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Adverse Effects of COVID-19 Vaccines in Immune Activation Mechanism

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ABOUT THE STUDY

The worldwide SARS-CoV-2 pandemic has resulted in significant loss of life, severe disruption of lives and livelihoods, and widespread economic, sociological, and psychological damage. The most serious threat from infection is severe COVID-19, which causes Acute Respiratory Distress Syndrome (ARDS), multi-organ failure, and death, but long-term sequelae from mild disease have also been reported. For the past year and counting, the high transmissibility, presence of asymptomatic carriers, and emergence of new variants have had a long-term impact on the global population. Vaccination is the most promising path back to "normal life"; here, we discuss how newly approved vaccines can mobilize innate and adaptive immune responses, the implications for their durability, and current and future challenges for population protection. Vaccine formulations approved Significant advances in cutting-edge vaccine technologies over the last decade have resulted in the approval of two main types of SARS-CoV-2 vaccines for emergency use, an unprecedented achievement in modern medical science. Pfizer and Moderna's approved vaccines use mRNA technology and Lipid Nanoparticle (LNP) delivery systems, whereas AstraZeneca, Johnson and Johnson, and Gam-COVID-vac (Sputnik V) use DNA delivered within non-replicating recombinant Adenovirus (AdV) vector systems. Both the mRNA and Adv vaccines encode the production of the SARS-CoV-2 spike (S) protein, which is the primary target for neutralizing antibodies produced during natural infection as well as therapeutic monoclonal antibodies. To date, phase III clinical trial results have shown that both the Pfizer/BioNTech (BNT162b2) and Moderna (mRNA1273) mRNA vaccines achieved 90%-95% efficacy in protecting against COVID-19, while the AdV vaccines (ChAdOx1 nCoV-19) and Gam-COVID-vac (Sputnik V) showed slightly lower efficacy (average 70% and 91%, respectively). As measured in blood 2-4 weeks after inoculation, both vaccine types produce significant neutralizing antibody and virus-specific T cell responses. These trials, which included over 100,000 participants, provide compelling justification for prompt and widespread vaccination of the global population. While the Adv vaccine platform has been approved for Ebola, the mRNA vaccine platform is a brand-new formulation.

As a result, we still have a lot to learn about how these vaccines mobilize the immune response, how long they last, and how to improve them to protect against new variants, strains, and disease manifestations. To stimulate adaptive immunity, a vaccine must contain a pathogen specific immunogenic as well as an adjuvant, which stimulates the innate immune system and provides the necessary second signal for T cell activation. An ideal adjuvant stimulates innate immunity without causing systemic inflammation, which could have serious consequences. Because of the intrinsic immune stimulatory properties of RNA, mRNA vaccines can serve as both immunogenic (encoding the viral protein) and adjuvant. Single-stranded RNA (ssRNA) and Double-stranded RNA (dsRNA) are recognized by various endosomal and cytosolic innate sensors upon entry into cells, where they play an important role in the innate immune response to viruses. Endosomal Toll-like receptors (TLR3 and TLR7) bind to ssRNA in the endosome, whereas inflammasome components like MDA5, RIG-I, NOD2, and PKR bind to ssRNA and dsRNA in the cytosol, resulting in cellular activation and the production of type I interferon and other inflammatory mediators. Current vaccines contain purified, *in vitro*-transcribed single-stranded mRNA with modified nucleotides to reduce binding to TLR and immune sensors, limiting type I interferon production and its inhibitory function on cellular translation. The LNP carrier protects the mRNA further, allows for lymphatic delivery, and promotes protein translation in Lymph Nodes (LNs). When the LNP enters the LN, it is engulfed by Dendritic Cells (DCs), which then produce and present the antigen to T cells, activating the adaptive immune response.

Preclinical and early human trial results show that both vaccines generate anti-S protein IgG and virus-specific neutralizing antibody responses for several months after vaccination, though T cell data is still being analyzed. This short-term persistence is likely sufficient to halt the spread of SARS-CoV-2 and start the path back to normalcy. However, the global spread of SARS-

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CoV-2, as well as the emergence of S protein variants, may limit vaccine efficacy.

SARS-CoV-2 eradication may be difficult due to reservoirs in unvaccinated individuals and/or other animal species. New vaccine formulations containing the variant S sequences and additional SARS-CoV-2 proteins could be developed, and annual or semi-annual SARS-CoV-2 vaccines could be administered for persistent strains and/or seasonal variants. The mRNA vaccine formulation is ideal for repeat or modified vaccination because different mRNAs containing mutant S proteins can be rapidly synthesized and included within the LNP carrier. In contrast, the Adv vector formulation generates Adv-specific immunity, which can limit the efficacy of repeated boosters due to immune-mediated vector clearance.

The unprecedented mass and simultaneous vaccination of the world's population will undoubtedly reveal heterogeneity in vaccination responses, with some individuals failing to produce robust antibody responses or being protected. Tissue-Resident Memory (TRM) cells, which are established in the lung during the initial infection and retained as non-circulating populations that mediate protective responses *in situ* upon viral re-challenge, can mediate immunity to respiratory viruses. TRM cells can be produced through site-specific vaccination with attenuated viral vaccine formulations. It would be interesting to see if intranasal delivery of mRNA vaccines can promote TRM cells and lung protection. Self-replicating mRNA vaccines (which mimic viral replication) may also boost protective T cell immunity.

Such alterations in formulation and delivery route could be used to optimize the vaccines according to immune status and age. In conclusion, the SARS-CoV-2 pandemic has accelerated the licensing of promising vaccine formulations that provide hope for fortifying our immune systems against the current and future emerging pandemics. Such formulation and delivery route changes could be used to optimize vaccines based on immune status and age. Finally, the SARS-CoV-2 pandemic has accelerated the approval of promising vaccine formulations, providing hope for fortifying our immune systems against current and future emerging pandemics.