



## Editorial

### The quest continues for perfect COVID-19 vaccine

Eradication of smallpox, near elimination of poliomyelitis and neonatal tetanus and substantial reduction in impact of measles are ranked amongst the greatest achievements of humankind ever. These triumphs are the outcomes of the availability and concerted use of potent, safe and affordable specific vaccines. In addition, protecting against 20 infectious diseases, the vaccines prevent 2-3 million deaths annually<sup>1</sup>.

Apart from natural infections, vaccines are considered as the safest and cost-effective intervention to induce protection against COVID-19. Will the vaccines currently undergoing clinical trials be able to achieve this critical milestone is not evident as of today. The entire world is looking forward to COVID-19 vaccine to bring a rapid end to the pandemic. The unprecedented global quest for COVID-19 vaccine is aimed at achieving what other public health interventions have not been able to accomplish till date to vanquish the pandemic. Vaccine is being touted as the most potent weapon to induce immunity - adequate in its immunogenicity and safety to cut short the virus transmission. The vaccine is primarily aimed to protect individuals and creating a pool of immune people that comprises 60-70 per cent of entire population<sup>2,3</sup>, thus inducing herd immunity.

#### Immunology and selection of antigen for COVID-19 vaccine

SARS-CoV-2 is a novel virus. The viral determinants that need to be attacked to confer immunity remain undefined. While there are favourable precedents from other respiratory viruses including coronaviruses<sup>4</sup>, there are apprehensions that vaccination may mimic rapidly declining natural immunity to SARS-CoV-2.

The antigen of choice for COVID-19 vaccine has been the SARS-CoV-2 spike protein, a type 1 protein that is metastable and should have correct

folding during the vaccine production and storage before deployment<sup>5,6</sup>. The neutralizing antibodies to be generated by natural infection or through vaccination act against the receptor-binding protein component that binds onto angiotensin-converting enzyme 2 and obstructs the entry of the virus into the cell. Initial evidence that only receptor-binding protein should be incorporated in the vaccine is being revisited with the knowledge that there are several areas outside receptor binding domain (RBD) that can be the potential targets for neutralizing antibody<sup>7</sup>.

Neutralizing antibodies are likely to produce vaccine-induced protection. However, as with some other coronaviruses, the immune response may have short-lasting immunity not exceeding one year<sup>8</sup>. In most instances, vaccines inducing T-cell response confer protection. T-cell-mediated immune responses through CD4+ and CD8+ provide broad and long-term protection against coronavirus infections. CD4+ T-cells activate B-cells which lead to the production of virus-specific antibody. CD8+ T-cells being cytotoxic, kill cells that have been invaded by the virus. In patients with COVID-19, T cellopenia has been observed in circulating CD4+ and CD8+ T-cells<sup>9-11</sup>. SARS-CoV-2-specific T-cells have been found in asymptomatic individuals or those with mild symptoms. Patients suffering from COVID-19 had fewer T-cells than healthy controls<sup>12</sup>.

#### Vaccine platforms

Perhaps never in the history of combating infectious diseases, so many vaccine candidates were in varying stages of development as are for the COVID-19 pandemic. Several new and diverse technology platforms are in use to expedite vaccine development<sup>13</sup>. In its description of the global landscape of COVID-19 vaccines, the WHO reports over 163 vaccines in pre-clinical evaluation and 52 in clinical evaluation as of December 2, 2020<sup>14</sup>. Broadly,

these vaccines can be categorized into five main types. These include: replicating and non-replicating viral vector-based vaccines, whole virus-based (inactivated or attenuated), nucleic acid-based (DNA and RNA), recombinant protein, peptide-based vaccines and virus-like particles (Table I)<sup>15,16</sup>.

Live attenuated vaccines closely resemble natural infection but have the potential of reverting to pathogenicity and causing disease among young and immunocompromised individuals<sup>17</sup>. Currently, no COVID-19 live attenuated vaccine is in clinical trial phase.

Inactivated vaccines have proven efficacy for several diseases and their productions can be easily scaled up. The modern vaccine manufacturing units provide appropriate biosafe environment for bulk production of inactivated vaccine. One of the Indian manufacturers (Bharat Biotech in collaboration with the ICMR-National Institute of Virology) is currently moving forward with clinical trial for this category of vaccine<sup>18</sup>.

Nucleic acid (DNA or RNA) vaccines have low cost of production in large volumes. Once taken up by the cells, these vaccines express the antigens that have been encoded in the nucleic acid. Currently, more than 10 platforms are being used to develop nucleic acid vaccines. Successful outcome shall herald a new era in vaccine technology, especially in pandemics when vaccines need to be designed, developed and disseminated swiftly<sup>15,19</sup>. Many leading global (Moderna Inc.) and Indian companies (Zydus Cadila)

are currently engaged in clinical trials on nucleic acid vaccines<sup>20</sup>.

Recombinant protein vaccines have a targeted approach towards a key antigen but warrant correct conformation of the protein<sup>15</sup>. The University of Oxford, in collaboration with private sector, has developed a chimpanzee adenovirus vaccine vector expressing the wild type S protein (ChAdOx1 nCoV-19, also known as AZD1222)<sup>21</sup>. Clinical trial on this vaccine is ongoing at multiple sites including in India.

Only one adenoviral vector-based vaccine has been approved by the Russian regulatory authorities<sup>22</sup>. Yet, global community awaits data from Phase 3 clinical trial to assure itself of the safety and efficacy of the Russian vaccine. Phase 3 clinical trial of Russian vaccine (Sputnik V) in India is under the approval process of the national regulatory authority<sup>23</sup>. Vaccine developed and manufactured by Pfizer has been licensed for use in the United Kingdom, United States of America, Canada and Bahrain<sup>24</sup>.

#### Potential risks associated with vaccines

An undetermined risk of COVID-19 vaccine causing disease enhancement or an acute autoimmune disease through a T-cell-mediated damage or adverse effect due to antibody is yet to be explored. Vaccines for many other diseases including influenza and measles have been associated with such unwanted and damaging events<sup>25</sup>. Such events may be detected through post-marketing surveillance of COVID-19 vaccine. It is essential to generate reliable data on

**Table I.** Overview of soon-to-be-available COVID-19 vaccines

Platform	Manufacturer/Supplier	Route of administration	Doses	Cold chain requirement (°C)
Inactivated	Bharat Biotech (Whole virion) Sinovac	IM	2	2-8
Viral vector Adenovirus	Oxford/Astra Zeneca/SII Gamaleya Research Institute/ Dr Reddy's Laboratory, India	IM	2	2-8
Protein Subunit (recombinant)	Novavax GSK/Sanofi Biological E, India	IM	2	2-8
mRNA	Moderna Pfizer	IM	2	-20 at 2-8 × 30 days -70 at 2-8 × 5 days
Live attenuated virus	Codagenix/SII	Inhalation	1, 2	2-8
DNA	Zydus Cadilla, India	Intradermal		2-8

IM, intramuscular; SII, serum Institute of India. *Source:* Ref. 24

long-term safety of vaccines to inspire confidence in communities and their acceptance of vaccines.

### Repurposed vaccines for COVID-19

In the absence of the specific immunizing agent, several other vaccines have been under investigation with the hypothesis that these vaccines may modify the response of the immune system of vaccines and enhance cytokine production to provide protection against COVID-19. These include BCG<sup>26</sup>, oral polio vaccine (OPV)<sup>27</sup> and MMR (measles, mumps, and rubella)<sup>28</sup>. For BCG vaccine alone, three multicentric randomized controlled trials are ongoing in three different countries<sup>29</sup>. A measles vaccine trial to evaluate its protection against COVID-19 is underway in Egypt<sup>30</sup>, and the USA is assessing the efficacy of OPV against SARS-CoV-2<sup>31</sup>.

### Production and deployment of vaccine

The world is estimated to need around 16 billion doses of vaccine in immediate future. It is a huge challenge to meet this global requirement in a short period. Fortunately, many national and intercountry agencies are providing substantial financial and technical support to vaccine manufacturers to build up their capacity. Development of vaccines is an expensive proposition. A dengue vaccine had cost around US\$ 1.5 billion<sup>32</sup>. Cost of investment in vaccine is miniscule as compared to the losses caused by the pandemic.

Many countries and organizations are supporting timely development and production of adequate quantities of vaccines and their access across the world. The Coalition for Epidemic Preparedness Innovations (CEPI) is supporting nine COVID-19 vaccine candidates<sup>33</sup>. Operation Warp Speed in the USA<sup>34</sup> is supporting six candidate vaccines. Great Britain has allocated £250 million for development of a COVID-19 vaccine and also established a vaccine task force<sup>35</sup> to support national development, discovery and approval of vaccines. GAVI (Global Alliance for Vaccines and Immunization) alliance and Bill and Melinda Gates Foundation have provided US\$ 300 million to Serum Institute of India for producing 200 million doses of COVID-19 vaccine, half of which have been earmarked for the low- and the middle-income countries<sup>36</sup>.

To facilitate and improve global access to COVID-19 vaccines, the WHO has hosted a global collaboration – Access to COVID-19 Tools (ACT)

Accelerator. It comprises the Bill and Melinda Gates Foundation, CEPI, Foundation for Innovative Diagnostics (FIND), GAVI Alliance, The Global Fund, Unitaid, Wellcome Trust, the WHO and the World Bank<sup>37</sup>. Within the ACT Accelerator is a vaccine pillar (COVAX) which is co-led by Gavi Alliance, CEPI, WHO and many other partners. This COVAX Facility has been set up to work with countries and vaccine manufacturers to develop, manufacture and ensure access to vaccine. The Facility provides governments with the opportunity to have access to and benefit from a large portfolio of COVID-19 vaccines. The goal of COVAX is to mobilize and deliver by 2021 at least two billion doses of quality-approved vaccines<sup>38</sup>. Negotiations with vaccine manufacturers for bulk purchase shall result in an affordable cost. It is proposed to distribute these vaccines for priority use by the high-risk populations (*viz.* healthcare and frontline workers), followed by for vaccinating up to 20 per cent of population as per national priority. Additional doses, if available, shall be made accessible to countries based on their needs and disease epidemiology<sup>39</sup>.

### Challenges

Development of and access to a vaccine against COVID-19 shall be a remarkable milestone but not the panacea to eliminate or contain the pandemic in short period. Challenges are numerous (Table II). These are financial, technical, logistical, social and strength of existing health system in developing countries to address the issue of universal mass vaccination, especially with limited experience in managing vaccination of adult population. Health authorities will have to decide that with initially limited availability of vaccine which category of people becomes priority population on the basis of risk assessment. They will have to consider the social and political ramifications of such decisions.

Logistics shall be a key consideration with all its complexities in reaching out to the entire population through an efficient deployment of the vaccine with a functional cold chain from production-to-vaccination journey.

The clinical trials are conducted in defined adult populations. The vulnerable populations are excluded from these. Since COVID-19 immunization is targeted for entire global population, it shall require prior evidence of efficacy and safety in several subpopulations, especially the elderly, pregnant women, children below 18 yr of age and those who are immunocompromised or living with

**Table II:** Challenges in vaccination against COVID-19

Category	Challenge
Political	Prioritization of vulnerable populations. Selection of vaccine based upon efficacy and cost. Timely procurement of vaccine and ethical distribution.
Programme management	Augmenting health system to reach out to target population. Making available sufficient and functional cold chain up to last mile.
Technical	Monitoring efficacy, persistence of protection and safety in community Phase and launching Phase 4 safety surveillance.
Operational	Timely procurement and efficient distribution. Managing cold chain. Enhancing capacity for efficient response. Data management. Community engagement including response to adverse reactions.
Epidemiological	Monitoring progress of pandemic and adjusting vaccination plans.
Research	Response to availability of second generation of better vaccines.
Financial	Mobilization of financial resources from within the country or through international development partners.

Source: Ref. 39

co-morbidities. Role of vaccine in protecting the elderly with or without co-morbidities (>60 yr of age) and inducing immunity in children in whom this coronavirus has the potential to cause paediatric inflammatory multisystem syndrome needs to be explored on priority through the generation of unequivocal scientific evidence<sup>39</sup>. Will the national and international regulatory bodies consider the impact of vaccines on these subpopulations which have not been evaluated in clinical trials or the licensure shall be restricted to adult and healthy population only or a universal immunization will be permitted, shall be a challenge for the regulatory bodies.

Basic technical issues that require unequivocal evidence-based responses include definition of the ideal protection, type and duration of immunity to reduce the disease, associated risk of disease potentiation and superiority of vaccination over the natural infection. The scientific community needs to accelerate efforts to produce evidence-based solutions for these issues.

### Conclusions

Unprecedented and globally coordinated research and efforts are likely to result in availability of some, if not several, vaccines against COVID-19 in the next few months. The challenge would be to ensure their optimal and cost-effective use.

Despite support from international community, the cost of procurement of vaccine and its deployment for every citizen may be exorbitant for most of the developing countries. While an affordable vaccine is

the need of the hour, high production and administration cost should force countries to innovate, prioritize and think out of the box to make the best use of this intervention with the sole objective to immediately eliminate the pandemic.

Earliest availability of COVID-19 vaccine is projected to be late 2020 to mid-2021. However, it may take several months before global demand as well as safety, immunogenicity and efficacy criteria are fully met. This emphasizes the need for strong advocacy and sustained implementation of proven public health preventive strategies including wearing masks, maintaining adequate social distance and isolation of infectious individuals leading to swift containment of outbreaks<sup>16</sup>.

**Conflicts of Interest:** None.

**Rajesh Bhatia**

Former Director, Communicable Diseases,  
World Health Organization South-East Asia  
Regional Office, New Delhi 110 002, India  
drrajesh.bhatia1953@gmail.com

Received October 8, 2020

### References

1. World Health Organization. *COVID-19 vaccines*. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>, accessed on September 27, 2020.

2. Randolph HE, Barreiro LB. Herd immunity: Understanding COVID-19. *Immunity* 2020; 52 : 737-41.
3. Kwok KO, Lai F, Wei WI, Wong SY, Tang JW. Herd immunity - estimating the level required to halt the COVID-19 epidemics in affected countries. *J Infect* 2020; 80 : e32-3.
4. Sariol A, Perlman S. Lessons for COVID-19 immunity from other coronavirus infections. *Immunity* 2020; 53 : 248-63.
5. Zheng M, Song L. Novel antibody epitopes dominate the antigenicity of spike glycoprotein in SARS-CoV-2 compared to SARS-CoV. *Cell Mol Immunol* 2020; 17 : 536-8.
6. Walls AC, Young JP, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 2020; 181 : 281-92.
7. Seydoux E, Homad LJ, MacCamy AJ, Parks KR, Hurlburt NK, Jennewein MF, *et al.* Analysis of a SARS-CoV-2-infected individual reveals development of potent neutralizing antibodies with limited somatic mutation. *Immunity* 2020; 53 : 98-105.e5.
8. Seow J, Graham C, Merrick B, Acors S, Steel KJ, Hemmings O, *et al.* Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. *medRxiv* 2020; doi: 10.1101/2020.07.09.20148429.
9. Janice Oh HL, Ken-En Gan S, Bertoletti A, Tan YJ. Understanding the T cell immune response in SARS coronavirus infection. *Emerg Microbes Infect* 2012; 1 : e23.
10. Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, *et al.* Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol* 2020; 17 : 541-3.
11. Chen Z, John Wherry E. T cell responses in patients with COVID-19. *Nat Rev Immunol* 2020; 20 : 529-36.
12. Tan M, Liu Y, Zhou R, Deng X, Li F, Liang K, *et al.* Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. *Immunology* 2020; 160 : 261-8.
13. Rauch S, Jasny E, Schmidt KE, Petsch B. New vaccine technologies to combat outbreak situations. *Front Immunol* 2018; 9 : 1963.
14. World Health Organization. *Draft landscape of COVID-19 candidate vaccines*. Available from: <https://www.who.int/publications/m/item/draft-landscape-of-COVID-19-candidate-vaccines>, accessed on December 2, 2020.
15. Tregoning JS, Brown ES, Cheeseman HM, Flight KE, Higham SL, Lemm NM, *et al.*, Vaccines for COVID-19. *Clin Exp Immunol* 2020; 202 : 162-192
16. Bhatia R, Abraham P. The enigmatic COVID-19 pandemic. *Indian J Med Res* 2020; 152 : 1-5.
17. Yong CY, Ong HK, Yeap SK, Ho KL, Tan WS. Recent advances in the vaccine development against Middle East Respiratory Syndrome-coronavirus. *Front Microbiol* 2019; 10 : 1781.
18. Indian Council of Medical Research. *COVID-19*. Available from: <https://vaccine.icmr.org.in/covid-19-virus>, accessed on October 3, 2020.
19. Tregoning JS, Kinnear E. Using plasmids as DNA vaccines for infectious diseases. *Microbiol Spectrum* 2014; 2 : PLAS0028-2014.
20. COVID-19 vaccine tracker. Available from: <https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker>; accessed on December 12, 2020.
21. Graham SP, McLean RK, Spencer AJ, Belij-Rammerstorfer S, Wright D, Ulaszewska M, *et al.* Evaluation of the immunogenicity of prime-boost vaccination with the replication-deficient viral vectored COVID-19 vaccine candidate ChAdOx1 nCoV-19. *NPJ Vaccines* 2020; 5 : 69.
22. Sputnik V. Vaccine. General information. Available from: <https://sputnikvaccine.com/about-vaccine/>, accessed on September 7, 2020.
23. Russian Direct Investment Fund. *RD'F and Dr. Reddy's to cooperate on clinical trials and supply of 100 million doses of sputnik V vaccine to India*. Available from: [https://www.drreddys.com/media/904781/sputnikv-india\\_dr-reddys.pdf](https://www.drreddys.com/media/904781/sputnikv-india_dr-reddys.pdf), accessed on October 3, 2020.
24. Pfizer BioNTech. *Pfizer and BioNTech celebrate historic first authorization in the U>S> of vaccine to prevent COVID-19*. Available from: <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-celebrate-historic-first-authorization>, accessed on December 10, 2020.
25. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, *et al.* Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *Am J Epidemiol* 1979; 110 : 105-23.
26. O'Neill LA, Netea MG. BCG-induced trained immunity: Can it offer protection against COVID-19? *Nat Rev Immunol* 2020; 20 : 335-7.
27. Chumakov K, Benn CS, Aaby P, Kottiril S, Gallo R. Can existing live vaccines prevent COVID-19? *Science* 2020; 368 : 1187-8.
28. Fidel PL Jr., Noverr MC. Could an unrelated live attenuated vaccine serve as a preventive measure to dampen septic inflammation associated with COVID-19 infection? *mBio* 2020; 11 : e00907-20.
29. Curtis N, Sparrow A, Ghebreyesus TA, Netea MG. Considering BCG vaccination to reduce the impact of COVID-19. *Lancet* 2020; 395 : 1545-6.
30. ClinicalTrials.gov. Identifier: NCT04357028. Measles Vaccine in HCW (MVC0VID19); 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT04357028>, accessed on October 7, 2020.
31. Global Polio Eradication Initiative. *The use of oral polio vaccine (OPV) to prevent SARS-CoV2*. Available from: <http://polioeradication.org/wp-content/uploads/2020/03/Use-of-OPV-and-COVID-20200421>, accessed on October 2, 2020.

32. Thomas SJ, Yoon IK. A review of Dengvaxia®: Development to deployment. *Hum Vaccin Immunother* 2019; 15 : 2295-314.
33. Coalition for Epidemic Preparedness Innovations. *CEPI establishes global network of laboratories to centralize assessment of COVID-19 vaccine candidates*. Available from: [https://cepi.net/news\\_cepi/cepi-establishes-global-network-of-laboratories-to-centralise-assessment-of-covid-19-vaccine-candidates/](https://cepi.net/news_cepi/cepi-establishes-global-network-of-laboratories-to-centralise-assessment-of-covid-19-vaccine-candidates/), accessed on October 3, 2020.
34. US Department of Health and Human Services. Fact Sheet, explaining Operation Warp Speed. Available from: <https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html>, accessed on October 4, 2020.
35. Govt. UK. *Government launches vaccine Taskforce to combat coronavirus*. Available from: <https://www.gov.uk/government/news/government-launches-vaccine-taskforce-to-combat-coronavirus>, accessed on October 3, 2020.
36. Serum Institute of India Pvt. Ltd. *Serum Institute of India to produce up to an additional 100 million COVID-19 vaccine doses for India and low-and middle-income countries in 2021*. Available from: [https://www.seruminstitute.com/news\\_sii\\_gavi\\_bmgf.php](https://www.seruminstitute.com/news_sii_gavi_bmgf.php), accessed on October 3, 2020.
37. World Health Organization. *The access to COVID-19 tools CACT accelerator*. Available from: <https://www.who.int/initiatives/act-accelerator>, accessed on October 4, 2020.
38. GAVI, The Vaccine Alliance. *COVAX explained*. Available from: <https://www.gavi.org/vaccineswork/covax-explained>, accessed on October 4, 2020.
39. Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: The current state of play. *Paediatr Respir Rev* 2020; 35 : 43-9.