Assessing the Progress of Various Novel SARS-CoV-2 Vaccine Tests and Clinical Trials

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Objective:

This meta-analysis will provide an overview of vaccines currently in clinical trial, detail the types of vaccines in novel development, and document the current progress in SARS-CoV-2 vaccine development.

Background:

The emergence of SARS-CoV-2 virus in late 2019 has led to more than 17,000,000 infections and over 600,000 deaths worldwide caused by the novel coronavirus disease, COVID-19². The outbreak has halted regular and necessary aspects of society, from schooling to economic growth, and has devastated families in the United States with fear, unemployment, and over 140,000 deaths.² Decreased quality of life, breathing issues, and comorbidities linger with the threat of infection.^{10, 16} With the difficulty in regulation and mitigation of spread, several pharmaceutical manufacturers are rushing to find a successful vaccine, bypassing typical development regulations and timelines. As countries' healthcare systems and economies are strained by targeted shutdowns, vaccine development has been fast tracked by most countries. The typical vaccination timeline can take up to a decade, involving multiple phases of thoroughly designed testing after drafting countless novel treatments; certain manufacturers have received funding and permissions to bypass regulations in order to reduce the havoc of the pandemic.¹⁰ Vaccines currently in accelerated clinical trial for COVID-19 involve various novel and traditional types, including adenovirus-based, mRNA, DNA, subunit, and killed types. With a successful and safe vaccine, countries struggling to bear the burden of a shut-down society and overloaded health care system may begin their recovery. The objective of this research is to assess the results, efficacy, and promise of current COVID-19 vaccine candidates in clinical trials.

Abstract:

The SARS-CoV-2 outbreak of winter 2019 and 2020 has boomed into a global pandemic of a highly contagious respiratory illness, COVID-19. This affliction causes severe acute respiratory distress and, for many with pre-existing conditions, can threaten to be fatal. Many pharmaceutical manufacturers have been allowed to accelerate their vaccination development, an otherwise lengthy and several stage process. Vaccines being developed are both novel and traditional; some target the spike protein, an agent in SARS-CoV-2 contagion, as recent studies showed that it produced polyclonal antibody responses and neutralized SARS-CoV-2 S-mediated entry, as well as the receptor binding domain. Animal testing used pre-clinical trial in Sinovac's PiCoVacc show promise to create SARS-CoV-2-specific antibody responses targeting S-specific and RBD-specific IgG in mice, which is why PiCoVacc was shown to mitigate the severity of the virus's symptoms in all rhesus macaques tested. Additionally, testing of Novavax's NVX-CoV2373 used live mice and baboon models and has shown promising results of high

affinity antibody responses targeting SARS-CoV-2¹⁵. In this pre-clinical trial, the spleens of animal models who received NVX-CoV2373 followed by a Matrix-M adjuvant, or an immune response boosting agent, showed increased frequencies of TFH cells and GC B cells, encouraging Novavax to continue into clinical trial stages¹⁵. Vaccine candidates have already produced post-clinical trial results. INO-4800, a DNA vaccine made by INOVIO, has passed phase 1 clinical trials, while demonstrating general safety in all volunteers and generating immunological response rates and T cell immune responses in 94% of the participants. Moderna and Pfizer show promise with mRNA vaccines, both for the spike protein and receptor domain¹²; these follow a novel approach and have currently moved into their phase two trials due to increased immune response and reduced adverse effects initially in clinic; Moderna's spike protein vaccine showed titers of antibody 2.1 times higher than those convalescent with the 100ug dosage, in addition to elevated T-cell response post inoculation for all tested doses.^{3,9} Another vaccine, known as ChAdOx1 nCoV-19, a chimpanzee adenovirus-vectored vaccine, has been tested on 1077 healthy adults through single and double doses. The results have shown that the single dose elicited both humoral and cellular responses against SARS-CoV-2, with a booster immunization augmenting antibody titers. Within the ChAdOx1 nCoV-19 groups, local and systemic reactions were more common⁵. Patients were randomly assigned single intramuscular injections of ChAdOx1 nCoV-19 at doses of 5×10^{10} viral particles or MenACWY⁵. After the vaccination procedure, participants were observed in the clinic for 30-50 minutes and asked to take note of any abnormal events during the 28-day follow up period⁵. Evaluating the adenovirus, mRNA, DNA, inactivated, and subunit vaccines currently in accelerated development by pharmaceutical manufacturers will allow for a comprehensive review of which vaccine is most ready for widespread use and can successfully and safely curtail further spread of SARS-CoV-2.

Materials and Methods:

Experiment	Manufacturer	Type of Vaccine: Specifics	Participants	Dosage/Administration
1 ^{3,9}	ModernaTX Inc.	mRNA-1273 <ul style="list-style-type: none"> Built with cholesterol, DSPC, PEG2000 DMG, and SM-102 (ionized lipid base). Lipid nanoparticle carrier to protect genetic material while safely administering into blood. mRNA-1273 encodes for the SARS-CoV-2 spike 	Results published for 45 adults aged 18-55 (by end of trial participant number reached 120) Eligibility involved healthy persons: non-child bearing persons with lack of	<ul style="list-style-type: none"> Non-randomized, open label trial 2 injections with varying dosages- the injection was intramuscular, done in the deltoid on the 1st and 29th day of trial Follow-ups scheduled for regular intervals up to a year post vaccination to observe

		(S) protein, which binds to allows virus to infect human cells.	pre-existing health conditions, prior exposure or affliction with COVID-19, substance usage, bleeding disorder, chronic disease	<ul style="list-style-type: none"> ○ Adverse effects ○ Vital signs alteration ○ Immunogenicity by titers of SARS-CoV-2 specific binding antibody (bAb) and specific neutralizing antibody (nAb) measured by ELISA
2 ⁵	Oxford/AstraZeneca	Adenovirus <ul style="list-style-type: none"> ● Expresses the SARS-CoV-2 spike protein 	1077 healthy adults (ages 18-55) <ul style="list-style-type: none"> ● show no history of SARS-CoV-2 or of COVID-19 symptoms ● All participants underwent screenings: full examination (medical history was reviewed) 	<ul style="list-style-type: none"> ● Single dose: Single intramuscular injections at doses of 5×10^{10} viral particles, randomly assigned ● Prophylactic paracetamol was allowed to be administered before vaccination in two of the five trial locations ● Double dose: 10 participants enrolled in the non-randomised, prime-boost group, two-dose schedule <ul style="list-style-type: none"> ○ Administered 28 days after first dose ● Control groups = meningococcal conjugate vaccine (MenACWY) ● Participants separated into four groups <ul style="list-style-type: none"> ○ Group 1: 1st phase of study with multiple check-ups ○ Group 2: cellular and humoral immunogenicity assessment ○ Group 3: 10 patients part of non-randomised group ○ Groups 4: patients who only had serum samples drawn for immunology and humoral assessments.

3 ⁸	INOVIO	INO-4800; DNA <ul style="list-style-type: none"> Made and designed by a proprietary DNA medicine platform using the genetic sequence of COVID-19 	40 healthy adults (ages 18-50)	Intradermal injections with 1.0 mg and 2.0 mg dose cohorts twice four weeks apart.
4 ⁶	SinoVac	PiCoVacc; Inactivated <ul style="list-style-type: none"> PiCoVacc was made by a strain, CN2, which was isolated from SARS-Cov-2 strains from 11 hospitalized patients bronchoalveolar lavage fluid samples. 	10 BALB/c mice; 24 rhesus macaques	Mice: 0, 1.5, 3, or 6 µg per dose or a 0 µg sham Rhesus Macaques: Intramuscular injections with 3.0 or 6.0 µg doses 3 times one week apart (for 4 macaques); Intramuscular injections with 1.5 or 6.0 µg doses 3 times one week apart (for 10 macaques); Other 10 macaques received a sham or placebo
5 ¹⁵	Novavax	NVX-CoV2373 <ul style="list-style-type: none"> Protein subunit Pre-fusion S-protein structure from mutated furin cleavage site to resist cleavage, uses 2 proline substitutions at apex of central helix 	<ul style="list-style-type: none"> 4 groups of 10 female BALB/c mice (aged 7-9 weeks, weighted 17-22 g) 4 groups of 2-3 olive baboons (aged 10-16 years) 	<p>Mice:</p> <ul style="list-style-type: none"> They were given intramuscular injections with either a single priming dose or prime/boost regimen that was 14 days apart with low dose range of 0.01 µg, 0.1 µg, 1 µg, or 10 µg of NVX-CoV2373 and 5 µg saponin-based Matrix-M adjuvant, another 10 mice given two doses of 10 µg of NVX-CoV2373 without adjuvant. 10 mice were in the control group. <p>Additional experiment with mice:</p> <ul style="list-style-type: none"> Groups of female BALB/c mice of 6 mice per group given 10 µg NVX-CoV2373 with or without 5 µg adjuvant administered in 2 doses 21 days apart; 3 mice = control group

				Olive Baboons: <ul style="list-style-type: none"> IM injection of either 1, 5, or 25 µg NVX-CoV2373 with 50 µg adjuvant, another group given 25 µg of NVX-CoV2373 without adjuvant. <ul style="list-style-type: none"> It was administered in 2 doses separated by 21 days.
6 ¹²	Pfizer Inc.	mRNA BNT162b1 <ul style="list-style-type: none"> Encodes for the SARS-CoV-2 receptor binding domain (RBD) that allows cellular infiltration 	Tested in 45 participants	Double Blind, randomized, (placebo) controlled trial <ul style="list-style-type: none"> at least four experimental candidates representing mRNA and target antigens, codes for optimized version of RBD antigen 24 subjects received two doses of 10 or 30 ug of BNT162b1, 12 received injection of 100 ug, and and 9 received 2 doses of placebo Neutralized titers observed after 7 and 28 days

Experiment 4

Figure A:

Hematological analysis in all 4 Macaques looking at the percentage of lymphocytes, including CD3+, CD4+, and CD8+.⁶

Figure B:

Hematological analysis in all 4 Macaques

looking at the key cytokines containing TNF-α, IFN-γ, and IL-2.⁶

Experiment 5

Figure A: Full-length diagram of the S protein with the S1 and S2 subunits.¹⁵

Figure B: “Representative reduced SDS-PAGE gel of purified full-length wild-type, indicated by WT, BV2365, and NVX-CoV2373.”¹⁵

Figure C: Images of NX-CoV2373 components using transmission electron microscopy and 2D class averaging.¹⁵

Results:

Experiment	Manufacturer/Vaccine Type	Outcome Measures/Results Observed	Immune Response//Adverse Effects	Scheduled for next phase or clinical trial?
1 ^{3,9}	ModernaTX Inc./mRNA	<ul style="list-style-type: none"> • Production of neutralizing antibodies- activity against SARS-CoV-2 • T-cell responses elevated 	<ul style="list-style-type: none"> • “Rapid” and response immune response showed • no serious adverse effects reported in interim results, but any notable events were reported at the 250 ug dose level; 21% of participants at this level reported 1+ severe events, most commonly post second dose including fatigue, fever, chills, headache • live SARS-CoV-2 spike protein levels panel compared with geometric mean titers in convalescent sera; phase 3 results of 100ug dose showed titers 3 times convalescent levels 	<ul style="list-style-type: none"> • Has shown safe and promising results • Because the preliminary results support their clinical development, they will onto phase three of their trials in three different countries to reach diverse populations and potentially test the vaccine on children.
2 ⁵	Oxford/AstraZeneca	<p>Local and systemic reactions were more common</p> <ul style="list-style-type: none"> • Headache, muscle ache, chills, etc. <p>A single dose elicited both humoral and cellular responses against SARS-CoV-2</p> <ul style="list-style-type: none"> • Spike-specific T-cell responses peaked on day 14 • Participants had neutralizing activity after receiving a booster dose 	<ul style="list-style-type: none"> • Participants who received the double doses had the strongest immune response • Participants who reported pain after vaccination, mostly mild to moderate in intensity <ul style="list-style-type: none"> ○ 67% in ChAdOx1 nCoV-19 group without prophylactic paracetamol ○ 50% in the ChAdOx1 nCoV-19 group with prophylactic paracetamol ○ 32% in MenACWY group • Participants who reported fatigue 	<p>The preliminary results supported the clinical development progression</p> <ul style="list-style-type: none"> • Phase three is in trial in three different countries

			<ul style="list-style-type: none"> ○ 70% in the ChAdOx1 nCoV-19 group without paracetamol ○ 71% in the ChAdOx1 nCoV-19 with paracetamol ○ MenACWY group: 48% of participants without paracetamol and 46% with paracetamol ● Participants who reported headaches <ul style="list-style-type: none"> ○ 68% in the ChAdOx1 nCoV-19 group without paracetamol ○ 61% in the ChAdOx1 nCoV-19 with paracetamol ○ MenACWY group: 41% of participants without paracetamol and 37% of participants with paracetamol. ● No Serious Adverse Effects 	
3 ⁸	INOVIO/DNA	<ul style="list-style-type: none"> ● INO-4800 determined as safe by week 8 	<ul style="list-style-type: none"> ● 94% of volunteers showed immunological response rates and T cell immune responses by week 6. ● 10 adverse events, but all of them were grade 1 in severity, most being redness at the place of injection. ● No one had a Serious Adverse Event (SAE) 	
4 ⁶	SinoVac/Inactivated	Mice: <ul style="list-style-type: none"> ● At week 6, 	Mice: <ul style="list-style-type: none"> ● None of the mice showed 	

		<p>SARS-CoV-2 S-specific and RBD-specific IgG levels were as high as a titer of 819,200 (>200 µg/ml) and 409,600 (>100 µg/ml), respectively</p> <ul style="list-style-type: none"> • RBD is the dominant immunogen • The amount of N-specific IgG induced was ~30-fold lower than that of antibodies targeting S or RBD in immunized mice • SARS-CoV-2-specific NABs developed after one week, increased by week 2 and by week 7, reached a titer up to 1500 for the low and medium doses and 3000 for the high dose, whereas the sham group did not develop any NABs <p>Rhesus Macaques:</p> <ul style="list-style-type: none"> • At week 2, Macaques developed S-specific IgG and NAb, which reached levels up to nearly 12,800 	<p>adverse effects</p> <ul style="list-style-type: none"> • Results show that PiCoVacc may not protect a recipient from the virus, but it may reduce the severity of the symptoms <p>Rhesus Macaques:</p> <ul style="list-style-type: none"> • The unvaccinated macaques had severe interstitial pneumonia, whereas vaccinated macaques were generally protected from the virus with only very mild and focal histopathological changes in a few lobes of lung, which could have been caused by the method of injection. • None of vaccinated macaques experienced fever, weight loss, appetite loss, abnormal mental health, abnormal blood changes, or any abnormalities in major organs compared to those who received a sham or placebo 	
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		<p>and nearly 50, respectively by week 3</p> <ul style="list-style-type: none"> No antibody-dependent enhancement (ADE) of infection was observed 		
5 ¹⁵	Novavax	<p>Mice: Virus Load:</p> <ul style="list-style-type: none"> 4 days post infection: placebo-treated mice had average of 10⁴ SARS-CoV-2 pfu/lung, mice w/ NVX-CoV2373 without adjuvant had 10³ pfu/lung, those with adjuvant had “limited to no detectable virus load.” <p>Weight Loss:</p> <ul style="list-style-type: none"> The mice with 10 µg prime/boost regiment with adjuvant protected against weight lost while those without adjuvant not protected. <p>Histopathology:</p> <ul style="list-style-type: none"> On Day 4: placebo treated mice exhibited denudation of epithelial cells in large airways, thickening of alveolar septam periarteiolar cuffing <ul style="list-style-type: none"> On Day 7: 	<p>Mice:</p> <ul style="list-style-type: none"> ICCS assays found that frequency of IFN-γ+m TNF-α+, and IL-2+ cytokine-secreting CD4+ and CD8+ T cells were significantly higher (p<0.0001) in spleens from vaccine with adjuvant than those without adjuvant. Those given adjuvant also showed significantly higher frequency of multifunctional CD4+ and CD8+ T cells. Spleen analysis showed that the adjuvant led to higher frequency of TFH and GC B cells. <p>Olive Baboons: IgG titers:</p> <ul style="list-style-type: none"> With the booster, anti-S protein IgG titers increased over log g (GMT = 33,000-174,000) after 1-2 weeks for all dose levels. Those who did not receive adjuvant had little to none found anti-S IgG titer (GMT < 125) after 	<ul style="list-style-type: none"> NVX-CoV2373 with Matrix-M adjuvant currently analyzed in multiple nonhuman primate models and phase 1/2 clinical trial

		<p>peribronchiolar inflammation with increased periarteriolar cuffing.</p> <ul style="list-style-type: none"> • Prime-only groups showed reduced inflammation at bronchi and arterioles at 10 µg and 1 µg dose <ul style="list-style-type: none"> ○ Prime/boost showed significant reduction in lung inflammation for all doses <p>Olive Baboons:</p> <ul style="list-style-type: none"> • No similar analysis done/reported as the mice 	<p>only 1 immunization.</p> <p>Antibodies:</p> <ul style="list-style-type: none"> • Those who received 1 immunization of 5 or 25 µg of vaccine + adjuvant showed low levels of hACE2 receptor blocking antibodies. • The receptor blocking antibody titers significantly increased after 1-2 weeks of booster for all dose groups that got the adjuvant (GMT= 150-600). • With 1 immunization with adjuvant, virus neutralizing antibodies increased (GMT = 190-446) for all dose groups. <ul style="list-style-type: none"> ○ However, those who got 25 µg NVS-CoV2373 without adjuvant did not have any antibodies found that block S-protein binding to the hACE2 receptor. • PBMCs from those who received 5 or 25 µg of the adjuvant had the most IFN-γ secreting cells, 5-fold greater than those who only got 25 µg of NVX-CoV2373 without adjuvant or 1 µg of vaccine with the adjuvant. • ICCS analysis showed that 5 µg of vaccine w/ adjuvant had largest frequency of IFN-γ+, 	
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			<p>IL-2+, and TNF-α+ CD4+ T cells, as well as that of CD4+ T cells.</p> <p>Comparing to recovered COVID-19 patients:</p> <ul style="list-style-type: none"> • The mean anti-S IgG levels were 7-fold higher in immunized baboons than convalescent serum. • The olive baboons had 7-8 fold higher binding and receptor inhibiting antibodies than COVID-19 convalescent serum. 	
6 ¹²	Pfizer Inc.	<ul style="list-style-type: none"> • Preliminary data tests safety and potential immunogenicity of a vaccine for SARS-CoV-2 built upon the receptor domain-coding mRNA • significant observed immunogenicity in the 100ug dose group 	<ul style="list-style-type: none"> • Day 28 (& days after second dose of 10 or 30 ug) elevated RBD-binding IgG antibodies, Geometric mean concentrations of antibodies were 8 and 46.3 times those of convalescent infected patients • Neutralizing antibody titers were 1.8 and 2.8 times convalescent • Side effects were localized and mild/moderate depending on the dosage, most commonly being pain at injection site but also including low-grade fever (more common post-second dose) • one participant who received the 100ug dose reported severe pain at the site of injection 	<ul style="list-style-type: none"> • Still in clinical study, will move on to Phase 2b/3 (safety/efficacy trial) to begin late July 2020 once results are thoroughly reviewed and approved

Limitations:^{7, 10, 11, 14, 15}

One definitive limitation to novel vaccination trials is the limited time frame in which the effects of inoculation could be observed; thus, potentially reduced immunity or adverse effects later on a clinical participant's timeline could not be accounted for while particular vaccine candidates move forward on accelerated development. Additionally, the preliminary clinical trials produced promising results with a small sample of about 45 participants; larger trials could better show potential adverse effects and a more comprehensive look into immune responses. Moving forward, researchers should await later phase trials to determine which vaccine provides the highest immune response in a larger patient population.

Discussion:

In-vivo vaccination trials in mammals such as Novavax with NVX-CoV2373 have shown that adding an adjuvant to a protein subunit-based vaccine leads to significantly strengthened and higher frequencies of multifunctional CD4+ and CD8+ T and GC B cells. As a result, higher affinity antibody responses in the animal models used have allowed Novavax to take the next steps to continue with a phase 1/2 clinical trial in nonhuman primate models. PiCoVacc, while not able to prevent the infection of SARS-CoV-2, showed the ability to protect macaques from more extreme symptoms of COVID-19. None of the mice or macaques experienced adverse effects allowing the inactivated virus vaccine to advance to human clinical trials.⁶ Current trials in clinic show much promise for a potential vaccine that can prevent not only contagion but infliction and symptoms of COVID-19; the mRNA based vaccine designs not only show increased immune response, but ModernaTX Inc.'s progress with the spike protein complex with mRNA 1273 show promise for a future of genetic-based vaccinations with little adverse effects while still initiating a substantial

immune response in comparison to convalescent levels of elevated antibodies and T-cells.

ModernaTX Inc.'s phase 1 and 2 trials will continue to check with patients within the next year, however have been given approval by federal regulation to progress into their phase III trial due to promising results.^{3, 9} Pfizer's build of the BNT162b1 mRNA candidate follows a similar, lipid nanoparticle build for an mRNA vaccine; while Pfizer is also progressing into the next stages of vaccine development, both mRNA vaccines are novel types.¹² They show promise for the future of genetic vaccines in lipid carriers, but have not been studied long enough to show the long-term effects on immunity to SARS-CoV-2.^{11, 14} Another clinical trial, Oxford and AstraZeneca's adenovirus vaccine (ChAdOx1 nCoV-19), has shown safe and promising results⁵. With the preliminary results of supporting their clinical development, they will proceed with phase three of their trials in three different countries to reach diverse populations and potentially test the vaccine on children⁵. In addition, ChAdOx1 nCoV-19 will be given to older age groups, health-care workers, and those who with high risk for SARS-CoV-2 exposure as a single-dose or

two-dose administration regimen in further trials to test the efficiency, safety, and immunogenicity of ChAdOx1 nCoV-19⁵. INOVIO's DNA vaccine, INO-4800, has also proven to be relatively safe with only 10 participants reporting mild adverse effects in their phase 1 clinical trials. INOVIO will advance to phase 2 and 3 clinical trials either in July or August.⁸

All vaccines in preliminary clinical trials have shown promising results, with little adverse effects and elevated immune response; the main comparison then, observed within the coming year as these trials are relatively recent, are the progression of immunity and ability to implement widespread vaccination to different groups of people based on adverse effects. The differences in the carriers and ease in administration in addition to the robustness of immune responses will be the deciding factors in determining which vaccine that has progressed into phase 2 and 3 trials will be most effective and approved to prevent further societal degradation caused by the contagion and fatalities of SARS-CoV-2 and COVID-19.

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