EXPERT REVIEW OF VACCINES
https://doi.org/10.1080/14760584.2022.2008245

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What are the challenges faced by COVID-19 vaccines?

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ARTICLE HISTORY Received 30 May 2021; Accepted 16 November 2021

KEYWORDS COVID-19; vaccines; T cell; adenovirus vector; lipid nanoparticle

Abbreviations: LNP: lipid nanoparticle; AdV: adenovirus vector; DCs: dendritic cells; PKR: dsRNA-dependent kinase; TLR: Toll-like receptors

The fast approval of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a result of the development of vaccine technologies in the last several years. The SARS-CoV-2 vaccines consist of mRNA, such as BNT-162b2 (Pfizer) and mRNA-1273 (Moderna), or DNA; viral vectors, including Ad26.COV2.S (Johnson & Johnson) and ChAdOx1 (AstraZeneca); lipid nanoparticles (LNPs). The majority of COVID-19 vaccines are intended to elicit immunological responses, preferably neutralizing antibodies (NAbs), against the SARS-CoV-2 spike protein (S protein). Several vaccines, including mRNA, adenoviral-vectored, protein subunit, and whole-cell inactivated virus vaccines, have shown effectiveness in phase III studies and have been granted emergency authorization in countries [1]. Clinical trials showed that mRNA vaccines from Pfizer/BioNTech and Moderna have a 20% higher efficiency compared with adenovirus vector (AdV) vaccines from ChAdOx1 [2]. As shown by blood assessment at 2–4 weeks after inoculation, both vaccination types produce substantial NAb titers and virus-specific T cell responses. These trials, which included over 100,000 participants, provide convincing evidence for the expeditious and extensive immunization of the world population [3]. In addition, recent clinical research with 30,420 volunteers revealed that the mRNA-1273 vaccine prevents COVID-19 illnesses, including severe disease, with 94.1% efficacy [4]. Nevertheless, the mRNA vaccine platform is a recently approved formulation during the crisis of COVID-19. Hence, we still need to learn how these vaccines activate the immune system, how long their effect lasts, and how to improve them to defend against new strains and mutant variants. Vaccines contain pathogen-specific immunogens that promote adaptive immunity and T cell activation and function as an appropriate adjuvant to activate the innate immunity, with T cell activation serving as an important second signal. A proper adjuvant stimulates the innate immunity without causing systemic inflammation that can have serious consequences. mRNA and AdV vaccines have intrinsic adjuvant properties to avoid acute side effects [4]. Mechanistically, RNA (single-stranded or double-stranded RNA [dsRNA]) is a perfect example of the two immunogens; it can carry several proteins with different encoding regions simultaneously and stimulate innate immune response through a number of cytosolic and endosomal innate sensors upon entry into cells. Several inflammasomes, such as dsRNA-dependent kinase, nucleotide-binding oligomerization domain 2, melanoma differentiation-associated gene 5, and retinoic acid-inducible gene I, can bind with RNA and stimulate inflammatory mediators. A valuable RNA vaccine undergoes mutation to reduce type I interferon (IFN) and minimize binding to Toll-like receptors (TLRs; i.e. TLR3/7). The LNP is used to allocate mRNA to dendritic cells (DCs) and stimulate an adaptive immune response by T cells [4]. By comparison, AdV vaccines consist of virus particles and can induce macrophages and DCs to reduce type I IFN through the binding of AdV to TLR9. Both types of vaccines stimulate type I IFN with different TLRs. These mechanisms may work against the new mutant variants of SARS-CoV-2 because in SARS-CoV-2 infection, the production of IFN-I is significantly inhibited, which can impede the adaptive immune response and worsen inflammatory illness in the later stages of infection. Type I IFN can improve the memory, survival, and differentiation of the B and T cells produced in the initial dosage. These data suggest that the inflammation associated with both vaccinations may help in the development and maintenance of short- to medium-term immunological memory [5]. For several months, both vaccinations create NAbs and S protein IgG. Furthermore, they exhibit a strong T helper (TH) 1 response and a low TH2 response. However, the related evidence is still lacking. This resistance will almost certainly be sufficient to halt the spread of SARS-CoV-2. Variants with increased transmissibility have evolved in the United Kingdom (B.1.1.7), South Africa (B.1.351), Brazil (B.1.1.248), and elsewhere, showing changes in the S protein, including the SARS-CoV-2 spike N-terminal domain and the receptor-binding motif of the Receptor Binding Domain (RBD) [6]. Notably, the results of human sera immunized with Pfizer-BioNTech (BNT162b2) mRNA vaccine against mutations E484K and N501Y are available, and they reveal an unexpectedly low immunization rate. How the immune system loses function in situations with a single mutation, especially the B cell, is unknown. The same event occurs when immune plasma with

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B.1.351 and B.1.1.7 variations is used. The B.1.351 has 11 mutations, whereas B.1.1.248 has 15 mutations, and both have E484K and N501Y mutations in common. The B.1.1.248 stimulates immunological neutralization more effectively than B.1.351 [7]. RNA and AdV vaccines stimulate CD8+ and CD4 + T cells, which produce cytotoxic and inflammatory mediators, and stimulate the reformation of B cells to plasma cells to produce antibodies. The gap between the first and second doses of both vaccines is 3–4 weeks. Both vaccinations have common adverse effects, such as intermittent fever, chills, and injection site pain, which can be relieved with the second dosage. Small alterations to innate cells, such as macrophages, increase the inflammatory response called 'trained or qualified immunity.' In addition, as of 11 June 2021, about 40.6 cases of myocarditis per million-second doses among males and 4.2 cases per million among females have been recorded in persons 12–29 years old who obtained mRNA COVID-19 vaccinations, according to data in the US Vaccine Adverse Events Reporting System. Nonetheless, following reports of heart inflammation cases caused by myocarditis and pericarditis after the vaccination with COVID-19 Pfizer and Moderna shots, the World Health Organization experts confirmed that the benefits of the vaccines continue to outweigh the risks in terms of reducing hospitalizations and deaths due to infection.

The global spread of S-protein variants of SARS-CoV-2 may be efficiently hampered by vaccines. In this regard, unvaccinated and carrier people and other susceptible transition organisms may carry the virus. Thus, updating the vaccine with a new and seasonal or predictive variants every 6 months will be beneficial to stop the spread of SARS-CoV-2 [7,8]. Antibody testing for sick and vaccinated persons is necessary, especially in the case of SARS-CoV-2 variants. Moreover, models and assays may be used to undertake a SARS-CoV-2 prophylactic test, and growth intervention can be accomplished by altering current techniques. Remarkably, despite the high accuracy of the measurement of immune pathway interaction in animal models and tests *in vivo* or *in vitro*, human infection may still not be entirely replicated. This issue may arise despite the extremely legitimate and sophisticated experimental techniques, resulting in incorrect recommendations for determining priorities in human immunological interaction routes. Safety connections must be identified in clinical cohorts. However, until such a moment, our current technique must concentrate on forecasts and making assumptions based on other viral infections.

Vaccination is more likely to provide protection than spontaneous infection [9]. Following the first immunization, there was a rise in interleukin-15, interferon gamma and C–X–C motif chemokine 10 (CXCL10) also known as interferon γ-induced protein 10 kDa (IP-10), which were enriched by tumor necrosis factor alpha and interleukin-6 after the second vaccination [10]. Vaccinated individuals need to have a record of the vaccines they have received (i.e. sequence, carrier, and mutation) because it is an important part of their health history. This record will be important for future evaluation and avoids any prospective risks. Besides, the second timely vaccination of BNT162b2 mRNA is critical, especially in the elderly population [11]. Furthermore, both males and females who received the Pfizer vaccination had considerably quicker viral suppression at day-22 than those who received the AZD1222 adenovirus vector (AstraZeneca-AZ) vaccine [12]. Clinically, Following SARS-CoV-2 immunization, multiple myeloma patients show a poor humoral response, particularly when treated with anti-CD38 or belamaf. This highlights the need of early immunization, potentially during a treatment-free period, as well as continued attention on infection control measures in non-responders [13]. The number of SARS-CoV-2 vaccines is expected to increase by the end of this year, and numerous countries may start the administration of different vaccines from various companies. Variations in vaccine response may be observed from the huge number of people who will receive vaccination, and several may fail to produce antibodies [14]. The mRNA vaccines are easy to modify, rapidly synthesized, and suitable for repeat dose compared with AdV vaccines. Nevertheless, the LNP carrier of mRNA and the vector of AdV may cause unexpected side effects. Consequently, several challenges may be introduced based on previous reasons, including the restricted number of doses due to side effects. Further, given the wide first-pass effect of nanomaterials after systemic distribution, inhalation administration methods are a potential option, particularly for treating illnesses other than those of the liver. Hence, a new vaccine that can be taken through inhalation and can stimulate tissue-resident memory T cells in the lung, which are formed at the initial infection, may be produced using mRNA vaccines because they can self-replicate (imitate viral replication) [15]. Such changes in vaccine formulation and distribution route can be used to tailor vaccines for people with different immune responses. This approach may strengthen our immune systems to face the COVID-19 pandemic and other prospective pandemics in the future.

Funding

This work was supported by Shandong Provincial Key Research and Development Program (Major Scientific and Technological Innovation Project) (2019JZZY021013) Shandong Provincial Key Research and Development Program (2019GSF108080), Funds for Youth Interdisciplinary and Innovation Research Groups of Shandong University (2020QNQT003) and Shandong University postdoctoral fellowship to Mohnad Abdalla.

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

A reviewer on this manuscript has disclosed that they have served as an investigator at Penn State Health for ACTT 1-4 (NIAID sponsored) and ACTIV-5-BET (NIH sponsored) for work not directly related to this manuscript. They also serve as a consultant for Axle Informatics for work not directly related to this manuscript. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

Author contributions

MA wrote the manuscript and designed the study, AAE and XJ contributed to manuscript revision. All authors approved the final version.

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