JAMA Insights

SARS-CoV-2 Vaccines

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Shortly after SARS-CoV emerged at the turn of the 21st century, the spike (S) protein (particularly in its prefusion [native] conformation) was identified as the immunodominant antigen of the virus.[1] Evaluation of patients with SARS-CoV-2 revealed that binding and neutralizing antibodies primarily target the receptor-binding domain of the S1 subunit.[2] Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response to SARS-CoV-2. The characteristics of this response would include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease (vaccine-induced response that led to paradoxically increased disease severity on viral challenge).[3]

Viewpoint

Multimedia

Several vaccine designs were evaluated by different groups during the development of a SARS-CoV-2 vaccine. The SARS-CoV-2 vaccines currently authorized for use, and others that have late-stage clinical data available, are summarized in the **Table**.

Inactivated and Protein Subunit Vaccines

One approach for vaccine development is creation of inactivated vaccines derived from virus grown in culture and then chemically inactivated, which may deliver stably expressed, conformationally native antigenic epitopes. Sinopharm and Sinovac are among the manufacturers farthest along in development of this type of vaccine, which have been evaluated by phase 3 trials that have attained international authorizations for use.

Another approach to vaccine development is delivery of the S protein as a recombinant protein subunit within one of several cell-based systems that support protein expression. This approach can protect immunized animals in vivo but has the theoretic risk of generating a polarized (T_H2 over T_H1) immune response that can be overcome, depending on the adjuvant used.[4] Novavax, using the saponin-based Matrix-M adjuvant, recently reported on its late-phase clinical trials in the UK, demonstrating vaccine efficacy against COVID-19 of 89%.[5] More than 60% of vaccines currently in development use a protein subunit approach, although none are authorized for use.

Viral Vector Vaccines

Viral vector vaccines use replication-deficient viruses engineered to express the genetic sequence of the antigen of interest in host cells. Replication-incompetent adenoviruses have been developed for HIV, tuberculosis, malaria, and Ebola virus.[6] This vaccination approach has had variable success, often limited by preexisting immunity to the adenovirus vector.[7] Using adenoviruses that have minimal preexisting immunity in the US and Europe, 2 vaccines have shown early promise: adenovirus serotype 26 vector vaccine (Ad26.CoV2.S; Johnson & Johnson) and chimpanzee adenovirus vector vaccine (ChAdOx; AstraZeneca). Both appear efficacious in preventing COVID-19–related hospitalization and death, but have varying efficacy in preventing clinical disease, particularly disease caused by the novel SARS-CoV-2 variants.

mRNA Vaccines

New advancements harnessing mRNA for vaccine delivery have the potential to greatly improve vaccine development for many pathogens. In these vaccines, lipid nanoparticles are used to protect the prefusion-stabilized S protein–encoding mRNA en route to the intracellular space. The host uses the mRNA to make the target protein (S protein in this case), which induces a coordinated immune response. Pfizer-BioNTech and Moderna have developed mRNA-based vaccines that demonstrate more than 90% efficacy against SARS-CoV-2 clinical disease in clinical trials. This high vaccine efficacy is associated with very few adverse events, although local and systemic reactogenicity to vaccine are common. There are many advantages to this approach, including speed of vaccine manufacturing (weeks) and ability to generate a T_H1 and T_H2 response. Studies are underway or planned to assess the efficacy of currently authorized vaccines in children and against common SARS-CoV-2 variants, and to assess whether repeat vaccinations containing mRNA coding for the variants can be effective.

Vaccines Are Available, What Next?

Once vaccines became available, barriers to administration included insufficient initial supply, vaccine delivery inefficiencies, and widespread vaccine hesitancy. These barriers limited the ability to vaccinate enough of the population to reach some measure of population immunity. Outside of the US, low- and middle-income countries have struggled to obtain even a minimum number of vaccine doses.

The slower-than-hoped-for vaccine rollout raises 2 important public health questions. The first is whether it is preferable to ensure maximal coverage by vaccinating as many people as possible with 1 dose (of the 2-dose vaccines) or to ensure maximal protection by strategically reserving doses to be used for the second dose. Based on the US Food and Drug Administration briefing materials submitted for Emergency Use Authorization, the Moderna vaccine is upwards of 80% efficacious 2 weeks after the first dose and the Pfizer-BioNTech vaccine is at least greater than 50% efficacious after the first dose. Second, optimizing vaccination strategies in people previously infected with SARS-CoV-2 offers another opportunity for dose sparing. A single dose of an mRNA vaccine might quickly and robustly boost a previously primed immune response following natural disease.

Vaccination is the most important strategy to end the pandemic. However, emergence of multiple SARS-CoV-2 variants with reduced susceptibility to disease- and vaccine-induced immunity threatens progress. Despite these ongoing threats, the efficacy of SARS-CoV-2 vaccines provides a real measure of hope for 2021.

Table. SARS-CoV-2 Vaccines

Vaccine	Manufacturer	Vaccine type	Antigen	Dose	Dosage	Storage conditions	Efficacy against severe COVID-19[a]	Overall efficacy	Current approvals
mRNA-1273	Moderna (US)	mRNA	Full-length spike (S) protein with proline substitutions	100 µg	2 Doses 28 d apart	−25° to −15 °C; 2-8 °C for 30 d; room temperature ≤12 h	100% 14 d After second dose (95% CI, not estimable to 1.00)	92.1% 14 d After 1 dose (95% CI, 68.8%-99.1%); 94.1% 14 d after second dose (95% CI, 89.3%-96.8%)	EUA: the US, EU, and UK
BNT162b2	Pfizer-BioNTech (US)	mRNA	Full-length S protein with proline substitutions	30 µg	2 Doses 21 d apart	−80° to −60 °C; 2-8 °C for 5 d; room temperature ≤2 h	88.9% After 1 dose (95% CI, 20.1%-99.7%)	52% After 1 dose (95% CI, 29.5%-68.4%); 94.6% 7 d after second dose (95% CI, 89.9%-97.3%)	EUA: the US, EU, and UK
Ad26.CoV2.S	Johnson & Johnson (US)	Viral vector	Recombinant, replication-incompetent human adenovirus serotype 26 vector encoding a full-length, stabilized SARS-CoV-2 S protein	5×10^{10} Viral particles	1 Dose	−20 °C; 2-8 °C for 3 mo	85% After 28 d; 100% after 49 d	72% in the US; 66% in Latin America; 57% in South Africa (at 28 d)	EUA process initiated in the US
ChAdOx1 (AZS1222)	AstraZeneca/ Oxford (UK)	Viral vector	Replication-deficient chimpanzee adenoviral vector with the SARS-CoV-2 S protein	5×10^{10} Viral particles (standard dose)	2 Doses 28 d apart (intervals >12 wk studied)	2-8 °C for 6 mo	100% 21 d After first dose	64.1% After 1 dose (95% CI, 50.5%-73.9%); 70.4% 14 d after second dose (95% CI, 54.8%-80.6%)	EUA: WHO/Covax, the UK, India, and Mexico
NVX-CoV2373	Novavax, Inc (US)	Protein subunit	Recombinant full-length, prefusion S protein	5 µg of protein and 50 µg of Matrix-M adjuvant	2 Doses	2-8 °C for 6 mo	Unknown	89.3% in the UK after 2 doses (95% CI, 75.2%-95.4%); 60% in South Africa (95% CI, 19.9%-80.1%)	EUA application planned
CVnCoV	CureVac/ GlaxoSmithKline (Germany)	mRNA	Prefusion stabilized full-length S protein of the SARS-CoV-2 virus	12 µg	2 Doses 28 d apart	2-8 °C for 3 mo; room temperature for 24 h	Unknown	Phase 3 trial ongoing	
Gam-COVID-Vac (Sputnik V)	Gamaleya National Research Center for Epidemiology and Microbiology (Russia)	Viral vector	Full-length SARS-CoV-2 glycoprotein S carried by adenoviral vectors	10^{11} Viral particles per dose for each recombinant adenovirus	2 Doses (first, rAd26; second, rAd5) 21 d apart	−18 °C (Liquid form); 2-8 °C (freeze dried) for up to 6 mo	100% 21 d After first dose (95% CI, 94.4%-100%)	87.6% 14 d After first dose (95% CI, 81.1%-91.8%); 91.1% 7 d after second dose (95% CI, 83.8%-95.1%)	EUA: Russia, Belarus, Argentina, Serbia, UAE, Algeria, Palestine, and Egypt
CoronaVac	Sinovac Biotech (China)	Inactivated virus	Inactivated CN02 strain of SARS-CoV-2 created from Vero cells	3 µg With aluminum hydroxide adjuvant	2 Doses 14 d apart	2-8 °C; Lifespan unknown	Unknown	Phase 3 data not published; reported efficacy 14 d after dose 2: 50.38% (mild) and 78% (mild to severe) in Brazil, 65% in Indonesia, and 91.25% in Turkey	EUA: China, Brazil, Columbia, Bolivia, Brazil, Chile, Uruguay, Turkey, Indonesia, and Azerbaijan
BBIBP-CorV	Sinopharm 1/2 (China)	Inactivated virus	Inactivated HB02 strain of SARS-CoV-2 created from Vero cells	4 µg With aluminum hydroxide adjuvant	2 Doses 21 d apart	2-8 °C; Lifespan unknown	Unknown	Phase 3 data not published; unpublished reports of 79% and 86% efficacy	EUA: China, UAE, Bahrain, Serbia, Peru, and Zimbabwe

Abbreviations: EUA, Emergency Use Authorization; UAE, United Arab Emirates; WHO, World Health Organization.

[a] Efficacy against severe disease, which includes COVID-19–related hospitalization, varies by age and by time after vaccination.

ARTICLE INFORMATION

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Published Online: February 26, 2021. doi:10.1001/jama.2021.3199

Conflict of Interest Disclosures: Dr Creech reported receiving personal fees from Altimmune for vaccine development and from Horizon for care of children with chronic granulomatous disease; grants from Merck for *Clostridioides difficile* treatment and from GlaxoSmithKline for *Staphylococcus aureus* vaccine development; and personal fees from Premier Healthcare for vaccine education, Astellas for serving on a vaccine study data and safety monitoring board, Karius Diagnostics, and Vir Biotechnology for monoclonal antibody development outside the submitted work. No other disclosures were reported.

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