International Journal of Immunology Research
www.immunologyjournal.in
Online ISSN: 2664-8873, Print ISSN: 2664-8865
Received: 10-09-2022, Accepted: 27-09-2022, Published: 14-10-2022 Volume 4, Issue 1, 2022, Page No. 9-13
DOI: https://doi.org/10.33545/26648865.2022.v4.i1a.10

Vaccines for SARS-CoV-2: How have they changed the landscape of COVID-19 pandemic

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Abstract
COVID-19 pandemic has brought about huge disruptions to our lives. COVID-19 vaccines have been developed and manufactured in a record timeframe. The use of COVID-19 vaccines has mitigated morbidity and mortality associated with COVID-19 to a large extent. This happened because these vaccines have been able to elicit immune memory and longstanding cell-mediated immunity in vaccinated individuals. Vaccine hesitancy and unequitable distribution of vaccines have been the two stumbling blocks to widespread vaccination of populations. As SARS-CoV-2 seems to enter endemic phase, there is need for vaccines administered through respiratory route, which hopefully would elicit mucosal immunity and sterilizing immunity eventually stopping interhuman transmission of the virus.

Keywords: SARS-CoV-2, COVID-19, COVID-19 vaccines, mucosal immunity, immune memory

Introduction

Coronavirus disease 2019 (COVID-19) pandemic is about to complete three years of its existence. During this period, it has not only caused enormous morbidity and mortality worldwide, it has also brought about devastating social, economic and educational disruptions.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)- the causative agent of COVID-19- is thought to have originated in horseshoe bats. It has been transmitted through yet-unknown intermediate host(s) to human beings via at least two spill-over events. This makes SARS-CoV-2 one of nearly 900 zoonotic pathogens known to have made leap from animals to human populations over millennia.

Infecting respiratory tract and causing asymptomatic infection are two crucial attributes for a pathogen to acquire pandemic potential. SARS-CoV-2 possesses both. But, even stealth viruses like SARS-CoV-2 need to overcome additional hurdles to spill over to new species. The greatest hurdle is a lock-and-key mechanism. The virus's surface antigens must be able to effectively bind host cell surface receptors to enter the cells and replicate. Minor differences in a virus surface protein's structure can prevent this "key" from unlocking the host's cellular machinery. In the case of SARS-CoV-2, the "key" is its spike protein and the "lock" is the angiotensin-converting enzyme 2 (ACE-2) receptors in humans and hundreds of other vertebrates. For coronaviruses found in bats, binding to the ACE2 receptor seems to be only major, and perhaps the only limiting factor to infectivity and transmissibility.[1] This property makes these viruses ever-present pandemic threat for human beings [2].

Different animals often have slight differences in their shared receptors. To bind them, viral proteins must undergo changes in their genetic sequence and resulting 3-dimensional structure. A few viruses, such as SARS-CoV-2, have the ability to rapidly tweak their keys to fit many locks. This ability of SARS-CoV-2 to adopt to different species and infect a large number of species has created a situation where new variants of the virus can emerge and spill back into human populations initiating a new disease dynamic [3].

Public health measure like quarantine has been able to contain the spread of SARS and MERS epidemics. Viral loads and transmissibility often peak prior to symptom-onset in case of SARS-CoV-2 infection [4]. This renders ineffective public health measures such as quarantine following illness. In the absence of an effective antiviral therapy, vaccination remains the only strategy to mitigate the ongoing SARS-CoV-2 pandemic. The rapid development of multiple COVID-19 vaccines has been a triumph of biomedical research and boon to the mankind.

Immune response to SARS-CoV-2 infection

Innate immune response constitutes the first line of defense against pathogen infection. Toll-like receptors (TLRs) sense invasion of SARS-CoV-2 into human cells and trigger innate immune response [5]. This involves secretion of type 1 interferons (IFNs), antiviral cytokines, and certain cellular responses, including neutrophils, monocytes and macrophages, dendritic cells and natural killer cells [6]. When the type 1 IFN response to infection with SARS-CoV-2 is early and robust, the viral load is quickly controlled, resulting in mild disease [7]. This is followed by normal-level T cell and B cell responses. This mostly occurs in young, healthy individuals

and after low-dose exposure. Betacoronavirus like SARS-CoV-2 possess multiple mechanisms targeting various innate immune components to evade host innate immune response. Sometimes host factors like genetic mutations in type 1 IFN pathways or development of immune-modulating autoreactive antibodies that antagonize IFN can lead to deficient innate immune response [2, 5]. Failure of timely and appropriate innate immune activation in such situations leads to robust viral propagation and this is directly associated with disease severity and mortality. These findings suggest that differences in transmissibility and disease severity between individual SARS-CoV-2 variants may be caused besides due to the mutations found in the spike protein, by their differential ability to manipulate the innate immune response [2].

Adaptive immune responses, second line of defense against viruses, involve antigen-specific recognition of viral epitopes. Humoral immunity to SARS-CoV-2 includes antibodies that bind the SARS-CoV-2 spike protein and either neutralize the virus or eliminate it through various effector mechanisms [8, 9]. Cellular immunity to SARS-CoV-2 includes virus-specific B cells and T cells, which provide long-term immunologic memory and rapidly expand on reexpoure to antigen. B cells produce antibodies, CD8+ T cells directly eliminate virally infected cells, and CD4+ cells provide help to support the immune responses. Humoral and cellular immune responses function in concert [10].

COVID-19 vaccines

Decades of basic research conducted during attempts to develop vaccines against SARS-CoV and MERS-CoV helped identify SARS-CoV-2 spike protein as antigenic target for vaccine development at a very early stage. This led to development and deployment of highly effective vaccines against SARS-CoV-2 within a year of the public reporting of its nucleotide sequence. The World Health Organization reported that more than 300 COVID-19 vaccines were in preclinical or clinical development as of May 6, 2022 [10]. The WHO has so far approved ten COVID-19 vaccines for global use [10]. These vaccines belong to four distinct vaccine platforms: inactivated virus vaccines (Sinopharm's Covilo, Sinovac's Coronavac, & Bharat Biotech's Covaxin), messenger RNA (mRNA) vaccines (Moderna's spikevax mRNA-1273 & Pfizer-BioNTech's Comirnaty BNT162b2), adenovirus vector-based vaccines (AstraZeneca's Vaxzevria & Covishield ChAdOx1 and Johnson & Johnson-Janssen's Ad26.COV2.S) and adjuvanted protein vaccines (Novavax's Nuvaxovid & Covovax NVX-CoV2373). mRNA vaccines have been used most widely in the United States and Europe. Their use in developing countries has been relatively limited mainly because of high cost, the need for frozen storage and distribution and business priorities of the pharmaceutical companies manufacturing these vaccines. The adenovirus vector-based vaccines offer the practical advantages of high stability with normal refrigeration and lower cost. As a result, they have been used more extensively in developing countries.

COVID-19 vaccination campaign has once again exposed the global health inequalities. In developed countries and in developing countries like India which were able to generate their own vaccine manufacturing capability, the coverage of fully vaccinated population has exceeded 70%, while in Africa, less than 15% of population has received full vaccination. It has been estimated that global COVID-19 vaccination saved approximately 20 million lives during the first year of the vaccine roll out [11]. A more equitable vaccine roll out that achieved the WHO target of 40% vaccination coverage in developing countries in 2021 would have saved 600,000 additional lives [11].

The Food and Drug Administration and the Centers for Disease Control have recently restricted the use of Ad26.COV2.S in the United States because of the rare but serious occurrence of vaccine-induced immune thrombotic thrombocytopenia (VITT). VITT has also been reported in Europe with ChAdOx1, at a rate of 13 to 39 cases per million vaccinated persons [12]. There is considerable geographical variation with regards to the reported incidence, with very few cases reported in non-European countries, despite extensive use of this vaccine in these countries [13]. Myocarditis and pericarditis have been reported as complications with mRNA vaccines, at a rate of 52-137 cases per million vaccinated adolescent boys and young men after the second dose. It is important to note that both thrombosis and myocarditis occur far more frequently after COVID-19 infection than after COVID-19 vaccination [10].

Vaccine performance and durability

The mRNA vaccines induce outstanding short-term neutralizing antibody (nAb) responses and protective efficacy. However, the high titer of nAb wanes after a few months, whereas Ad26.COV2.S induces lower initial antibody responses with greater durability [10]. Based on the phase 3 trials, primary vaccination with the ChAdOx1 vaccine has an efficacy of 72% against symptomatic SARS-CoV-2 infection with longer dose intervals within the 4-12 week range are associated with greater vaccine efficacy [13]. Studies of antibodies following primary immunization with ChAdOx1 vaccine against variants of concern (VOC) Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) show that neutralizing activity is variably lower than against the ancestral strain [14-16]. A test-negative, case-control study done in India during the surge in SARS-CoV-2 infections between April and May, 2021 suggested that two doses of the ChAdOx1 vaccine provide modest protection (63.1%) against infection with the SARS-CoV-2 Delta variant and high levels of protection (81.5%) against moderate-to-severe COVID-19 [17]. A mechanistic study was performed on 59 healthy individuals of the same cohort who had received two doses of ChAdOx1 vaccine and had no evidence of SARS-CoV-2 infection at the time of enrollment. The results of the study suggested that although infection with a VOC remained a possibility due to reduced neutralization by the vaccine-elicited antibodies that primarily prevented virus entry into host

cells, the protection against severe disease was most likely provided by durable vaccine-induced T-cell mediated immune response conferred by the vaccine [17].

Immunological memory to SARS-CoV-2 infection and COVID-19 vaccines

Immune memory forms the basis for protective immunity against a micro-organism. There are four components of immune memory- memory $CD8^+$ cells, memory $CD4^+$ cells, memory B cells (B_{Mem}) and circulating antibodies. Immune memory to SARS-Cov-2 virus can be elicited in three ways- after infection with SARS-CoV-2 (natural immunity), after COVID-19 vaccination (vaccine-induced immunity) or hybrid immunity. Hybrid immunity is the combination of infection-induced immunity and vaccine-induced immunity. It can happen when previously infected person undergoes COVID-19 vaccination or when infection (breakthrough infection) occurs in previously vaccinated individual. Hybrid immunity results in more robust protection against COVID-19 than either previous infection-immunity or vaccine-induced immunity [18, 19]. These types of antigen exposure(s)- infection-induced memory, vaccine-induced memory, and hybrid immunity- each have distinct characteristics of immune memory [20]. Although adenoviral vector vaccines initially elicit substantially lower antibody responses than mRNA vaccines, T cell memory appears to be similar in magnitude and percentage responders between the two vaccine types. The most prominent characteristic of hybrid immunity is the impressive improvement in nAb titers and the breadth of neutralization of SARS-CoV-2 variants. The other crucial advantage of both hybrid and natural immunity is the development of local tissue immunity.

Natural infection with respiratory viruses like SARS-CoV-2 induce both mucosal antibody responses (secretory immunoglobulin A- sIgA) and systemic antibody responses. The upper respiratory tract is thought to be mainly protected by sIgA, whereas the lower respiratory tract is mainly thought to be mainly protected by IgG.[21] Presence of sIgA in respiratory secretions prevents re-infection of upper respiratory mucosa with SARS-CoV-2. This is known as sterilizing immunity and this stops human-to-human transmission of the virus and promotes herd immunity. Natural infection also leads to the development of tissue-resident memory (T_{RM}) $CD8^+$ cells in the upper respiratory tract. T_{RM} are important category of T cells for protective immunity by providing immune memory in tissues in the nasal passages, oral cavity, throat, and lungs [20].

Vaccines that are administered intramuscularly or intradermally induce mainly IgG. Currently approved COVID-19 vaccines are administered intramuscularly. So, although they effectively reduce severity of disease and symptomatic cases, but they still allow for asymptomatic infection to take place.[22] In July 2021 delta variant outbreak in Provincetown, Massachusetts, genomic and epidemiologic data showed clear evidence of viral transmission between vaccinated persons [23].

Cellular immune responses are induced by both mRNA vaccines and adenovirus vector-based vaccines and have shown greater durability than serum antibody titers. It is likely that SARS-CoV-2 vaccines will continue to provide effective protection against severe disease even after nAb titers wane [10].

In immunocompromised persons, both antibody and T-cell responses to COVID-19 vaccines are reduced, the degree of reduction is dependent on the extent and type of immunosuppression [24, 25]. Additional vaccine doses and prophylactic treatment with monoclonal antibodies are recommended in them to boost their protection.

SARS-CoV-2 variants of concern and booster doses of COVID-19 vaccines

In late 2020, ancestral strain of SARS-CoV-2 suddenly transitioned into a new strain. After that, the process of emergence of new variants replacing old variants has continued. It seems the virus is slowly adapting to human host because the newer variants are more transmissible but less virulent. The latest variant dominating the pandemic is omicron ((B.1.1.529). The omicron lineage has rapidly splintered into subvariants BA.1, BA.1.1, BA.2.12.1, BA.4 and BA.5. Omicron has more than 50 mutations, including more than 30 mutations in spike protein, which has resulted in substantial escape from nAb responses elicited by vaccination or prior infection with a non-omicron variant [26]. Multiple studies have shown that nAbs induced by all primary vaccine regimens show little cross-reactivity with omicron but that boosting leads to a substantial increase in omicron nAbs. However, these increased nAb titers, as well as clinical effectiveness, have been shown to wane by 4 months after a third mRNA immunization. After a fourth mRNA immunization, protection against infection with SARS-CoV-2 omicron has been reported to wane after just 4 weeks, although protection against severe disease lasts longer.[10] In contrast to nAbs, vaccine-induced memory responses and cell-mediated immunity are long-lived and provide protection against severe disease. Boosting every 4 to 6 months to maintain high serum nAbs titers may not be a practical or desirable long-term strategy. Boosting also exposes individuals to immune-mediated side-effects of COVID-19 vaccines. Current vaccine supplies could save more lives if used in previously unvaccinated populations, than if used as boosters in vaccinated populations [27]. There is need to use booster based on robust scientific evidence and not for political reasons.

Ideally, COVID-19 vaccines should be recommended no more than annually and preferably less frequently, and a broad range of booster options should be available to the public. The use of vaccine platform with improved durability is highly desirable [10].

Future COVID-19 vaccine strategies

The expectation at the time of launch of COVID-19 vaccines was that they would halt transmission of virus. This was based on the high titer of nAbs produced and robust protective efficacy provided by mRNA vaccines at peak immunity. However, rapid waning of nAb titer and emergence of variants with high transmissibility and

significant antibody escape has necessitated recalibration of these goals. Present COVID-19 vaccines provide long-term protection against severe disease, hospitalization, and death from current and future variants. They are not able to provide substantial protection against transmission of the virus.

Future research should focus on the role of mucosal humoral and cellular immunity at the site of inoculation (upper respiratory tract), which may play a critical role in protection against SARS-CoV-2 infection [10, 22]. Sterilizing immunity after vaccination is desirable to prevent the spread of infection from vaccinee, which can be especially dangerous in hospital settings while managing frail patients. Respiratory delivery of vaccines is needed to achieve sterilizing immunity against SARS-CoV-2. At least 14 mucosal vaccines have progressed to the first phase of clinical trials as of 14 December 2021.[22] Intranasal vaccine INCOVACC (BBV154) jointly developed by University of Wisconsin-Madison, FluGen and Bharat Biotech has received emergency use approval in September 2022 by the regulatory authorities in India for use in adults above the age of 18 years.

Heterogenous prime-boost (mix-and-match) regimens, which involve combinations of different types of vaccines, are also being investigated as a strategy for improving the magnitude and durability of humoral and cellular immunity, as compared with either type of vaccine alone [28, 29].

Interim results of phase 2-3 study of bivalent omicron-containing mRNA-1273.214 booster vaccine has just been published. Compared to mRNA-1273 vaccine, this vaccine elicited higher nAb response against omicron without evident safety concerns [30].

In addition, early research on the development of pan-sabecovirus and pan-betacoronavirus vaccines is underway [10].

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