteins stimulate viral killing.[7]

Innate immune response

Current knowledge on the innate immune response to SARS-CoV-2 is limited. However, the innate immune response to RNA viruses, in general, is initiated by recognition of viral RNA and extracellular and endosomal Toll-like receptors (TLR) by the Pattern recognition receptors (PRRs). This triggers downstream cascade leading to secretion of cytokines such as proinflammatory tumor necrosis factor alpha (TNF-a), interleukin-1 (IL-1), IL-6, and IL-18. Together, they induce antiviral cascades in target cells and potentiate the adaptive immune response. If present early and properly localized, type-1 interferon (IFN-I) can effectively limit coronavirus (CoV) infection. However, it is also known that coronaviruses like SARS-CoV-1 are known to evade this cascade by inhibition of IFN-I induction and signaling. It is very likely that SARS-CoV-2 also achieves a similar effect, as suggested by the lack of robust type I/III IFN signatures from infected cell lines, primary bronchial cells, and a ferret mode.[8] It has been demonstrated that non-structural protein 1 (nsp1) of the SARS-Cov-2 virus suppresses host gene expression leading to translational shutdown and suppression of innate immune responses.[9] Recently, it has also been suggested that the poor interferon response in COVID-19 cases is due to the presence of a variant ORF3b gene in SARS-CoV-2, unlike SARS-CoV-1. This variant is a potent interferon antagonist, suppressing induction of type I IFN more efficiently than SARS-CoV-1.[10]

This also explains, at least partially, the role of immune dysregulation in the pathogenesis of COVID-19. The innate immune response is the first immune response to the virus, but it has possibly not received the attention it deserves. The authors believe that if any vaccine/therapy is aimed here to tackle the virus, the whole cascade of cell/organ damage and complications can be averted. For example, Golanka et al.[11] have strongly proposed to explore the possibility of the use of "flagellin" to induce innate immune response that can help clear the virus. Interestingly, the flagellin induces TLR5 activation of the innate immune response mediated via interleukin (IL)-22 that is independent of IFN response. Since IFN response is impaired by the SARS-CoV-2 virus, this pathway could be particularly useful.

Humoral responses

Most patients of COVID-19 develop IgM, IgG, and IgA antibodies against 'N' and 'S' viral proteins but have their distinct kinetic profiles. Further, the titers and kinetics vary significantly with the age of patients and the severity of illness.[12,13] There is a gradual waning of titers, but long-term data are not available.

Generation of anti-'S' protein neutralizing antibodies (NAbs) are considered critical for an effective immune response against SARS-CoV-2. The receptor-binding domain (RBD) and other epitopes on the 'S' protein of the virus are employed as immunogens to produce NAbs.[14] Various approaches are adopted to express 'S' protein *in vivo*, such as nucleic acid structures and virus vectors. Alternatively, other

vaccine platforms like recombinant protein particles and inactivated virus vaccines can directly deliver this protein.[15]

There is an inverse correlation between NAbs titers and ensuing viral loads during the early stages of infection. However, the NAbs titers are directly correlated with the more severe subsequent disease.[16–18] It has been suggested that the transient elevation of NAbs in mild cases of SARS-CoV-2 infections is very similar to that in case of other coronavirus infections that cause the common cold.[19] This is like what was seen during the SARS-CoV -1 outbreak where an initial more robust NAbs response resulted in a much better outcome.[20]

In contrast to influenza infection where a strong IgA response is unusual, severe cases of COVID-19 have been shown to have a strong IgA response.[21,22]

There is a poor understanding of the correlation between the serum NAbs titers and viral concentration in vital body fluids to the ultimate disease severity. The NAbs titers may be much higher in mucosal fluids than in serum because the virus is rarely detected in blood, thus explaining the dichotomy to some extent.[20]

Overall, the exact role of antibodies to the SARS-CoV-2 infection is not yet well elucidated. The level of protective NAbs titers against the COVID-19 disease is also not known. Most animal studies have shown that SARS-CoV -2 vaccination results in the reduction of viral loads and amelioration of the disease, but fail to prevent infection, i.e. to provide a sterilizing immunity.[23,24] Though extrapolation of small animal studies findings to human exposure response to the SARS-CoV-2 virus may not always be reliable; nevertheless, these data provide confidence that an immunogenic vaccine may produce protective antibodies. Vaccine challenge studies in macaque models have indicated a NAb ID50 titer in the estimated range of 100–500 is required to achieve sterilizing immunity.[16]

SARS-CoV-2 'S' protein neutralizing monoclonal antibodies

The characteristics of neutralizing monoclonal antibodies (nMAbs), isolated from COVID-19 cases, may provide some useful information on the desired "targets" for vaccine candidates. Both neutralizing and non-neutralizing epitopes are detected on 'S'-proteins. The most potent and efficient nMAbs were directed against ACE2 receptors, but this effect was not always correlated. It was also noted that despite having a high affinity for RBD, some nMAbs failed to block ACE2 receptor binding.[25]

Wec et al. have identified 200 NAbs that efficiently cross-neutralize many human coronaviruses (HCoVs), including the SARS-CoV-2 virus, by targeting multiple conserved sites on the 'S' protein.[26] These NAbs have the potential not only as a therapeutic intervention but may also be employed in developing an effective universal beta-coronavirus vaccine. Efforts are also on to develop monoclonal antibodies as one of the strategies to manage COVID-19 patients. It has been recently demonstrated a new monoclonal antibody (LY-CoV555) can lead to a 72% reduction in the risk of hospitalization with severe disease.[27]

T-cell immune responses

Most of the SARS-CoV-2 vaccine candidates are based on the induction of neutralizing antibodies against the 'S' protein of the virus. However, T-cell responses also play a significant role in the elimination of the virus during an active infectious phase and later in the recovery of the COVID-19 patients.[28] Few recent studies have demonstrated the presence of 'S'-reactive CD4 + T cells in 83% of COVID-19 patients, as well as in 34% of SARS-CoV-2 seronegative healthy donors.[29,30] They suggest that 'S' protein-specific T cells in healthy individuals may represent cross-reactive antibodies formed after past exposure to HCoVs that cause common cold or SARS-CoV-1.[31] Le Bert et al[32] have very recently demonstrated that these preexisting T-cells recognize various epitopes of nucleocapsid protein (NP) of SARS-CoV-2. A surprising finding in their study was that in patients with such cross-reactive T-cells but with no history of SARS-CoV-1 or COVID-19 or contact with any of these demonstrated higher homology to conserved epitopes of animal beta-coronaviruses rather than human coronaviruses that cause the common cold. Further, they show that patients recovered from SARS-CoV-1 17 years ago still possess virus-specific memory T cells displaying cross-reactivity to NP of SARS-CoV-2.[32] Whether these cross-reactive CD4 + T cells are relevant in influencing clinical outcomes and providing protective immunity is only speculative at this stage.[33,34] Further, the 'S' protein-specific CD4 + T-cell response was well correlated with the antibodies titers targeted against the RBD which denotes that T-cell immunity is critical in eliciting a humoral immune response against SARS-CoV-2.

What precise role T-cell immunity plays in contracting disease or attenuation of already acquired infection is not adequately understood; this is another reason why diverse vaccine approaches need to be pursued. The moderate to severe cases of SARS-CoV-2 infection are also known to be associated with lymphopenia with drastically reduced numbers of both CD4+ and CD8 + T-cells. It has been demonstrated that the severity of lymphopenia (especially CD8+ cells) correlates with the disease severity and mortality of ICU-admitted patients. And this reduction is not only due to cytokine (e.g. IFN-γ)-induced suppression and cytokine (e.g. IL-6)-induced killing but also due to the recruitment of these cells in the lungs (leading to decrease in peripheral blood) in such severe cases. Considering the fact that patients with mild symptoms typically present with normal or slightly higher T cell counts, it appears that latter is an important factor: but this continues to be controversial.[8,35] During the outbreak of SARS-CoV-1, studies noticed a favorable clinical outcome correlated with the number of virus-specific CD4 + T cells.[36]

Studying SARS-CoV-1-specific T cell immunity may help in further understanding of SARS-CoV-2 infection. Unlike the CD4 + T-cell response that is largely directed at the "S" protein, the immunogenic epitopes for CD8 + T-cells are distributed across several SARS-CoV-1 proteins (S, N, and M, as well as ORF3). Similar findings have been seen in a small study on COVID-19 patients also.[35] Animal studies on SARS-CoV-1 spike ('S') DNA vaccine elicited both humoral and cellular immunity in response to a pool of entire overlapping 'S'

peptides.[36] To develop an effective vaccine, it is crucial to define the functional dominant epitopes of 'S' protein for T cells in HCoVs, but there is a significant knowledge gap here. Further, the T-cell response might be significantly affected by specific HLA (Human Leucocyte Antigen) polymorphisms.[9] Nevertheless, a vigorous T-cell response indicates that SARS-CoV-2 vaccination is also likely to result in long-term immunity.[37]

It is now known that SARS-CoV-2 infection provokes vigorous memory T-cell responses in both seropositive and seronegative individuals even with asymptomatic or mild COVID-19. It implies that natural exposure may prevent recurrent episodes of severe disease in seronegative individuals also; however, this cannot be said with certainty as of date.[9]

Coordination between various arms of immunity

The key to successful immune response to SARS-CoV-2 infection is the coordinated CD4 + T cell, CD8 + T cell, and antibody (Ab) responses, which protect against the severe disease. Notably, this coordination of humoral and cellular immune responses is disrupted in elderly people (≥ 65 years) that result in severe illness and mortality. Paucity of naive T cells is also associated with aging and poor disease outcomes.[38]

Herd immunity estimates

The world is working to develop and distribute the vaccine at the earliest, since mass vaccination of the population at large is considered to be the best, fastest and safest way to develop what is called as *population* or *herd immunity* that has the potential to block the relentless spread of this pandemic. Herd immunity is achieved by immunization of a large proportion of the population and it protects the nonvaccinated, immunologically naïve, and immunocompromised individuals by reducing the percentage of vulnerable hosts to a level below the transmission threshold. The percentage of the population that needs to be immunized to achieve this varies with the infectivity of the target pathogen. For example, for smallpox, it needed 80% of the immunized population to break the chain of transmission, while this percentage is 91–94% for the measles virus. For SARS-CoV-2, this percentage has been estimated to be ~67%, assuming that the basic reproductive number (R_0) of the virus is three, i.e., one infected individual infects three new individuals.[39] Hence, to block disease transmission, the mass vaccination programs should aim to cover at least two-third of the target population.

Specific issues and challenges involved in the development of SARS-CoV-2 vaccines

The development of an effective SARS-CoV-2 vaccine poses some additional challenges/issues that need to be sorted out:

Route of administration

Route of administration of a vaccine can also impact its effectiveness. A group of researchers working on vaccination strategy for SARS-CoV-1 and MERS-CoV found that employing an intranasal route for vaccination induces humoral and cellular responses in the respiratory tract leading to higher protection levels in mice.[33,40] In a recent animal study[41] involving human ACE transgenic mice, an intramuscular dose of a chimpanzee adenovirus-vectored vaccine encoding a prefusion stabilized spike protein (ChAd-SARS-CoV-2-S) induced robust systemic humoral and cell-mediated immune responses and protected against lung infection and pathology but failed to confer sterilizing immunity. In contrast, a single intranasal dose of the same vaccine-induced high levels of NAbs, promotes systemic and mucosal immunoglobulin A (IgA) and T cell responses, and almost entirely prevented SARS-CoV-2 infection in both the upper and lower respiratory tracts. Considering this and the fact that even natural SARS-CoV-2 infection induces mucosal IgA response, it would have been prudent had more vaccine manufacturers explored this route. This is especially crucial when a vaccine is being considered as an important strategy to halt the pandemic. Thus, the authors believe that it is unfortunate that none of the candidates that are currently under clinical trials is exploring the nasal route of vaccination, although it is recognized that many types of vaccines are intrinsically nonimmunogenic by the intranasal route.

The type and number of antigens

While targeting the 'S' glycoprotein in vaccine development could be ideal for inducing NAbs, it may be worthwhile to look for other antigens for extra benefits. For instance, the 'N' protein is more conserved between SARS-CoV-1 and MERS-CoV strains and induces a good amount of long-lived memory T-cells in humans.[42] The 'N' protein can provide a potentially viable addition to 'S' protein to accord cross-protective and long-lasting T-cell immunity against SARS-CoV-2.

Recently, Dai, L et al.[43] have identified a dimeric form of MERS-CoV RBD that can be targeted as a more effective immunogen, since RBD-dimer has been shown to significantly increase NAbs titers compared to the conventional monomeric form. This can be generally applied to other HCoVs vaccines to developing a universal beta-coronavirus vaccine effective not only against MERS but SARS-CoV-1 and 2 also.

Another issue in the development of the SARS-CoV-2 vaccine involved is the number of antigens to be incorporated in a vaccine candidate. Some experts have expressed the need for having more than one antigen to broaden its immunogenicity.[5] Since the SARS-CoV-2 is a single-stranded RNA virus which is more prone to mutate frequently, and already one mutation in the RBD of the 'S' gene has been identified leading to two lineages of the virus: "L type" and "S-type" (even though their significance in eventual immunogenicity of the vaccine is still undecided).[44–46] More recently, "D614G mutation" in the key 'S' protein has been demonstrated to increase the infectiousness of the virus, although the disease severity is not altered; and this mutated strain is now the dominant strain globally.[47] In general, a longer period of circulation of the virus in the community gives ample opportunity for selection pressure and thus the development of such mutations that could even be immunologically relevant. For example, at least 10 mutations such as N234Q, L452R, A475V, V483A make the virus resistant to neutralizing antibodies.[48] Additional mutations in the virus

may lead to a phenomenon referred to as 'original antigenic sin' in influenza immunology parlance with resultant disease enhancement after exposure that may render vaccines ineffective.[49] Like the influenza vaccine, we may have to update the vaccine formulation in the future, in case immunologically significant mutation(s) occur in the "S" protein.

Immune enhancement of the disease

Clinical trials need to evaluate the potential harms in addition to the efficacy. Sometimes, the disease runs a more severe course paradoxically in individuals who are vaccinated. There are two immune-mediated mechanisms of such a phenomenon: first, an Ab-dependent enhancement (ADE), in which there is increased binding efficiency of virus-antibody complexes to FcR-bearing cells, which triggers viral entry. Thus, the viral entry might be facilitated by these antibodies, bypassing the specific receptor-mediated entry.[50] This phenomenon reflects the production of 'inefficient' antibodies by the vaccine which are incapable of thoroughly neutralizing the virus owing to low affinity or low concentration or nonspecific nature ("cross-reactive antibodies").[51] These inefficient antibodies, along with a type-2 T-helper cell (Th-2)-biased immune response lead to Ab-mediated enhancement of infection. Such a phenomenon has been noted with RSV, Dengue, Ebola, and human immunodeficiency virus (HIV) vaccine candidates, feline coronavirus vaccine, and in *in-vitro* studies of the SARS-CoV-1 vaccine.[51–53] Very recently, similar concerns regarding vaccine enhancement of disease have been raised regarding certain SARS-CoV-2 vaccine candidate approaches.[30] There is a weak binding of human antibodies against common-cold causing coronaviruses and S-protein of SARS-CoV-1.[54] Lv et al. demonstrate similar cross-reactivity between SARS-CoV -1 and SARS-CoV-2 infected patients and immunized mice. However, these antibodies were non-neutralizing to conserved epitopes in the 'S' protein of SARS-CoV-2.[55] Whether such non-neutralizing antibodies can lead to an 'ADE' like response in the future cannot be ruled out and hence needs to be evaluated carefully in the clinic.

The second mechanism is 'vaccine-associated enhanced respiratory disease' (VAERD). It is a distinct clinical syndrome that was noted in young children in the 1960s when inactivated measles virus and respiratory syncytial virus (RSV) vaccines were tested. This happened because the vaccines contained conformationally incorrect antigens, resulting in a relatively high ratio of binding Ab to neutralizing antibody that causes immune complex deposition and complement activation leading to worsening of respiratory disease. Another mechanism of VAERD could be allergic inflammation associated with the vaccine.[56]

Duration of immunity and the need for boosting

Waning of immune responses is known with most HCoV infections.[57] The common-cold coronaviruses like HCoV-229E and HCoV-OC43 are known to provide immunity that lasts only a few weeks to months.[58] These coronaviruses do not provide lasting protection as challenge experiments suggest, despite having a detectable Ab.[59] In a recent prospective study, 10 individuals were observed over 35 years (1985--2020) for their antibody responses against N-protein fragment of four different common-cold coronaviruses.[60] Protective immunity was ill-sustained, waned substantially by 6-month postinfection, and frequent reinfections were noticed after 1 year of initial infection. In another study,[59] individuals were experimentally infected with endemic alpha-coronavirus 229E and it was found that high Ab titers were generated after 2 weeks but these rapidly declined in the following 11 weeks and by 1 year, the mean Ab titers had reduced further but they were still higher than before the first virus challenge. Subsequent virus challenge leads to reinfection (as determined by virus shedding) yet individuals showed no cold symptoms.[59]

The studies done on those recovered from SARS-CoV-1 in 2003–2004 show that the antibodies are detectable until about 2 years after recovery. However, the T-cell-based immunity lasts much longer, at least until 6 years[61,62] or even longer up to 17 years.[32] In a study of 56 convalescing patients with SARS-CoV-1,[56] titers of IgG antibodies and NAbs against SARS-CoV -1 were evaluated. The IgG and NAbs antibodies titers peaked after 4 months of the onset of disease and waned thereafter. The IgG antibodies remained measurable in all patients until 16 months after the onset of the disease but became undetectable in 11.8% of cases after 24 months.[57] In the studies done with MERS-CoV, the neutralizing antibodies are noticed to persist for 34 months, whereas T-cell responses last until 2 years following the infection.[63]

The above studies demonstrate that the immunity against early HCoVs can persist for a year or so, but protective cutoff titers could not be identified. However, in the case of SARS-CoV -1, it was seen that virus-specific T cells persisted for several years, suggesting that T cells may confer long-term immunity.[64] To date, our knowledge on durability of the immunity after natural infection with SARS-CoV-2 is incomplete. Considering many differences in the viral characteristics like transmission potential and neutralization sensitivity between various coronaviruses, it would not be wise to extrapolate data from past studies. Adding another complexity to the existing ambiguities is the timing of the appearance of antibodies following SARS-CoV-2 infection. It is known that the immune response in SARS-CoV-2 is not very rapid, and only 11.8% of the cases develop neutralizing antibodies by day-7 (reaching 100% by day-90).[65] Further studies on the persistence of memory responses to COVID-19 will aid in understanding long-term protection. Promising results on long-term persistence of antiviral antibodies against SARS-CoV-2 were found from a large study from Iceland. The researchers found that 91% of those who recovered tested positive for the presence of anti-SARS-CoV-2 antibodies, and these antibodies did not decline within 4 months after diagnosis.[66] Although SARS-CoV-2 infection may blunt long-lived Ab responses, immune memory might still be achieved through virus-specific memory T cells. SARS-CoV-2-specific T cells were detectable in Ab-seronegative-exposed family members and convalescent individuals with a history of asymptomatic and mild COVID-19.[67] A preprint by Rodda et al.[68] provides a longitudinal analysis of humoral and cellular memory responses in 15 individuals who recovered from mild COVID-19. Sustained neutralizing IgG antibodies

and memory B cells, expressing B cell receptors capable of neutralizing the virus when produced as antibodies, were detectable 3 months after symptom onset. Additionally, SARS- CoV-2- specific memory T cells persisted for more than 3 months. These cells proliferated and produced T helper 1 (TH1) and TH17 cell-associated cytokines upon antigen restimulation. Collectively, these data suggest that mild COVID-19 infection induces sustained memory responses that exhibit functional hallmarks associated with potent antiviral immunity. Further studies will be needed to fully dissect immunological memory responses, their durability, and their contribution to long-term protection from SARS- CoV-2 reinfection.

Seow et al.[19] studied the sequential samples of 65 RT-PCR-confirmed cases of COVID-19 and found that the IgM and IgA binding to the "S" protein declines rapidly after 20–30 days of onset of symptoms. Further it was found that the magnitude of NAbs titer depends on disease severity, but the average time to peak remains almost the same: around 23 days of onset of symptoms. Since the titers are lesser in those with mild symptoms, it was demonstrated that the titers declined to about baseline levels by 50 days of onset, while in those with severe symptoms, the titers were significant even up to 94 days of follow up. There was another interesting finding of this study: In contrast to what was expected, there was no difference in immune response in severe COVID-19 patients with the persistent hyper-inflammatory state as compared to severe cases without that phenotype.[19]

The precise understanding of the Ab dynamics and the duration of immunity induced by the candidate vaccines will be of paramount significance in ascertaining the need for the booster doses of the vaccines. Despite significant knowledge gaps in immune responses, most vaccine candidates are focussing on eliciting a robust and durable NAb response to provide protection from infection. Vaccine candidates tested thus far in challenge studies have elicited modest NAb responses.

'Endpoint' for assessing efficacy

There is much debate on what should be the ideal 'primary endpoint' to demonstrate the effectiveness of a SARS-CoV-2 vaccine. It could be either protection from the infection ('sterilizing immunity') or attenuation of the disease severity. The latter would require a close assessment of the impact of vaccination on the disease severity in different epidemiological and medical settings. Since most of the enrolled subjects for vaccine efficacy trials are going to be young, healthy adults, extrapolating the results for the elderly with comorbidities would be a cumbersome exercise for the researchers. As asymptomatic transmission may constitute quite a significant percentage (up to 40%) of total cases of the disease,[69,70] a far greater number of subjects would need to be enrolled for the efficacy trials with monitoring of both serologic and clinical endpoints. Lack of precise knowledge of incidence rates and transmission dynamics of SARS-CoV-2 adds to challenges in developing clinical trial protocols with serological endpoints.[71] Differentiating immune responses elicited by the vaccination to those resulting from the wild infections would pose another challenge. A specific sensitive assay would be required to resolve this issue.

Dosing issues

To avoid the failure of vaccine candidates in phase-3 trials, one key issue is the correct identification of dose that best balances efficacy and safety. The SARS-CoV-2 is more lethal in the elderly age-group and in those with comorbidities and thus this group is the one which needs the vaccine the most. However, the immune response in this category is in general suboptimal as compared to young healthy individuals, thus requiring a higher dose. This poses another challenge to the ongoing efficacy trials of SARS-CoV-2 vaccines.

Fear and concern about COVID-19 Vaccines

Since the beginning of the COVID-19 pandemic, there have been much misinformation and conspiracy theories that have the potential to reduce vaccine uptake. The antivaccination movement is already promoting hesitancy and resistance. Hence, World Health Organization (WHO) recommends a preemptive provaccination strategy that psychologically inoculates the population and maximizes uptake of vaccines as they become available. Similarly, the safety concerns as perceived by the media/public should be preemptively addressed.[72]

Postlicensure challenges

The challenges to the use of an effective SARS-CoV-2 vaccine do not end even when the vaccine is licensed. There are few other challenges ahead of largescale introductions of an effective vaccine. Many of the vaccine candidates are being developed by firms that have never brought a vaccine to market or use technologies that have never resulted in a licensed vaccine and billions of doses of the vaccine would be required soon after it is licensed. This would be beyond the capability of most vaccine manufacturers[73] and could bring up unforeseen issues (e.g. insufficient glass vials/syringes/logistics) and delays. The initial aim would be to have at least two billion doses available by the end of 2021, which should be enough to protect high risk and vulnerable people, as well as frontline healthcare workers. Even though new technologies and manufacturing plants can be built to sustain production, equitable distribution in a way that the vaccine is accessible to those who need it the most would be a significant challenge. A lot of planning at the global and country-level has already been started to tackle this challenge suitably.

Status of vaccine development: progress so far

WHO took some critical steps to strengthen much-needed global collaboration.[74] The agency has proposed an innovative concept of an international, multi-centric, individually randomized controlled clinical trial for evaluation of candidate vaccines in parallel with a joint placebo group, rather than a separate trial for an individual vaccine candidate. This has been called a 'Solidarity Vaccine Trial,' which will make it possible to evaluate individual vaccine candidate within 3–6 months of it being made available for the trial. It is proposed to be a rolling trial with an adaptive design where

various vaccine candidates would enter the trial on an ongoing basis and those failing the trials would be dropped from further testing.[75,76] However, this seems not to have caught the imagination of most vaccine developers, and most of them are proceeding with their independent vaccine trials.

Numerous unique factors have helped the journey of vaccine candidates to the clinical trial stage be reduced to a few months as compared to the usual period of 3–9 years: prior knowledge of the key role of the 'S' protein in coronavirus pathogenesis and evidence that NAbs against this protein is important for protective immunity; the evolution of nucleic acid vaccine technology platforms that let the rapid development of millions of doses once a genetic sequence is known, development activities that have been conducted in parallel, rather than sequentially and, of course, the political will and funding considering the dire need.

Past experiences with other coronavirus vaccines

The SARS-CoV-2 vaccine candidates and their developers are fortunate to have some past-experience of working on the development of other coronavirus vaccines. Already, much work had been done toward developing a vaccine against SARS-CoV-1 in 2003, and MERS in 2012 during their past pandemics. Inactivated vaccines, viral and bacterial vector vaccines, recombinant protein subunit vaccines, DNA vaccines, and live attenuated vaccines–all have been worked upon.[28,77] SARS-CoV-2 being a similar virus, all that work and evidence collected, is going to come useful for faster development of the vaccine.

Approaches to developing a SARS-CoV-2 vaccine: the vaccine platforms

Efforts to develop a specific vaccine against COVID-19 started at the very beginning of the pandemic. The first much-needed breakthrough came within weeks of isolation of the virus, when the first genome of the virus was published and made freely available to researchers globally. Thereafter, the virus has since been sequenced more than 3,000 times, charting both the original genome and its mutations.[78] The first vaccine safety trials in humans started in March, but the road ahead is full of uncertainties.[79] In May 2020, the US Administration announced a new project titled 'Operation Warp Speed' to accelerate the development, manufacturing, and distribution of SARS-CoV-2 vaccines, therapeutics, and diagnostics. The 'Warp Speed' has finally selected five vaccine projects to receive billions of dollars in federal funding and support even before there is proof that the vaccines work.[80] These five vaccine candidates are developed by Moderna, AstraZeneca-University of Oxford, Johnson & Johnson, Merck, and Pfizer.[81] Each developer has adopted a specific yet somewhat different approach.

Efforts to develop a SARS-CoV-2 vaccine were initiated in different countries with exceptional urgency. About 200 vaccines are in development, with over 40 currently in the clinical trial stage.[2] Many different vaccine platforms have emerged, from traditional technology like recombinant-inactivated protein to novel approaches like nucleic acid-based vaccines. This multipronged approach is quite fathomable and justified considering the uncertainty over the success of all the candidates, the unprecedented fast-tracking of vaccine development, and the enormous global requirement of the licensed product that cannot be met by a few traditional vaccine manufacturers. Each of these vaccine platforms has distinct characteristics, 'pros and cons,' and is in different stages of development. Table 1 summarizes the key attributes of different vaccine platforms.[2,3,16,79,81,82] Nucleic acid-based and adenovirus-based vaccine platforms are interesting ones: but it is worthwhile to note that to date, they can be called as "concepts" only since no vaccine on these platforms has ever been licensed. So, it is unknown whether mRNA encoded antigens can practically confer sufficient protection against the pathogens. As far as adenoviral vector vaccines are concerned, such vaccines have disappointed in past and one reason for failure as been preexisting immunity to adenovirus that hampers the immune response. Although both platforms have some hypothetical production benefits over other traditional platforms, the uncertainty is apparent.

Animal trials

Animal studies are challenging and sometimes, in the absence of a proper animal model, difficult to interpret unambiguously. For SARS-CoV-2, the non-human primate (NHP) model mimics mild to moderate infection in humans while the hamster model mimics severe infection. However, data from hamsters are limited currently.[83] Seven NHP trials of the candidate SARS-CoV-2 vaccines in the macaque challenge model have been published so far.[84–90] They include three adjuvanted inactivated vaccines (PiCoVacc by Sinovac, BBIBP-CorV, and BBV152 by BBIL), two nonreplicating adenovirus vector vaccines (ChAdOx1nCOV-19 by AstraZeneca and Ad26COVS1 by Janssen), one mRNA vaccine (mRNA-1273 by Moderna), and one protein subunit, nanoparticle vaccine (NVX CoV2373 by Novavax)[84–90].

All animals vaccinated with the low or medium potency doses of the seven test vaccines became infected with milder disease following a challenge dose of the SARS-CoV-2 virus compared to the control group. Nevertheless, considerable differences were noticed among these vaccine candidates. All the vaccinated monkeys treated with the ChAdOx1 vaccine became infected when challenged.[85] In contrast, the other adenoviral vector vaccine candidate (Ad26COVS1 vaccine) and the inactivated candidate vaccines fared much better than the ChAdOx1 vaccine in resisting infection.

Highest anti-S protein antibodies titers were elicited by the nanoparticle vaccine NVX CoV2373 followed by mRNA-1273, BBIBP-CorV and Ad26COVS1, and lowest in PiCoVacc-vaccinated macaques.[83] However, it is not known whether the titers made any difference to the outcome since all the animals in the seven tested vaccine candidates' groups were protected from the clinical disease and there was >100-fold differences in the antibodies titers. This finding raises doubt on the sole protective role of anti-S antibodies induced by these vaccine candidates. Furthermore, T cell response was not assessed in all NHP trials, and only ChAdOx1nCOV-19 and mRNA −1273 candidates had a reasonably good cellular response.[83] Whether

Table 1. Landscape of SARS-CoV-2 candidate vaccines: Vaccine platform, their attributes, and status of development (References:[2,3,16,79,81,82]).

Vaccine platform	Vaccine candidates under clinical trials*	Safety	Speed of development	Global distribution and scalability	NAb production	T-cell immune responses	Advantage	Disadvantage	Existing example/ Same platform for non-HCoV candidates
Inactivated	Seven	Some concerns	Medium	Feasible	Moderate	Probably lower	-Traditional & easy to develop -Preserve virus particle structure -Can be formulated with various adjuvants	-Possible hypersensitivity -Th-2 bias? -Possible ADE?	SARS
Live attenuated	None	Significant concerns	Slow	Feasible	Probably high	Probably good	-Highly immunogenic -Good cellular responses -Can be given intranasally that can induce mucosal immunity too	-Substantial safety concerns (Reversion to virulent strain) -Cold chain requirement, -Risk to immunocompromised	Several (OPV, MMR, Varicella, Influenza, etc)
Non-Replicating Viral Vector	Nine	High	Medium	Feasible	Moderate	Probably good	-Despite a live virus vaccine, safety not an issue, -should elicit better immune responses than killed/subunit vaccines -Good cellular responses	-Selection of safe vector-a must. -Immune response to vector may render vaccine less effective	Ebola, MERS, influenza, TB, Chikungunya, Zika, MenB, plague
Replicating Viral Vector	Three	Some concerns	Medium	Feasible	Probably good	Good	-Mimic natural infection "dose sparing effect" (less dose required as compared to non-replicating viral vector vaccine-Often induce innate immune response too -Some vectors may be given intranasally and induce mucosal immunity	Selection of safe vector-a must. -Immune response to vector may render vaccine less effective	HIV
RNA	Six	High	Fast	May be difficult	Moderate	Probably good	-Rapid development. -Easy to make	- No approved RNA vaccines -Unlikely to induce mucosal immunity -Required frozen storage: big challenge in developing and underdeveloped countries	multiple candidates in the pipeline
DNA	Four	High	Fast	Some concerns	Moderate	Probably good	Rapid development; Easy to make	-Low immunogenicity -Approved for veterinary cases; -No approved vaccines for use in humans	None (multiple candidates in the pipeline)
Protein Subunit	Thirteen	High	Slow	Feasible	High	Probably lower	-High safety profile -Consistent production -High NAbs production	-Need appropriate adjuvant, -Cost-effectiveness may vary	RSV, CCHF, HPV, VZV, Influenza, Ebola
VLP	Two	High	Slow	Feasible	High	Probably lower	-Multimeric antigen display -Preserve virus particle structure	-Require optimum assembly condition	Flu, Rotavirus, Norovirus, West Nile virus, Cancer, HPV

** For a complete list of vaccine candidates in Clinical Trials and preclinical stages, visit: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines* VLP: vaccine-like particle

T-cell immunity or mucosal IgA or some other factor yet to be explored was a significant determinant of protective immunity against COVID-19 disease is still unknown. It is comforting to find no evidence of any serious negative effect of the tested vaccines including ADE during these trials; however, the past experiences with other vaccines indicate that there is no guarantee that such serious adverse effects would not occur in human trials.[91]

Although detailed comparisons of results of various animal trials have been published,[83] but interpreting such comparisons is fraught with danger: Challenge doses and routes vary, vaccine regimens and schedules vary as well. Importantly, while all studies report neutralization data, differences in assays can introduce huge biases. Furthermore, most studies did not determine the level of infectious virus in the upper and lower respiratory tracts and measured viral RNA or subgenomic RNA by PCR.

In conclusion, the animal trial results suggest that despite marked variability in the titers of elicited NAbs levels, none of the vaccines provided sterilizing immunity to the virus challenge at usual doses, the gold standard for any vaccine-induced immunity. They may provide only partial protection.[91]

Clinical trial results

As stated above, over 40 vaccine candidates are in different stages of clinical evaluation. At least 10 vaccine candidates (Sinovac's inactivated PiCoVacc (CoronaVac), University of Oxford/AstraZeneca's ChAdOx1, Moderna's mRNA vaccine, CanSino Biological Inc./Beijing Institute of Biotechnology's Adenovirus type-5 vector vacccine, Gamaleya Research Institute's Adeno-based (rAd26-S+ rAd5-S) vaccine, Janssen Pharmaceutical Companies' Ad26COVS1 vaccine, Wuhan Institute of Biological Products/Sinopharm and Beijing Institute of Biological Products/Sinopharm's respective-inactivated vaccines, BioNTech/Fosun Pharma/Pfizer's RNA vaccine and Novavax's protein subunit nanoparticle vaccine) have already initiated phase 3 studies.[2]

CanSino Biological's Ad5-vectored COVID-19 vaccine was found tolerable and immunogenic at 28 days post-vaccination in a phase 1 study.[92] In a phase 2 trial, this vaccine at 5×10^{10} viral particles induced significant titers of NAbs responses and seroconversion in 97% (92–99) subjects after 4 weeks following a single immunization. Specific T-cell responses assessed by interferon γ enzyme-linked immunospot assay were observed in 88% (81–92) of 129 participants in the 5×10^{10} dose group. The vaccine is found safe without any serious adverse reactions.[93] Of note, this vaccine is licensed to be used in the Chinese military.[83]

In the phase 1 dose-escalation trial of *Moderna's mRNA-1273 vaccine*, 45 subjects (18 to 55 years of age) were vaccinated with two doses of test vaccine at 28 days apart. The vaccine-induced a good amount of NAbs titers in all participants, highest in the highest dose group (250-μg). Second dose boosted the titers. Systemic adverse events after the prime seemed to be dose dependent.[94] This trial was expanded[95] to include 40 older adults, who were stratified according to age (56–70 years or ≥71 years). All the participants were assigned sequentially to receive two doses of either 25 μg or 100 μg of vaccine administered 28 days apart. After the second immunization, serum neutralizing activity was detected in all the participants by multiple methods. Binding- and neutralizing-Ab responses appeared to be similar to those between the ages of 18 and 55 years and were above the median of a panel of controls who had donated convalescent serum. The titers were higher with a 100 mcg dose than with a 25 mcg dose. The vaccine elicited a strong CD4 cytokine response involving type 1 helper T cells. No serious adverse events were noted. The 100mcg dose was selected for use in the phase III trial.

The phase 1/2, single-blind, randomized-controlled trial of ChAdOx1 demonstrates a peak spike-specific T-cell responses on day 14. Anti-spike IgG responses rose by day 28 and were boosted following a second dose after 4 weeks of the first dose. The NAb responses against SARS-CoV-2 were detected in 91% of participants after a single dose when measured in MNA80 and in 100% when measured in PRNT50. After a booster dose, all participants had neutralizing activity. There were no serious adverse events related to ChAdOx1 nCoV-19.[96] The ChAdOx1 vaccine from the AstraZeneca-Oxford group, is the first candidate to go for phase 3 trials involving 10,000 healthy volunteers of 18–65 age group.[81]

A nonrandomized open-label phase 1/2 trial of BioNTech/Pfizer's BNT162b1, a lipid nanoparticle formulated nucleoside modified mRNA vaccine encoding the RBD of the SARS-CoV -2 'S' protein in healthy adults found two doses of 1 to 50 μg of the test vaccine-elicited robust CD4+ and CD8 + T cell responses (Th-1 type) and strong RBD-specific Ab responses.[97] More recently, randomized, placebo-controlled ongoing trial of two lipid nanoparticle–formulated, nucleoside–modified RNA vaccine candidates (BNT162b1, which encodes a secreted-trimerized SARS–CoV–2 receptor-binding domain, or BNT162b2, which encodes a prefusion stabilized membrane-anchored SARS–CoV–2 full-length spike) has demonstrated similar dose-dependent SARS–CoV –2– neutralizing geometric mean titers (GMTs), comparable to or higher than the GMT of a panel of SARS–CoV–2 convalescent sera. Since BNT162b2 was associated with less systemic reactogenicity, particularly in older adults, it has been selected as the vaccine candidate for Phase 2/3 large-scale safety and efficacy evaluation.[98] This trial is currently underway.

Gamaleya Institute developed a heterologous COVID-19 vaccine consisting of two components, a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for spike glycoprotein (rAd26-S and rAd5-S). Its open, nonrandomized phase-I/IItrial[99] in healthy adults (18–60 years) showed 100% seroconversion on day-42. Cell-mediated responses were also detected in all participants on day 28. The vaccine was well tolerated with no serious adverse effects.

Sinovac reported its inactivated vaccine CoronaVac's double-blinded placebo-controlled phase-II trials conducted on 600 healthy volunteers of 18–59 age. The 2-week interval with both doses resulted in low neutralization titers with GMTs around 1:30, the 4-week interval fared slightly better in the 1:60 range 28-day post boost. Overall, more than 90% of the individuals seroconverted. Of note, the authors also stratified the titers by age. The 18–39-year-old had clearly higher Ab responses than older individuals, suggesting that perhaps

higher doses or different adjuvants might be needed for the elderly. The safety profile of the vaccine was excellent and both doses were comparable to placebo1.[100] No grade 3 adverse reactions were reported. The phase-III trials in adults and the elderly are underway.

Randomized, observer-blind placebo-controlled Phase-I trial of Novavax's NVX-CoV2373 in 131 healthy adults aged 18–59 has been recently published. Novavax is using a recombinant version of the full-length 'S' protein with the polybasic cleavage site deleted and the two stabilizing proline mutations expressed in insect cells and purified by membrane extraction. This leads to the rosette formation of S via its hydrophobic tails (similar to Sanofi's FluBlok recombinant HA-based vaccine) which was termed 'nanoparticle' by Novavax. The antigen was formulated with or without the saponin-containing adjuvant Matrix-M and given at doses of 5 or 25ug in a 3 week interval prime boost regimen. The immune response was poor with the nonadjuvanated vaccine but was very good with adjuvanated one and booster dose resulted in a significantly better response. CD4+ responses were evaluated 7 days post-boost and both adjuvanted groups showed a robust Th1 polarized response. Local reactogenicity and systemic events were milder after the first dose than after the second dose and were mostly driven by the adjuvant.[101]

Although all these trials are not directly comparable due to different assays and readouts being used in different trials; however, it seems that the recombinant vaccine is highly immunogenic, ChAdOx and the mRNA candidates are fairly immunogenic and inactivated and the AdV5 vaccine are less immunogenic in terms of neutralizing antibodies. In terms of tolerability, the inactivated vaccines and recombinant protein vaccines seem to perform relatively well, followed by the mRNA vaccines which show increased reactogenicity after the second vaccination followed by the Adenovirus-vectored vaccines.[83] Thus, the data are cautiously optimistic.

Approaches to speed up 'development-to-licensing' process

Researchers the world over are considering options to expedite the vaccine production process. Unprecedently, both the trials and manufacturing processes are going side-by-side to deliver the vaccines at the earliest. Various novel approaches to speed up the process are explored.

Skipping exploratory work on vaccine design

Data from SARS-CoV-1 and MERS CoV vaccine development saved time and the initial step of exploratory vaccine design was basically skipped. In many cases production processes were just adapted from existing vaccines or vaccine candidates and in certain cases preclinical and toxicology data from related vaccines could be leveraged. This led to the start of a first clinical trial as early as March 2020 (NCT04283461).[83]

Skipping animal studies

There have been suggestions that traditional animal trials may be skipped or rushed through if the other HCoV vaccine that has been tested in animals is used as a template to develop a vaccine against SARS-CoV-2. However, since skipping animal trials for a vaccine against a new human pathogen would be an unusual occurrence, it demands extensive ethical deliberations and assessment of risk: benefit ratio before taking any such decision.[5] Few of the vaccine developers have taken an alternative approach: they completed the animal studies of their candidates in parallel with ongoing human trials.[83–86]

Umbrella clinical trials

This approach could be used to test several candidates under a single study protocol to compare findings of different trials by standardizing decisions like criteria for recruitment and endpoints selection. There could be other logistical benefits also, such as having a single placebo arm for different trials to cut down on the cost and the overall size of the trials.[102]

Parallel clinical trials

Phase I and II clinical trials of many candidates have been conducted in parallel/simultaneous or overlapping with each other. Further phase III clinical trials have begun after just interim analysis of phase I/II trials in many, if not most vaccine candidates.

Human challenge trials

These trials in which a small number of volunteers are vaccinated and then challenged with live virus dose to measure vaccine efficacy rapidly rather than waiting for natural infection. Such trials have been done previously with several agents, generating important information.[103] Some researchers are endorsing this 'controversial' approach as a 'desperate measure' for the sake of accelerated delivery of the vaccines,[103] others are advocating a more cautious approach, addressing all the ethical issues involved in these trials.[104–106]

This is because the controlled human infection is not free from flaws associated with the safety of the participants and adopted methodology.[107,108] Although the COVID-19 is considered a mild disease in young, healthy individuals, some unpredictable risks to the volunteers do persist. Moreover, we are yet to discover a single proven effective therapy for COVID-19 to rescue participants with complications from such a trial.[5] Furthermore, the challenge virus strain of SARS-CoV-2 will be of low pathogenicity, which may not lead to severe respiratory pathology observed in many serious COVID-19 patients. Hence, the limited efficacy observed in young, healthy adults may not be a true representative of the effectiveness among older adults with comorbidities, nor would it demonstrate the diminution of transmissibility to main vulnerable groups.

No doubt, in a rapidly evolving pandemic, there may be some justification for adopting such an unconventional hurried approach. However, the ethical issues arising from safety concerns warrant a careful appraisal by an independent panel of ethicists, clinical trialists, regulators, and vaccinologists. In an unconventional and highly controversial move, China's Central Military Commission has recently approved the use of their Ad5-nCoV vaccine for their military personnel without undergoing the crucial phase III trial.[108] A similar step taken by Russia has also resulted in outrage in the global scientific community.[109] This also goes against the detailed guidelines laid by the WHO for the target product profiles for COVID-19 vaccines.[110] Krause et al.[111] have rightly expressed the fear that

political or economic pressures lead to the rapid introduction of a vaccine based on an underpowered trial and is found to be a weakly effective vaccine, in reality, it would have a cascading effect. This is because the vaccinated individuals would consider themselves "immune" and would not follow the other COVID-19-control measures. Further, other weak (or even weaker) vaccines might get licensed based on just statistical noninferiority (so-called bio-creep). That is why the WHO[110] recommends that the COVID-19 vaccine should demonstrate bare minimum efficacy of 50% (preferably at least 70%) with a lower limit of the confidence interval of at least 30%. US-FDA also recommends the same.[112] Logically, we should be moving forward with vaccine development at financial risk, while no corners should be cut in terms of safety evaluation.[83]

Another risk of speed over quality is the further erosion of trust in science by communities at risk. COVID-19 has already exposed the gap between science and practice, and the importance of working with communities to educate them about COVID-19 risk, prevention, and treatments. By setting the performance bar far lower in COVID-19 vaccine development than what would otherwise be acceptable, we would unwittingly redefine the concept of a vaccine from a long term, effective preventive public health tool to what could amount to a population-wide suboptimal chronic treatment. This might be good for business but could prove damaging to global public health.[113]

Future scenarios

There are several reasons why it is difficult to predict the outcome and future performance of the candidate vaccines. First, there is no agreeable 'endpoint' on the extent of disease amelioration since most vaccine candidates in animal studies failed to prevent SARS-CoV-2 infection. A critical prerequisite of a successful efficacy trial is the presence of a significant number of infected individuals at the trial sites. However, now the disease is waning in most of the European, Chinese and the US sites where major trials are either ongoing or soon to be started. Second, the specific immune 'correlate of protection' for SARS-CoV-2 antibodies is not known, and that may further confound the efficacy assessment. The animal studies have pointed toward the irrelevance of the magnitude of antibodies titers induced by the few candidates. However, the scenario may be different in humans. If exceedingly high antibodies titers are required for protection, then those candidates eliciting only modest titers of antibodies would need to be boosted by either the same or a different vaccine candidate.

Moore and Klasse[16] have analyzed different future scenarios. The most-favorable scenario would be to expect the efficacy trials of many candidate vaccines to succeed and provide robust protection against the COVID19. In that scenario, the vaccines that can be rapidly produced in bulk amount (e.g. mRNA, DNA, adenovirus vectors) shall be the first choice. A scenario may emerge where a nucleic acid-based (like mRNA vaccine) vaccine work better if boosted by an inactivated vaccine. Alternatively, an adenovirus vector vaccine may need to be augmented by a recombinant protein candidate. Since these vaccines may not be developed in a single country, and some in different geographical locations, extraordinary cooperation, mutual understanding, and commitment would be required at the global level to deliver the vaccine to the needy population.

The most unfavorable scenario would be if any of the vaccines elicit a 'nonprotective' immune response that aggravates the disease in the recipients who get infected with SARS-CoV-2. This situation might prove to be a very damaging outcome that could ignite antivaccine sentiments among the masses.

The way forward

Whatever be the future scenario, it is apparent that we need unprecedented global collaboration and cooperation among national governments, funders, academia, health organizations, regulators, and manufacturers irrespective of their geographical locations.[114] The challenge is not only to develop safe and effective COVID-19 vaccine(s) but also their equitable distribution as was discussed above. WHO in collaboration with GAVI, the vaccine alliance, and Coalition for Epidemic Preparedness Innovations (CEPI) has initiated an extraordinary and unique global collaboration, known as 'COVAX', a COVID-19 Vaccines Global Access facility.[115] COVAX plans to pool economic resources of its member countries to achieve two objectives: enable vaccine developers to make high-risk investments for the development of vaccines and subsidize vaccine costs for middle-and low-income countries. By joining COVAX, both self-financing countries and funded countries will gain access to this portfolio of vaccines, as and when they prove to be both safe and effective. This initiative possibly represents the world's best bet of bringing the ongoing phase of this pandemic to a swift end. Similar collaborations would be needed at regional and country levels too so that a fair distribution of the vaccine is achieved. Partnerships between vaccine developer and manufacturer are being forged for common good.

For instance, Serum Institute of India, the world's largest vaccine producer by the number of doses produced has entered into manufacturing agreements with three vaccine developers (AstraZeneca, Novavax, and Codagenix) to help supply their experimental COVID-19 vaccine candidates.[116] The challenges of limited efficacy data in extremes of age and those with comorbidities, availability of adequate doses of the vaccine, and logistics will force us to prioritize the target vaccinees in the initial phase. This also requires collaboration, planning, and intersectoral coordination at various levels. Mammoth efforts are on in that direction too.

Sustained global collaboration, public support, and technological advancements would hopefully modernize the pandemic vaccine enterprise during the current crisis. Decades of global experience of vaccine development teach a straightforward rule of thumb: "Expect the unexpected." Thus, while optimism is crucial to move forward, one should not forget the lessons of the past: including the tale of the tortoise and the hare!

Disclosure of potential conflicts of interest

I hereby declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

ORCID

Vipin M. Vashishtha http://orcid.org/0000-0003-1097-117X

Author Contributions

VMV conceived the idea, searched the relevant material, and wrote the first draft of the manuscript. PK helped in the review and critical appraisal of the draft. VMV and PK wrote the final version of the review. Both VMV and PK read and approved the final manuscript.

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