The narrow road to a COVID-19 vaccine

Sir,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the enveloped single-stranded positive-sense RNA virus of large 30 kb genomic size belonging to Coronaviridae family. Coronaviruses had been a cause of common cold with many serotypes, no lifelong immunity to disease, no latency, and no vaccine. A recent study reported prevalence of the seasonal coronavirus at 4% in patients with respiratory illness and 10.7% of all respiratory viruses detected.[5] The most common respiratory viruses detected were rhinoviruses (range, 15.3%–46.2%), influenza viruses (13.4%–34.0%), and respiratory syncytial virus (10.1%–21.9%). In SARS 2003 outbreak in Guangdong Province, China, 87% of patients reported antibodies to SARS-CoV in their serum after recovery.[2]

There are unprecedented collaborations going on to develop safe and effective SARS-CoV-2 vaccines, however, there are certain considerations that need to be looked at critically. Coronaviruses experience a high frequency of mutation during each round of replication, including the generation of a high incidence of deletion mutations. At least 25 nonsynonymous mutations and one deletion mutation have been reported till date in the spike protein of SARS-CoV-2,[3] which is the main immunogen of SARS-CoV-2 mRNA candidate vaccine of Moderna, AZD1222 of Oxford University-AstraZeneca, and many other candidate vaccines. Different clades of SARS-CoV-2 have evolved across the globe due to ongoing genetic variations which could variably impact its stability, pathogenicity, and vaccine response. Emergence of newer clades (subtypes) is a natural process of evolution for important surface immunodominant proteins of these viruses and may not necessarily make it more pathogenic; however, prevalence of different clades may increase the capability of the virus to escape neutralization by host immune response. Therefore, induction of multiple spike proteins from different clades in upcoming vaccines will allow immune recognition of a broad spectrum of SARS-CoV-2 antigens enhancing the potency of vaccine and perhaps initiation of long-lasting immune protection.

Vaccine-induced serum IgG needs to be virus neutralizing because generation of high quantities of nonneutralizing antibodies may favor antibody-dependent enhancement of virus entry into cells resulting in enhanced COVID severity.[4] Further, the antibody titer needs to be generated in sufficient amount following vaccination.

One of the major issues that concern the vaccine development is that correlates of immune protection are not clearly understood for COVID infection. For example, the minimum accepted antibody titer following vaccination for protection from hepatitis B virus is 10 IU/L. However, for COVID-19, it is presumed that neutralizing antibodies may offer protection but may not be long lasting; at the same time, the role of T-cells in protection is yet to be clearly understood. Parenterally administered inactivated vaccines may fail to induce sufficient secretory IgA antibody response which prevents attachment of viruses to the mucosal surface of the respiratory tract. Local mucosal immune response is very important for protection from respiratory infections, and it predominantly involves secreted IgA along with cytotoxic T-cell response. T-cells support disease attenuation and protect against complications even without specific antibodies. The vaccine must be able to activate the innate arm as it strongly influences adaptive immunity and is crucial for long-lasting response after vaccination.

The time of SARS-CoV-2 vaccine availability is going to be crucial. Moderna mRNA vaccine Phase 3 trial will end in December 2020, and even if successful in protecting COVID-19, it may take few more months after December 2020 to be available outside the US. Oxford University-AstraZeneca AZD1222 has recently published the results of Phase 1/2, single-blind, randomized controlled trial. Moreover, the preliminary results demonstrated their safety as well as induction of both humoral and cell-mediated immune responses.[3] The indigenous Covaxin inactivated vaccine must also complete 3 months of Phase 1/2 and 6 months of Phase 3 trial to ensure proper safety and effectiveness, however, it could be outpaced by the pandemic. A preventive vaccine is given to individuals who are not exposed to pathogen. The much anticipated Uhambo HIV vaccine trial which was a modified version of successful Thai RV144 vaccine recently failed in South Africa. An important reason of failure was that South Africa had a new HIV infection rate at 1% in men and 4% in women compared to 0.3% in Thailand. The vaccine protection is overcome by repeated exposure to the virus.

Although there is no long-lasting immunity associated with past coronavirus diseases, the rate of re-infection or suspected reactivation of SARS-CoV-2 is reported extremely low till now. Plasma therapy from recovered COVID-19 patients is showing the encouraging result.
to critical COVID-19 patients which indicate toward development of a protective immune response following COVID-19 infection in Indian population. We must hope that in the absence of a protective vaccine, wearing a face mask and physical distancing may probably allow only subclinical antigenic exposure with full recovery to develop protective adaptive immunity among nonvulnerable population. Vulnerable population which includes people with comorbidities needs to remain more cautious and vigilant till a successful vaccination.

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Conflicts of interest

There are no conflicts of interest.

Shesh Prakash Maurya, Namrata Das¹, Hitender Gautam, Ravinder Singh, Bimal Kumar Das

Department of Microbiology and Infectious Diseases, National HIV Reference Laboratory and Immunology Laboratory, All India Institute of Medical Sciences, New Delhi, ¹Intern, Department of Medicine, Maharishi Markandeshwar Medical College and Hospital, Solan, Himachal Pradesh, India

Address for correspondence:
Dr. Bimal Kumar Das
Department of Microbiology and Infectious Diseases, National HIV Reference Laboratory and Immunology Laboratory, All India Institute of Medical Sciences, New Delhi, India.
E-mail: tezpur.bimal@gmail.com

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