

An Update on the Leading COVID-19 Vaccines

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Abstract

We reviewed the COVID-19 vaccines that reached phase III of clinical development. For each of the 10 vaccines identified, we described the technology used for vaccine development, the available data from phase III clinical trials, data on vaccine safety, and the role of new SARS-CoV-2 variants on vaccine efficacy.

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Introduction

There are exceptional ongoing efforts to develop effective vaccines against SARS-CoV-2 with the goal to control the current COVID-19 pandemic. According to the World Health organization, as of March 1, 2021, there are 182 vaccines in preclinical development and 74 vaccines in different phases of clinical development.[1] We performed a literature review with the objective to evaluate vaccine efficacy, safety and technology of the COVID-19 vaccines that have reached phase III of clinical development.

Methods

Vaccines that reached phase III of clinical development

COVID-19 vaccines that had reached phase III of clinical development were identified. These vaccines were classified in two groups: the vaccines that completed phase III studies (no longer recruiting participants), and the vaccines in ongoing phase III studies (still recruiting participants). These groups were further classified according to the quality of the data currently available to review the efficacy and safety of each vaccine. Priority was given to data obtained from studies published in peer-reviewed journals, followed by data obtained from press release documents.

Vaccine technology

For each of the vaccines that reached phase III clinical trials, the technology used for the development of the vaccine was identified. These technologies fall into two categories: protein-based vaccines, used to inject participants with SARS-CoV-2 proteins, and gene-based vaccines, used to inject participants with SARS-CoV-2 genetic material.

Vaccine phase III clinical trial data

The data from phase III clinical trials were summarized for vaccines with data available from peer-reviewed publications and vaccines with only press-released data. The vaccines were ordered according to the number of COVID-19 cases used to calculate their efficacy, prioritizing studies with a greater number of COVID-19 cases. We also evaluated the generalizability of their respective study data, as determined by the number of study subjects and the number of countries participating in the trial.

Vaccine safety data

Data concerning the safety of the vaccines was obtained from peer-reviewed publications as well as press release documents.

Vaccine efficacy and SARS-CoV-2 variants

A review of peer-reviewed publications was performed to evaluate vaccine efficacy in relation to emergent SARS-CoV-2 variants.

Results

Vaccines that reached phase III of clinical development

We identified 10 vaccines that reached phase III of clinical development. The classification of these 10 vaccines according to phase III clinical trial status—completed or ongoing—and availability of clinical trial data is depicted in **Figure 1**.

Vaccine Technology

The technology used in the development of these 10 vaccines is depicted in **Figure 2**. Four vaccines used a protein-based technology, and six vaccines used gene-based technology.

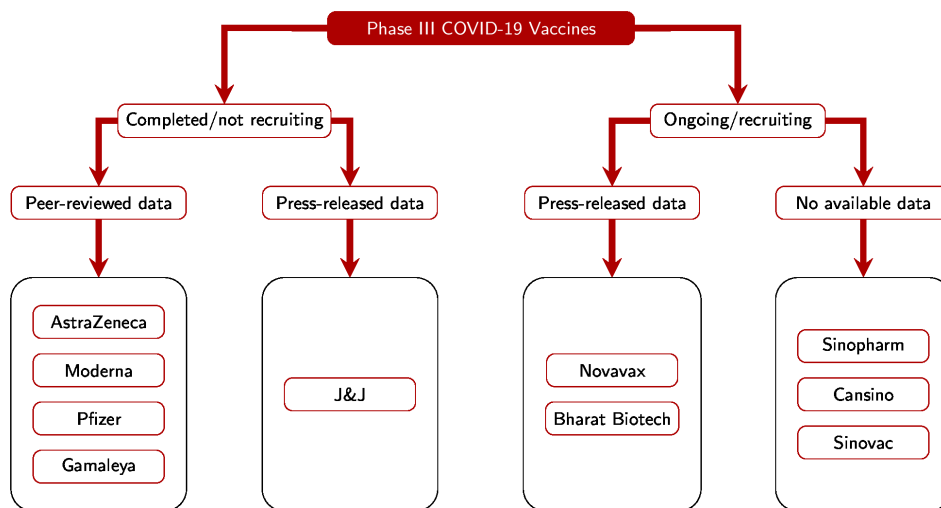


Figure 1. Vaccines that reached phase III of clinical development.

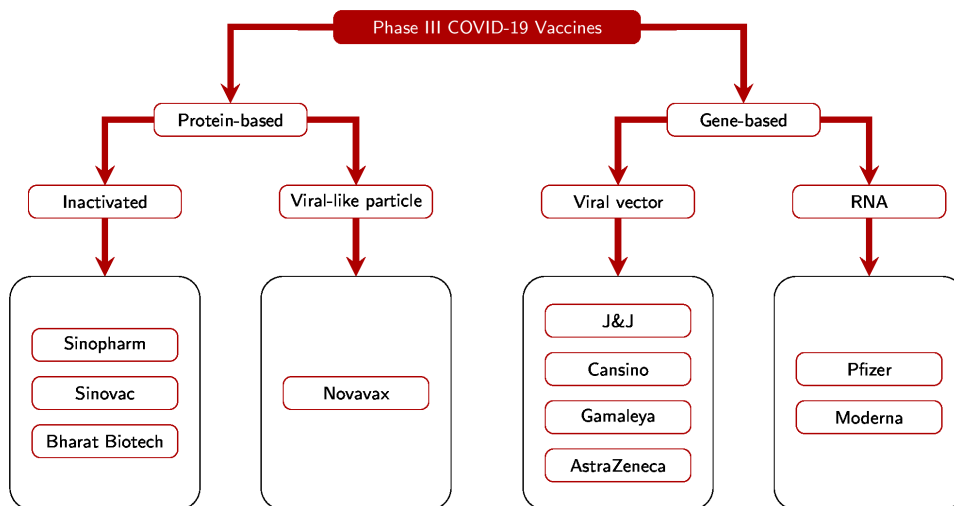


Figure 2. Phase III vaccines categorized by technology.

Table 1. Vaccines with peer-reviewed data.

Vaccine	Type	Participants			COVID-19 Cases	Efficacy (95% CI)	Phase III Trial Site	No. of doses (days apart)
		Enrolled	Vaccine	Placebo				
Mod-NIH	RNA	30,420	15,210	15,210	196	94.1 (89.3–96.8)	USA	2 (28)
Pfi-BNT	RNA	43,448	21,720	21,728	170	94.6 (89.9–97.3)	USA, Germany, Turkey, South Africa, Brazil, Argentina	2 (21)
Oxf-Ast	Viral vector	23,848	12,082	11,766	131	70.4 (54.8–80.6)	UK, South Africa, Brazil	2 (28)
Gamaleya	Viral vector	21,977	16,501	5,476	78	91.6 (85.6–95.2)	Russia	2 (21)

MOD-NIH: mRNA-1273, developed by Moderna and the National Institutes of Health.[2]

Pfi-BNT: BNT162b2, developed by Pfizer and BioNTech.[3]

Oxf-Ast: Covishield/ChAdOx1 nCoV-19 (AZD1222), developed by Oxford University and AstraZeneca.[4,5]

Gamaleya: Sputnik V/Gam-COVID-Vac, developed by the Gammaleya Research Institute.[6,7]

Vaccine phase III clinical trial data

Four vaccines have completed phase III clinical trials with data available in peer-reviewed journals. Our review of the data from these clinical trials in relation to vaccine efficacy, number of trial participants, number of cases of COVID-19, and location of trial sites is described in **Table 1**. We identified three vaccines with phase III clinical trial data from press release documents. The review of the available data for these vaccines is described in **Table 2**.

Vaccine safety data

Some recipients of the vaccines under discussion have reported mild to moderate adverse events. Local adverse events include pain at injection site, erythema, pruritus and lymphadenopathy. Systemic adverse events include fatigue, headache, fever, chills, nausea and vomiting. The Pfizer vaccine was associated with four cases of severe adverse events, including shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia.[3] Initially, three cases of transverse myelitis (TM) and one case of multiple sclerosis (MS) were associated with Oxford-AstraZeneca vaccine, in response to which, the study was placed on temporary hold for careful independent review of each case.[2] It was determined that only 1 case of TM in the vaccine group was a vaccine-related adverse event, while the remaining 2 cases of TM—one in the vaccine group, the other in placebo group—were unrelated to the vaccine.[2] Further independent investigation revealed that the patient in the vaccine group who developed MS 10 days after receiving the first dose had pre-existing, underlying, unrecognized MS; thus, this case was also found to be unrelated to the vaccine.[2]

Pfizer/BioNTech reported six deaths during their study, two from the vaccine group and four from the placebo group. However, the investigators concluded that these deaths were not related to the vaccine or to the placebo.[3] Gamaleya investigators reported three deaths during the study, but none of these was reported to be associated with the vaccine.[6] Johnson & Johnson also reported three deaths that were not related to the study.[8] Oxford-AstraZeneca reported five deaths, one in the vaccine group and four in the placebo group.[4] The death in the vaccine group was deemed unrelated to the vaccine or to COVID-19, while in the placebo group, there was one death due to severe COVID-19 leading to hospitalization 21 days after the first placebo dose. The remaining three deaths in the placebo group were unrelated to COVID-19 or to the vaccine.[4]

Vaccine efficacy and SARS-CoV-2 variants

Data on the potential efficacy of four vaccines against new SARS-CoV-2 variants, as well as the origins of the variants and the locations of their mutations, are described in **Table 3**. There are currently no available data on the impact of the new COVID-19 variants on the severity of the disease, but the UK variant (B.1.1.7) and Brazil variant (P.1) have been found to be more transmissible than the original SARS-CoV-2 virus.[25] In a recent study, the Pfizer/BioNTech vaccine demonstrated poor efficacy against the South Africa variant (B.1.351).[29]

Table 2. Vaccines with press-released data.

Vaccine	Type	Participants			COVID-19 Cases	Efficacy (95% CI)	Phase III Trial Site	No. of doses
		Enrolled	Vaccine	Placebo				
J & J	Viral vector	44,325	19,866	NA	469	66% (NA)	USA, Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa	1
Nov-HHS	Recombinant spike protein nanoparticle	15,000	NA	NA	62 (6:56)†	89.3% (75.2–95.4)	UK	2
		4,400 (Phase 2b)	NA	NA	44 (15:29)†	60% (19.9–80.1)	South Africa	
		16,000	NA	NA	NA	NA	USA, Mexico	
BB-NIV	Whole-virion inactivated	25,800	NA	NA	NA	NA	India	2

J & J: Ad26.CO2-S, developed by Johnson & Johnson.[8,9]

Nov-HHS: NVX-CoV2373, developed by Novavax and the Department of Health and Human Services.[10–12]

BB-NIV: Covaxin/BBV152, developed by Bharat Biotech and the National Institute of Virology.[13]

†Total (vaccine:placebo)

Table 3. SARS-CoV-2 variants.

Name	Origin	Location of Mutations	First Reported	First Reported (US)	Vaccine Effectiveness
B.1.1.7 [25]	UK	Mutation in RBD* of spike protein at position 501: amino acid asparagine (N) replaced with tyrosine (Y).†	UK, September 2020	December 2020	Pfizer/BioNTech (in vitro studies) [26]
		P618H replacement on the spike proteins.			Novavax (NVX-CoV2373) 89.3% efficacy [10]
		Deletion at positions 69 and 70 of spike protein.			Covaxin/BBV152 Bharat Biotech (in vitro studies) [27]
B.1.351 [25]	South Africa	Eight lineage-defining mutations in the spike protein	South Africa, October 2020	January 2021	Pfizer/BioNTech (in vitro studies) [26]
		Spike protein, including K417N, E484K, N501Y			Janssen (Phase III trial, 95% S.A. population) [8,9]
					Novavax (NVX-CoV2373) 60% efficacy [10] Moderna (mRNA-1273) [30]
P.1 [25]	Brazil	17 unique mutations, including 3 in RBD of spike protein	Japan, January 2021	January 2021	Janssen [8,9] Novavax (NVX-CoV2373) [10]
CAL.20C [28]	USA (Southern CA)	Cluster 20C consists of 5 mutations:—ORF1a: I4205V, ORF1b: D1183Y, S: S13I; W152C; L452R (S13I and W152C in the N-terminal domain, and L452R in RBD)	Los Angeles (CA), July 2020	July 2020	Unknown

*RBD: Receptor binding domain.

† The shorthand for this mutation is N501Y.

Discussion

Here, we reviewed the available data on the 10 vaccines that have—as of March 1, 2021—reached phase III of the clinical development process. Data from peer-reviewed publications is available for only four vaccines. The existing evidence concerning vaccine efficacy and safety is encouraging, but we still do not have data on vaccine effectiveness and possible long-term complications. As more vaccines come into the market, it will be important to define which vaccines will be the most effective in preventing COVID-19, as well as achieving herd immunity.

The existing data on vaccine efficacy against the emerging SARS-CoV-2 variants are very limited. Only four vaccines (Pfizer/BioNTech, Novavax, Johnson & Johnson, and Bharat Biotech) have demonstrated efficacy against these variants; in the cases of Pfizer/BioNTech and Novavax, these effects have only been documented in vitro. No data are available on the efficacy of any vaccine against the California variant (CAL.20C). Future research should appraise COVID-19 vaccines on the basis of variant coverage. With an increasingly broad range of vaccines available, the potential risks and benefits of combining different vaccines also require study.

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